Bijlage 2

DE BRAUW
BLACKSTONE
WESTBROEK

Rechtbank Noord-Nederland, locatie Leeuwarden
Zaak- en rolnummer: C/17/190788 / HA ZA 23/172
Zitting: 21 februari 2024

CONCLUSIE VAN ANTWOORD

inzake:

Albert BOURLA,
wonende te Greenwich, Verenigde Staten van Amerika

Gedaagde sub 11,
advocaten: mr. D.C. Roessingh en mr. M. Bredenoord-Spoek

tegen:

1. [redacted] wonende te Sneek, gemeente Súdwest-Fryslân,
2. [redacted] wonende te Sneek, gemeente Súdwest-Fryslân,
3. [redacted] wonende te Sneek, gemeente Súdwest-Fryslân,
4. [redacted] wonende te Doetinchem,
5. [redacted] wonende te Doetinchem,
6. [redacted] laatstelijk wonende te Zaandam, gemeente Zaanstad,[1]
7. [redacted] wonende te Leeuwarden,

(tezamen [redacted] **e.a.**" en afzonderlijk aangeduid bij hun achternamen)

eisers,

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[1] Geschorst wegens overlijden. Zie akte beraad schorsing ex artikel 225 lid 2 Rv (...) van 22 november 2023 en de akte na beraad schorsing ex artikel 225 lid 2 Rv van 10 januari 2024.

advocaten: mr. A.G.W. van Kessel en mr. P.W.H. Stassen

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Dr. Albert Bourla ("**Bourla**") concludeert voor antwoord als volgt.

1 INLEIDING

1. Het SARS-CoV-2 virus (het "**Coronavirus**") bestaat echt. Net zo echt is COVID-19, de zeer besmettelijke en mogelijk levensbedreigende ziekte van de luchtwegen veroorzaakt door het Coronavirus.

2. Kort na zijn ontstaan, op 11 maart 2020, had de infectie zich verspreid naar 114 landen wereldwijd en verklaarde de Wereldgezondheidsorganisatie (de "**WHO**") de uitbraak van het Coronavirus tot een wereldwijde pandemie.[2] Door deze pandemie zijn wereldwijd ongeveer 700 miljoen mensen besmet geraakt met COVID-19 en zijn bijna zeven miljoen mensen overleden.[3] Alleen al in Nederland zijn meer dan acht miljoen bevestigde COVID-19-infecties geregistreerd, met meer dan 22.000 doden tot gevolg.[4]

3. Vanzelfsprekend werd de COVID-19 pandemie vrijwel onmiddellijk de grootste zorg van regeringen, bedrijven en maatschappelijke organisaties over de hele wereld toen deze begin 2020 de kop opstak. Regeringen van over de hele wereld riepen farmaceutische bedrijven op om een vaccin te ontwikkelen. Pfizer en BioNTech behoorden tot de eersten die deze verantwoodelijkheid op zich namen, samen met andere farmaceutische bedrijven zoals Moderna, Janssen en AstraZeneca.[5] Al in de loop van 2020 voerde Pfizer klinische studies uit en nog datzelfde jaar slaagde zij erin een voorwaardelijke handelsvergunning te krijgen van regelgevende instanties, onder andere in de EU. Deze goedkeuringen werden verleend op basis van uitgebreide gegevens die werden verkregen tijdens de klinische studies, die aantoonden dat het Pfizer/BioNTech-vaccin

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2 WHO, *WHO Director-General's opening remarks at the media briefing on COVID-19* , 11 maart 2020 (**Bourla-1**), toegankelijk via www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020

3 data.who.int/dashboards/covid19/cases?n=c

4 covid19.who.int/region/euro/country/nl

5 Voor een volledige lijst van COVID-19 vaccins die zijn goedgekeurd door het EMA, zie EMA, *COVID-19 medicines* (**Bourla-2**), toegankelijk via www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines

("**Comirnaty**")[6] voldeed aan de wettelijke normen voor veiligheid, werkzaamheid en productiekwaliteit.

4. De verwoesting en het verlies aan mensenlevens als gevolg van de pandemie werd beperkt en uiteindelijk grotendeels overwonnen door een gezamenlijke inspanning van regeringen, burgers, bedrijven en de wetenschappelijke gemeenschap. Met name vaccins, waaronder Comirnaty, droegen in grote mate bij aan het afremmen van de pandemie. Op 5 mei 2023 verklaarde de WHO dat de COVID-19 pandemie officieel voorbij was.[7] Wetenschappelijke analyses laten zien dat de COVID-19-vaccins alleen al tijdens de eerste twee jaren van de pandemie wereldwijd ongeveer 14 tot 19 miljoen sterfgevallen hebben voorkomen.[8]

5. Desondanks omarmde een (gelukkig, klein) deel van de bevolking verschillende samenzweringstheorieën, waaronder dat het Coronavirus zelf een hoax is, dat de vaccins ertegen giftig zijn, of dat de COVID-19 pandemie een samenzwering is van "de mondiale elite" om een of ander illegaal en/of immoreel doel te bereiken.

6. [redacted] e.a. kunnen helaas tot dit deel van de bevolking worden geschaard – net als overigens huisarts Van Walraven die kennelijk bereid is gevonden 'medische verklaringen' af te geven ten behoeve van deze procedure. [redacted] e.a. beweren dat COVID-19 geen ziekte is, maar dat dit fenomeen is verzonnen als onderdeel van een project genaamd The Great Reset, dat was gepland en gericht op het forceren van een totale herordening van de wereld. Volgens [redacted] e.a. werd dit project geïnitieerd door NGO's, in het bijzonder het World Economic Forum ("**WEF**"), gefinancierd door de Wereldbank en in Nederland uitgevoerd door de gedaagden in deze procedure. Het vaccineren van de gehele bevolking met een COVID-19 vaccin zou deel hebben uitgemaakt van dit project.[9] De concrete aanleiding voor deze theorieën van [redacted] e.a. vormt kennelijk het boek 'The Great

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6 Het Pfizer/BioNTech COVID-19 vaccin staat ook bekend als BNT162b2. Deze namen kunnen door elkaar worden gebruikt.

7 WHO, *Statement on the fifteenth meeting of the IHR (2005)*, 5 mei 2023 (**Bourla-3**) , toegankelijk via www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

8 The Lancet, *Global impact of the first year of COVID-19*, 23 juni 2022 (**Bourla-4**), toegankelijk via www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900320-6

9 Zie onder meer dagvaarding, nrs. 2, 61-65, 117-125, 186 en 198.

Reset', waarin wordt geschetst hoe de wereld er na COVID-19 volgens de auteurs uit zou *kunnen* zien.[10] Niets meer en niets minder. De complottheorie van [redacted] e.a. kent dan ook geen enkele feitelijke basis.

7. In deze procedure stellen [redacted] e.a. specifiek dat (i) Bourla en de andere gedaagden hen opzettelijk en onrechtmatig hebben misleid door de Nederlandse bevolking (waaronder [redacted] e.a.) op te roepen zich te laten vaccineren tegen COVID-19, terwijl zij wisten of moesten weten dat het vaccin niet veilig en niet effectief was en (ii) zij daardoor schade hebben geleden.

8. Deze verwijten zijn onjuist. Bourla heeft [redacted] e.a. niet misleid, noch anderszins onrechtmatig jegens hen gehandeld. In werkelijkheid heeft Bourla, in zijn rol als CEO van Pfizer, een bijdrage geleverd aan de ontwikkeling van een vaccin tegen COVID-19 dat effectief is en een gunstig veiligheidsprofiel heeft. Dat maakt het extra wrang dat Bourla nu persoonlijk wordt gedagvaard en met voornoemde verwijten wordt geconfronteerd. De door [redacted] e.a. geformuleerde vorderingen vertonen fundamentele procedurele en inhoudelijke gebreken. Procedureel valt op dat de vorderingen tegen de verschillende gedaagden nauwelijks – of in veel gevallen in het geheel niet – met elkaar samenhangen, zodat een vordering tegen de in de Verenigde Staten woonachtige Bourla op grond van Nederlands procesrecht in beginsel niet aan de Nederlandse rechter kan worden voorgelegd.[11] Daarnaast voldoen [redacted] e.a. niet aan hun stelplicht. Inhoudelijk hebben de vorderingen ook geen kans van slagen. [redacted] e.a. leggen de rechtbank een op punten onbegrijpelijk samenraapsel voor van (onderling en met de vordering) ongerelateerde, niet-onderbouwde en onjuiste beweringen. De vorderingen van [redacted] e.a. dienen daarom te worden afgewezen.

9. In deze conclusie van antwoord zal Bourla de stellingen van [redacted] e.a. weerleggen, voor zover deze begrijpelijk zijn en betrekking

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10 Dit boek is onder andere geschreven door de heer Schwab, de voorzitter van het WEF. Het WEF is een organisatie gericht op het tot stand brengen van internationale samenwerking en initieert onder de noemer The Great Reset het delen van inzichten en informatie over een mondiale aanpak van de maatschappelijke en economische crisis volgend op de pandemie (*Aanhangsel Handelingen II* 2021/22, 2541, antwoord op vraag 4).

11 Zie verder paragraaf 2.1 over rechtsmacht.

hebben op hem, op Pfizer en/of op de kwaliteiten van Comirnaty. Daarbij wordt de volgende opbouw gehanteerd:

- in hoofdstuk 2 zal Bourla enkele van de meest in het oog springende procedurele gebreken van de vorderingen van [redacted] e.a. belichten;
- in hoofdstuk 3 zal Bourla de feitelijke beweringen van [redacted] e.a. weerleggen; en
- in hoofdstuk 4 zal worden toegelicht waarom de vorderingen geen rechtsgrondslag hebben.

2 PROCEDURELE OPMERKINGEN

2.1 Bourla zal de bevoegdheid van de rechtbank niet betwisten, maar kan niet geacht worden de bevoegdheidsvereisten te aanvaarden

10. De rechtbank Noord-Nederland, locatie Leeuwarden is onbevoegd om kennis te nemen van de vorderingen tegen Bourla. In de randnummers 296-297 van de dagvaarding verwijzen [redacted] e.a. slechts naar artikel 107 Rv, dat ziet op interne of relatieve bevoegdheid. [redacted] e.a. hebben niet uiteengezet – laat staan gemotiveerd – waarom en op welke grondslag de rechtbank internationale bevoegdheid zou hebben over de vorderingen tegen Bourla. Zouden zij artikel 7 lid 1 Rv (dat het juiste kader biedt) in overweging hebben genomen, dan zouden zij niet succesvol zijn geweest. Zij zijn namelijk niet in de buurt gekomen van het stellen van een zodanige samenhang tussen hun vorderingen tegen de beoogde ankergedaagde, de heer Hofstra, en hun vorderingen tegen Bourla. De rechtbank Noord-Nederland, locatie Leeuwarden zou - na haar ambtshalve beoordeling - zich daarom eenvoudig onbevoegd kunnen verklaren ten aanzien van de vorderingen tegen Bourla. Dat gezegd hebbende, zijn de vorderingen van [redacted] e.a. zo evident ongegrond dat Bourla geen rechtsmachtverweer zal opwerpen ten gunste van het voor eens en altijd inhoudelijk behandelen van de vorderingen.[12]

[12] Hiermee kan Bourla niet worden geacht in te stemmen met een van de vereisten voor bevoegdheid van de Nederlandse rechter, zoals dat tussen de vorderingen tegen Bourla en die tegen de andere gedaagden een zodanige samenhang bestaat in de zin van artikel 7 Rv.

2.2 Vorderingen moeten worden afgewezen bij gebrek aan onderbouwing

11. [redacted] e.a. hadden de benodigde feiten dienen te stellen, en, bij betwisting daarvan, deze feiten moeten bewijzen, om de door hen gewenste rechtsgevolgen te kunnen inroepen. Met een beroep op artikel 6:162 BW stellen zij dat (i) zij zijn misleid; (ii) zij zonder die misleiding geen COVID-19 vaccin hadden genomen; en (iii) zij als gevolg van het vaccin schade hebben geleden.

12. In deze stellingen ligt kennelijk besloten dat [redacted] e.a. een COVID-19 vaccin hebben genomen. In dat geval had van hen in ieder geval verwacht mogen worden dat zij zouden hebben gesteld *welk* vaccin zij *wanneer* zouden hebben genomen[13] en (ii) dat zij deze vaccins hebben genomen als gevolg van de beweerde misleiding. [redacted] e.a. hebben zelfs deze elementaire punten niet gesteld. Hun vorderingen kunnen reeds daarom niet worden toegewezen. Daarnaast ontbreken deugdelijke stellingen en een deugdelijke onderbouwing over (i) de aard van de vermeende misleiding en (iii) hun beweerde schade.

13. Bourla meent ondanks het voorgaande dat de rechtbank wel een oordeel kan vellen over de stellingen die wel door [redacted] e.a. worden ingenoemen. Hoewel de dagvaarding van 65 pagina's bol staat van gefabuleerde stellingen die soms kant noch wal raken en waarvan de relevantie niet steeds duidelijk is, is het Bourla wel duidelijk wat [redacted] e.a. trachten te bereiken. Bourla betwist al hetgeen [redacted] e.a. bij de inleidende dagvaarding hebben gesteld, behoudens voor zover uit deze conclusie blijkt dat Bourla de juistheid van enige stelling van [redacted] e.a. erkent.Bourla reageert zo goed en zo kwaad als het kan op de suggesties van [redacted] e.a..

3 DE VORDERINGEN HEBBEN GEEN FEITELIJKE BASIS

14. In dit hoofdstuk zullen het algemene toelatingsproces voor vaccins in de EU (paragraaf 3.1) en de specifieke ontwikkeling van Comirnaty

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13 Alleen voor [redacted] volgt uit productie 91 welk vaccin zij wanneer zou hebben genomen.

(paragraaf 3.2) worden besproken. Vervolgens zullen de specifieke stellingen van [redacted] e.a. worden weerlegd (paragraaf 3.3).

3.1 Algemeen toelatingsproces voor vaccins in de EU

3.1.1 Het verkrijgen van een handelsvergunning

15. Alle vaccins van Pfizer worden in eerste instantie ontwikkeld en getest in een laboratorium. Als de eerste tests gunstig zijn, worden deze gevolgd door klinische studies van toenemende omvang, waaronder gerandomiseerde gecontroleerde studies die het nieuwe vaccin vergelijken met een bestaand vaccin of placebo.[14]

16. De resultaten van het ontwikkelingsprogramma worden ingediend bij de juiste bevoegde instantie, samen met uitgebreide farmaceutische gegevens met betrekking tot de productie van het vaccin, voor de aanvraag van een handelsvergunning.

17. Op Europees niveau beslist de Europese Commissie over verlening van een handelsvergunning, na reglementaire en wetenschappelijke beoordeling door het Europees Geneesmiddelenbureau (het "**EMA**") en haar adviescomité, het Comité voor geneesmiddelen voor menselijk gebruik (het "**CHMP**").[15]

18. Als het EMA na grondig onderzoek concludeert dat de afweging van de voordelen en risico's in verband met het gebruik van het vaccin positief is, kan het EMA besluiten om een handelsvergunning aan het product te verlenen. Het vaccin en de goedgekeurde productinformatie voor beroepsbeoefenaren in de gezondheidszorg en ontvangers van het vaccin worden dan in de markt beschikbaar.

19. Die handelsvergunning kan ook voorwaardelijk worden verleend, bijvoorbeeld in noodsituaties in verband met een bedreiging van de volksgezondheid vastgesteld door de Wereldgezondheidsorganisatie

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[14] In dit geval werd het kandidaat-vaccin Comirnaty vergeleken met een placebo, omdat er geen bestaande COVID-19-vaccins waren.

[15] Het wettelijk kader voor de toelating, vervaardiging en distributie van geneesmiddelen in de EU is voornamelijk vastgelegd in Richtlijn 2001/83/EG tot vaststelling van een communautair wetboek betreffende geneesmiddelen voor menselijk gebruik en Verordening (EG) nr. 726/2004 tot vaststelling van communautaire procedures voor het verlenen van vergunningen en het toezicht op geneesmiddelen voor menselijk en diergeneeskundig gebruik en tot oprichting van een Europees Geneesmiddelenbureau.

of door de EU in het kader van Beschikking nr. 2119/98/EG.[16] Artikel 4 lid 1 van Verordening (EG) nr. 507/2006 bepaalt hierover het volgende:

> "*Een voorwaardelijke vergunning kan worden verleend wanneer het comité vaststelt dat, ofschoon geen volledige klinische gegevens betreffende de veiligheid en de werkzaamheid van het geneesmiddel zijn verstrekt, aan alle volgende eisen is voldaan:*
>
> *a) de in artikel 1, punt 28 bis, van Richtlijn 2001/83/EG gedefinieerde afweging van de voordelen en risico's van het geneesmiddel is positief;*
>
> *b) het is waarschijnlijk dat de aanvrager die volledige klinische gegevens kan verstrekken;*
>
> *c) er wordt voorzien in onvervulde medische behoeften;*
>
> *d) de voordelen voor de volksgezondheid van de onmiddellijke beschikbaarheid van het geneesmiddel op de markt zijn groter dan het risico dat verbonden is aan het feit dat nog aanvullende gegevens moeten worden verstrekt.*"

20. Het EMA bevestigt dat de voorwaardelijke handelsvergunning een pragmatisch instrument is voor goedkeuring van een geneesmiddel dat voorziet in een onvervulde medische behoeft.[17] Eerdere goedkeuring via een voorwaardelijke handelsvergunning doet geen afbreuk aan de garanties dat het geneesmiddel voldoet aan de strenge EU-normen voor veiligheid, werkzaamheid en kwaliteit en dat er na goedkeuring voortdurend uitgebreide gegevens worden gegenereerd. Aanvullende informatie kan wel worden aangeleverd, zoals bijvoorbeeld over de bescherming bij specifieke groepen zoals kinderen en zwangere vrouwen. Een voorwaardelijke handelsvergunning is een jaar geldig en kan vervolgens jaarlijks worden verlengd. Zodra uitgebreide klinische gegevens zijn ingediend, kan het CHMP aanbevelen de voorwaardelijke handelsvergunning om te zetten in een standaard handelsvergunning.

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16 Verordening (EG) nr. 507/2006 van de Commissie voorziet in de verlening van een "*voorwaardelijke vergunning*" voor het in de handel brengen van bepaalde geneesmiddelen die binnen het toepassingsgebied van Verordening (EG) nr. 726/2004 vallen.

17 EMA, *Conditional marketing authorisation* (**Bourla-5**), toegankelijk via www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation

3.1.2 Geneesmiddelenbewaking na toelating

21. Het veiligheidsprofiel van een geneesmiddel kan niet volledig vastgesteld worden tijdens de ontwikkeling vóór toelating. Het is met name mogelijk dat zeer zeldzame bijwerkingen zelfs in grote klinische onderzoeken niet worden geïdentificeerd. Om nieuwe veiligheidsinformatie zo snel mogelijk te identificeren, worden daarom voor alle geneesmiddelen geavanceerde procedures voor geneesmiddelenbewaking geïmplementeerd nadat het in de handel is gebracht.[18]

22. Bij elke aanvraag van een handelsvergunning in de EU wordt een ontwerp van een risicomanagementplan (een "**RMP**") ingediend. Na goedkeuring maakt het RMP deel uit van de handelsvergunning. Een RMP kan ook aanvullende geneesmiddelenbewakingsactiviteiten bevatten die voorwaarden vormen voor de handelsvergunning.[19]

23. Routinematige geneesmiddelenbewakingsactiviteiten houden in dat de houder van de handelsvergunning bijwerkingen waarvan hij kennisneemt, moet registreren en aan de bevoegde regelgevende instanties moet melden.[20] In gevallen waarin meldingen van vermoedelijke bijwerkingen resulteren in een bevestigd veiligheidssignaal, leidt dit tot passende actie, waaronder het bijwerken van de productinformatie, zoals goedgekeurd door de regelgevende instanties.

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18 De belangrijkste EU-wetgeving met betrekking tot de geneesmiddelenbewakingsverplichtingen van vergunninghouders is Richtlijn 2001/83/EG, Verordening (EG) nr. 726/2004 en Uitvoeringsverordening (EU) nr. 520/2012 van de Commissie. De EU-wetgeving wordt aangevuld met gedetailleerde richtsnoeren die het EMA samen met de hoofden van de geneesmiddelenautoriteiten heeft uitgebracht over goede geneesmiddelenbewakingspraktijken voor zowel regelgevers als de industrie. Zie EMA, *Good pharmacovigilance practices* (**Bourla-6**), toegankelijk via ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/good-pharmacovigilance-practices

19 Zie EMA, *Comirnaty risk management plan*, oktober 2023 (selectie) (**Bourla-7**) voor de huidige versie van Comirnaty RMP. Vindbaar, zoals van tijd tot tijd bijgewerkt, op ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf.

20 Zie voor meer informatie EMA, Periodic safety update reports (PSURs) (**Bourla-8**), toegankelijk via ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/periodic-safety-update-reports-psurs#:~:text=PSURs%20are%20pharmacovigilance%20documents%20intended,time%20points%20after%20its%20authorisation.

3.2 Ontwikkeling, goedkeuring en geneesmiddelenbewaking van Comirnaty en andere COVID-19 vaccins

24. De hiervoor geschetste procedure werd gevolgd bij de ontwikkeling, goedkeuring en geneesmiddelenbewaking van Comirnaty. Voor zover Bourla weet op basis van openbaar beschikbare informatie, geldt hetzelfde voor COVID-19 vaccins die door andere fabrikanten worden geproduceerd.[21]

3.2.1 Klinische proeven (vóór goedkeuring)

25. Op 13 maart 2020 gaf Pfizer een verklaring uit waarin het de biofarmaceutische industrie opriep om samen te werken in de strijd tegen COVID-19. In die verklaring verwees Pfizer reeds naar het contact met BioNTech in verband met de ontwikkeling van een potentieel mRNA-vaccin tegen het Coronavirus.[22] Een daadwerkelijke intentieverklaring tussen deze twee partijen werd aangekondigd op 17 maart 2020.[23] Op 9 april 2020 verstrekten zij nadere details over hun samenwerking inclusief de intentie om tegen eind april 2020 te beginnen met klinische studies van kandidaat-vaccins, afhankelijk van goedkeuring door de regelgevende instanties.[24]

26. Op 23 april 2020 is een onderzoek gestart naar de selectie van kandidaat-vaccins op basis van dosering. Dit resulteerde in de selectie van een van de vier kandidaat-vaccins, BNT162b2 (Comirnaty), toegediend in een schema van twee doses van 30 microgram.[25]

27. De werkzaamheid en veiligheid van BNT162b2 werd vervolgens onderzocht in een grote klinisch studie die werd uitgevoerd in de

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21 EMA, *COVID-19 vaccines development, evaluation, approval and monitoring* (**Bourla-9**), toegankelijk via www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-COVID-19/treatments-vaccines/vaccines-COVID-19/COVID-19-vaccines-development-evaluation-approval-monitoring

22 Pfizer, *Pfizer Outlines Five-Point Plan to Battle COVID-19*, 13 maart 2020 (**Bourla-10**), toegankelijk via www.pfizer.com/news/press-release/press-release-detail/pfizer-outlines-five-point-plan-battle-COVID-19

23 Pfizer, *Pfizer and BioNTech to Co-Develop Potential COVID-19 Vaccine*, 17 maart 2020 (**Bourla-11**), toegankelijk via investors.pfizer.com/Investors/News/news-details/2020/Pfizer-and-BioNTech-to-Co-Develop-Potential-COVID-19-Vaccine-03-17-2020/default.aspx

24 Pfizer, *Pfizer and BioNTech Announce Further Details on Collaboration to Accelerate*, 9 april 2020 (**Bourla-12**), toegankelijk via www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-further-details-collaboration

25 ClinicalTrials.gov, *A Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-2019 in Healthy and Immunocompromised Adults*, 13 januari 2022 (**Bourla-13**), toegankelijk via clinicaltrials.gov/ct2/show/study/NCT04380701

Verenigde Staten, Duitsland, Zuid-Afrika, Turkije, Argentinië en Brazilië.[26] Hieraan namen bijna 44.000 mensen deel, van wie ongeveer 50% Comirnaty kreeg en ongeveer 50% een placebo.[27] De resultaten toonden aan dat de werkzaamheid van het vaccin tegen een in het laboratorium bevestigde symptomatische COVID-19-infectie – die ten minste zeven dagen na de tweede dosis optrad, en zonder dat er aanwijzingen waren van een eerdere COVID-19 infectie – 95% was bij personen van 16 jaar of ouder (met acht COVID-19 gevallen in de vaccinatiegroep vergeleken met 162 COVID-19 gevallen in de placebogroep).[28]

28. Van de bijna 44.000 ingeschreven proefpersonen die op de afsluitdatum van de gegevens (14 november 2020) in de veiligheidsdatabase waren opgenomen, was het percentage dat werd teruggetrokken vanwege bijwerkingen zeer klein (0,2% in de vaccingroep en 0,1% in de placebogroep).[29] Er waren geen gemelde sterfgevallen bij deelnemers aan het onderzoek die geacht werden verband te houden met het vaccin.[30]

3.2.2 Goedkeuring

29. Tijdens de COVID-19 pandemie is gebruikgemaakt van verschillende mechanismen waarover het EMA beschikt om de wettelijke beoordeling van geneesmiddelen in het kader van volksgezondheidscrises te versnellen. Deze omvatten:

- de procedure in het kader van Verordening (EG) nr. 726/2004, die voorziet in een regelgevingsbeoordeling met een termijn van 150 dagen om advies uit te brengen na ontvangst van een

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26 Studie C4591001; zie ClinicalTrials.gov, *Study to Describe the Safety, Tolerability, Immunogenicity [...]*, 28 februari 2023 (**Bourla-14**), vindbaar via clinicaltrials.gov/ct2/show/NCT04368728

27 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf, p. 75-76.

28 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf, p. 131.

29 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf, p. 94 e.v.

30 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf, p. 109.

aanvraag van een handelsvergunning, in plaats van de 210 dagen die het EMA gewoonlijk krijgt;

- een "rolling review" waarbij het EMA gegevens van klinische proeven kan beoordelen naarmate deze beschikbaar komen en voordat een formele aanvraag voor een handelsvergunning is ingediend; en
- de oprichting van een taskforce door het EMA om te zorgen voor een snelle en gecoördineerde reactie op de pandemie.[31]

30. Deze versnelde procedures veranderen niets aan de inhoudelijke productvereisten en de gevestigde beoordelingsprincipes, maar zijn erop gericht om, binnen tijdschema's die passen bij de specifieke situatie, de productbeoordeling zeer efficiënt in te richten.

31. De eerste gegevens over Comirnaty werden op 5 oktober 2020 door BioNTech bij het EMA ingediend in het kader van het rolling review-proces, gevolgd door de formele aanvraag van een handelsvergunning op 30 november 2020.[32]

32. Het CHMP voerde een strenge evaluatie uit van de farmaceutische, preklinische en klinische gegevens over Comirnaty en concludeerde dat de beschikbare gegevens met betrekking tot de kwaliteit, veiligheid en werkzaamheid van Comirnaty aantoonden dat de afweging van de voordelen en risico's gunstig was.[33]

33. Na het positieve advies van het CHMP heeft de Europese Commissie op 21 december 2020 een voorwaardelijke vergunning verleend voor het in de handel brengen van Comirnaty.[34] De voorwaardelijke vergunning is op 3 november 2021 door de Europese Commissie verlengd en op 10 oktober 2022 omgezet in een standaard handelsvergunning, op basis van de vaststelling dat aan alle

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31 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

32 EMA, *EMA starts second rolling review of a COVID-19 vaccine*, 6 oktober 2020 (**Bourla-16**), toegankelijk via ema.europa.eu/en/news/ema-starts-second-rolling-review-covid-19-vaccine

33 EMA, *Comirnaty Assessment report*, 19 februari 2021 (**Bourla-15**), toegankelijk via ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf, p. 138.

34 OJEU, 24 december 2020 (**Bourla-17**), toegankelijk via eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=OJ:C:2020:447I:FULL

specifieke verplichtingen die bij de oorspronkelijke verlening van de voorwaardelijke vergunning waren opgelegd, was voldaan of dat deze waren geherclassificeerd en dat er geen redenen meer waren om de vergunning voorwaardelijk te laten.[35]

3.2.3 Aanvullende geneesmiddelenbewaking voor COVID-19 vaccins

34. Gezien de bijzondere omstandigheden van de COVID-19-pandemie heeft het EMA samen met de nationale bevoegde autoriteiten in de lidstaten – waaronder de Inspectie Gezondheidszorg en Jeugdzorg van het Nederlandse ministerie van Volksgezondheid, Welzijn en Sport – een specifiek geneesmiddelenbewakingsplan voor COVID-19-vaccins opgesteld (het "**EMA-plan voor geneesmiddelenbewaking**").[36] Het EMA-plan voor geneesmiddelenbewaking omvatte actieve verzameling van gegevens over zeldzame potentiële risico's, snelle beoordeling van nieuwe veiligheidsinformatie, snelle evaluatie van veiligheidskwesties die de afweging van de voordelen en risico's zouden kunnen beïnvloeden, actieve bewaking van kwetsbare groepen mensen en snelle communicatie van nieuwe veiligheidsinformatie. Naast de toepassing van bestaande procedures bepaalde het EMA-plan voor geneesmiddelenbewaking dat houders van een handelsvergunning maandelijks beknopte veiligheidsrapporten en periodieke veiligheidsverslagen moesten indienen, met informatie over gemelde bijwerkingen, ongewenste voorvallen van speciaal belang en verkoopgegevens. De EU-lidstaten werden belast met het verzamelen van gegevens over de blootstelling aan de vaccins, die gebruikt moesten worden voor de interpretatie van de veiligheidsgegevens.[37]

35. De vermoedelijke bijwerkingen zijn geregistreerd, onderzocht en gerapporteerd aan de relevante regelgevende instanties, waaronder EMA en het Nederlandse ministerie van Volksgezondheid, Welzijn en

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35 OJEU, 24 december 2020 (**Bourla-17**), toegankelijk via eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=OJ:C:2022:457:FULL, p. 3.

36 Zie EMA, *Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines* (**Bourla-18**), toegankelijk via ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf

37 Zie EMA, *Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines* (**Bourla-18**), toegankelijk via ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf, p. 3, punt 5.3.

Sport, in overeenstemming met de toepasselijke vereisten voor geneesmiddelenbewaking. Dergelijke gegevens zijn onafhankelijk geanalyseerd door regelgevende instanties en door Pfizer/BioNTech om eventuele nieuwe veiligheidssignalen (dat wil zeggen: informatie over een nieuw of bekend ongewenst voorval dat mogelijk wordt veroorzaakt door een geneesmiddel en nader onderzoek vereist) te identificeren. Na onderzoek worden passende maatregelen genomen, waaronder, indien goedgekeurd door de regelgevende instanties, een wijziging van de productinformatie.. Pfizer en BioNTech hebben te allen tijde samengewerkt met de bevoegde autoriteiten en voldaan aan hun geneesmiddelenbewakingsverplichtingen met betrekking tot Comirnaty.[38]

3.2.4 Tussenconclusie

36. Comirnaty is onderworpen aan strenge tests en regelgevende beoordelingen voordat het in de EU werd geïntroduceerd. Het resultaat van deze beoordeling was duidelijk: Comirnaty bleek zeer effectief (95%) te zijn in het voorkomen van symptomatische COVID-19 infecties. Wetenschappelijk onderzoek suggereert dat COVID-vaccins, waaronder Comirnaty, wereldwijd bijna 20 miljoen sterfgevallen door COVID-19 hebben voorkomen, wat zich proportioneel zou vertalen naar ongeveer 44.500 geredde levens alleen al in Nederland.[39]

37. Sinds de marktintroductie wordt de werkzaamheid, veiligheid en productiekwaliteit van Comirnaty nauwlettend in de gaten gehouden door zowel Pfizer als de bevoegde regelgevende instanties. Deze voortdurende beoordelingen blijven bevestigen dat Comirnaty, zoals inmiddels bijgewerkt om rekening te houden met de mutaties van het Coronavirus, voldoet aan alle wettelijke vereisten, waaronder met betrekking tot veiligheid: Comirnaty bleek weinig en over het algemeen milde en kortdurende bijwerkingen te veroorzaken.[40] De

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38 Zie ook paragraaf 3.3.4.

39 Watson O. e.a., *Global impact of the first year of COVID-19 vaccination: a mathematical modelling study*, 23 juni 2022 (**Bourla-19**), toegankelijk via https://www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900320-6

40 Zie www.ema.europa.eu/en/medicines/human/EPAR/comirnaty: onder What are the risks associated with Comirnaty: "*The most common side effects with Comirnaty are usually mild or moderate and get better within a few days after vaccination. These include pain and swelling at the injection site, tiredness, headache, muscle and joint pain, chills, fever and diarrhoea.*"

gezondheidswinst van de vaccinatie woog dan ook op tegen de bijwerkingen.[41]

3.3 Het betoog van [redacted] e.a. is een verzameling samenzweringstheorieën en al als zodanig vastgestelde onwaarheden vermomd als feiten

38. [redacted] e.a. negeren dat er van tijd tot tijd nieuwe besmettelijke ziektes opduiken en dat er mogelijk maatregelen moeten worden genomen om levens te redden. In plaats daarvan beweren [redacted] e.a. dat het fenomeen dat minstens twee jaar lang bijna ieders leven beheerste - het Coronavirus - niet echt was.

39. In een poging deze maatregelen te verklaren, komen [redacted] e.a. met vage en vergezochte samenzweringstheorieën waarbij NGO's, regeringen, media, internationale organisaties en bedrijven betrokken zouden zijn. Bourla zal in deze paragraaf ingaan op de feitelijke beweringen van [redacted] e.a. Bourla herhaalt dat beweringen die onbegrijpelijk worden genoemd of anderszins niet direct aan de orde komen, moeten worden beschouwd te zijn betwist.

3.3.1 Onjuiste voorstelling van zaken over het ontwikkelingsproces van Comirnaty

40. In de kern lijken [redacted] e.a. te stellen dat Pfizer te snel is begonnen met het testen van een vaccin tegen het Coronavirus. In het bijzonder benadrukken zij dat Pfizer enkele dagen nadat de Chinese autoriteiten op 10 januari 2020 de genetische code van het Coronavirus hadden vrijgegeven, met het testen begon.[42] [redacted] e.a. onderbouwen deze stelling niet. Zij verwijzen in deze context naar productie 47. Deze productie bevat echter slechts blote stellingen zonder dat die van een externe bron afkomstig lijken te zijn, en in ieder geval geen informatie over het ontwikkelingsproces van een COVID-19 vaccin. [redacted] e.a.

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41 Zie ook Gezondheidsraad, *Advies-COVID-19 vaccinatie BioNTech-Pfizer*, 24 december 2020 (**Bourla-20**), toegankelijk via www.gezondheidsraad.nl/binaries/gezondheidsraad/documenten/adviezen/2020/12/24/covid-19-vaccinatie-biontech-pfizer/Advies-COVID-19-vaccinatie-BioNTech-Pfizer.pdf, p. 4.

42 Zie dagvaarding, nrs. 41, 148, 163, 165 en 200. In nr. 41 wordt de datum van vrijgave van de genetische code ten onrechte vermeld als 8 januari 2020.

hebben bovendien niet uitgelegd – en Bourla niet begrepen – waarom voornoemde stelling relevant zou zijn voor de ingestelde vorderingen.

41. Desondanks zal Bourla kort uitleggen (i) hoe Pfizer en haar commerciële partner BioNTech, naast andere farmaceutische bedrijven, in staat waren om te beginnen met het testen van een Coronavaccin kort nadat zij de genetische code van het Coronavirus hadden ontvangen, en (ii) hoe het mogelijk werd om de vaccinatiecampagne te starten binnen ongeveer een jaar na het begin van de pandemie.[43]

Ad (i): Snel opstarten van initiële tests

42. Simpel gezegd hoefde Comirnaty niet vanaf nul te worden ontwikkeld. Pfizer en haar commerciële partner BioNTech konden bij de ontwikkeling van Comirnaty gebruikmaken van een aantal oplossingen voor het gebruik van mRNA-technologie en het bereiken van effectieve toediening van het vaccin die al tientallen jaren waren onderzocht en getest.[44] Dit omvat onder andere (a) het gebruik van mRNA technologie, en (b) het afgiftesysteem van de werkzame stof in de cellen (lipide nanodeeltjes).

(a) mRNA

43. Messenger ribonucleic acid ("**mRNA**") is een nucleïnezuur dat aanwezig is in alle levende cellen. Het bevat instructies voor de aanmaak van specifieke eiwitten. Menselijke cellen maken vele duizenden eiwitten die nodig zijn voor het functioneren van het lichaam. Elk van deze eiwitten is geassocieerd met een unieke mRNA-sequentie.

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43 Overigens zijn er veel openbaar toegankelijke publicaties over het ontwikkelingsproces van Comirnaty. Zie bijvoorbeeld Lewis, L.M. e.a., *The Race to Develop the Pfizer-BioNTech COVID-19 Vaccine: From the Pharmaceutical Scientists' Perspective*, 18 september 2022 (**Bourla-21**), toegankelijk via www.ncbi.nlm.nih.gov/pmc/articles/PMC9482796

44 Overigens lijken ook [redacted] e.a. zelf te erkennen dat er al vóór 2020 een aanzienlijke hoeveelheid werk op dit gebied was verricht. Dit blijkt uit hun bewering dat Pfizer "*sinds medio 2011 bezig was met de ontwikkeling van mRNA-vaccins voor het bèta coronavirus*", en uit hun verwijzing naar een reeks octrooiaanvragen door Moderna voor de periode 2015-2020 (dagvaarding, nr. 215, onder verwijzing naar productie 72). Hoewel deze octrooien niets te maken hebben met Pfizer en tijdstechnisch niet aansluit bij de bewering van [redacted] e.a., laat het in ieder geval wel zien dat eerder wetenschappelijk onderzoek, in dit geval naar andere coronavirussen, nuttig kan zijn voor later onderzoek, in dit geval voor de ontwikkeling van een vaccin tegen COVID-19. Zie ook https://www.pfizer.com/science/innovation/mrna-technology

44. mRNA werd voor het eerst ontdekt in 1961 in het Institut Pasteur in Frankrijk.[45] Sinds die tijd hebben veel onderzoekers het therapeutische potentieel ervan onderzocht, inclusief mogelijk gebruik in vaccins. Met name de oprichters van BioNTech en andere onderzoekers doen al meer dan 30 jaar onderzoek naar het therapeutische potentieel van mRNA.[46,47]

45. Comirnaty bevat een vorm van mRNA die in een laboratorium werd bereid om te coderen voor het spike-eiwit van SARS-CoV-2. Na toediening van Comirnaty gebruiken cellen het mRNA om dit virale spike-eiwit te produceren. Dit wordt op zijn beurt door het immuunsysteem herkend als een vreemd eiwit, waardoor antilichamen worden aangemaakt. Zodra het lichaam antilichamen heeft gemaakt tegen het virale spike-eiwit, blijven deze in het lichaam en kan het immuunsysteem snel reageren om de ontvanger van het vaccin tegen infectie te beschermen als het wordt blootgesteld SARS-CoV-2.[48] Voor de volledigheid: personen aan wie Comirnaty of een ander mRNA-vaccin wordt toegediend, worden alleen blootgesteld aan het doelantigeen of eiwit dat door het mRNA wordt gecodeerd. De toediening van het vaccin leidt niet tot besmetting met het virus zelf.

46. Het bovenstaande betekent dat aan het begin van de pandemie het technologisch al mogelijk was om mRNA te maken dat codeert voor het spike-eiwit van SARS-CoV-2.

47. Pfizer/BioNTech waren in staat om verschillende kandidaat-vaccins te maken kort nadat de Chinese autoriteiten de genetische code van SARS-CoV-2 hadden vrijgegeven. Daarna konden Pfizer/BioNTech de eerste laboratoriumtests uitvoeren en – afhankelijk van het verkrijgen van de vereiste wettelijke goedkeuringen – de eerste

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45 Institut Pasteur, *Discovery of messenger RNA in 1961*, 15 februari 2021 (**Bourla-22**), toegankelijk via www.pasteur.fr/en/home/research-journal/news/discovery-messenger-rna-1961#:~:text=We%20can%20be%20sure%20that,protect%20them%20against%20COVID%2D19

46 BioNTech, *The History of BioNTech - The Road to a New Era of Immunotherapy* (**Bourla-23**), toegankelijk via www.biontech.com/int/en/home/about/who-we-are/history.html

47 De Nobelprijs voor Fysiologie en Geneeskunde van 2023 werd bijvoorbeeld gegeven aan onderzoekers op wiens werk Pfizer bouwde bij het modificeren van het mRNA van het Coronavirus voor Comirnaty; zie Press release *The Nobel Prize in Physiology or Medicine 2023*, 2 oktober 2023 (**Bourla-24**), toegankelijk via www.nobelprize.org/prizes/medicine/2023/press-release/

48 Bettini, E., *SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond*, 2021 (**Bourla-26**) , toegankelijk via www.ncbi.nlm.nih.gov/pmc/articles/PMC7918810

klinische tests uitvoeren om de meest veelbelovende kandidaat te identificeren.

(b) Lipide nanodeeltjes

48. Het gebruik van mRNA-technologie in vaccins werd aanvankelijk beperkt door het feit dat mRNA gevoelig is voor enzymatische afbraak voordat het in de cellen terechtkomt. Daarom werd er veel onderzoek gedaan naar het verbeteren van de stabiliteit van het RNA en het overwinnen van de problemen bij de toediening door middel van een reeks mogelijke benaderingen,[49] waaronder het gebruik van lipiden en lipidenanodeeltjes. Een lipide nanodeeltje (een "**LNP**") is in feite een afgiftesysteem dat ervoor zorgt dat de werkzame stof – in het geval van Comirnaty mRNA dat codeert voor het SARS-CoV-2 spike-eiwit – intact blijft tot het de cel binnendringt.[50] De LNP-technologie was al meer dan tien jaar bekend en werd reeds op grote schaal gebruikt voor de effectieve toediening van een aantal geneesmiddelen.[51] Pfizer/BioNTech hoefde het wiel in dit opzicht dus niet opnieuw uit te vinden.

49. Daarom konden Pfizer/BioNTech beginnen met de ontwikkeling van vaccinkandidaten kort nadat ze in januari 2020 de genetische code van SARS-CoV-2 te weten waren gekomen..

Ad (ii): Versnelde vooruitgang in de ontwikkelingsstadia van vaccins

50. Het kandidaat-vaccin dat uiteindelijk bekend zou worden onder de naam Comirnaty doorliep alle reguliere ontwikkelings- en testfasen.[52] Het ontwikkelingsproces werd niet versneld door het overslaan van deze stadia – die bedoeld zijn om de veiligheid en effectiviteit van het vaccin te garanderen – maar door het elimineren van knelpunten en het doorlopen van parallele trajecten. Zonder uitputtend te willen zijn,

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49 Wadhwa et al., *Opportunities and Challenges in the Delivery of mRNA-Based Vaccines*, januari 2020 (**Bourla-27**).

50 Zie ook paragraaf 3.3.3.

51 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed

52 Zie paragraaf 3.2.

zal Bourla enkele van de belangrijkste factoren noemen die hebben bijgedragen aan een kortere ontwikkelingsduur van Comirnaty.

(a) Snelle resultaten dankzij een groot aantal vrijwilligers en de snelle verspreiding van het Coronavirus

51. Pfizer was in staat om bijna 44.000 vrijwilligers te werven in een tijdsbestek van minder dan vier maanden voor de laatste fasen van de klinisch studie. Dit steekt gunstig af bij eerdere ervaringen met het werven van vrijwilligers; het duurde bijvoorbeeld meer dan twee jaar om slechts 101 vrijwilligers te werven voor de klinische onderzoeken naar het vaccin tegen hondsdolheid in 2013. Dit alleen al bespaarde ongeveer twee jaar ontwikkelingstijd.[53]

52. Daarnaast betekende de snelle verspreiding van het Coronavirus dat het aantal ziektegevallen dat nodig was om een statistisch onderbouwde conclusie te trekken over de werkzaamheid van Comirnaty veel sneller werd bereikt dan gebruikelijk.[54] De besmettingsgraad die nodig was om de werkzaamheid van Comirnaty te beoordelen, werd ongeveer 1,5 jaar sneller bereikt dan wat in het verleden gebeurde bij sommige andere virussen.[55]

(b) Prioritering door de bevoegde overheidsinstanties

53. Het is algemeen bekend dat de regelgevende instanties in de VS, de EU en elders de ontwikkeling van vaccins tegen het Coronavirus vanaf begin 2020 zwaar hebben geprioriteerd.[56] Simpel gezegd stonden kandidaat-vaccins tegen het Coronavirus vooraan in de rij. Dit hield onder andere in dat prioriteit werd gegeven aan het beoordelen van

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53 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed

54 De effectiviteit van een vaccin wordt gemeten door het aantal (ernstige) gevallen van COVID-19 binnen een bepaald tijdsbestek na vaccinatie te vergelijken tussen de vaccin- en placebogroepen. Daarom moeten voldoende deelnemers aan klinische proeven ziek worden voordat een statistisch onderbouwde conclusie over de doeltreffendheid van het vaccin kan worden getrokken.

55 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed

56 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed; zie ook EMA, *COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines*, 4 mei 2020 (**Bourla-28**), toegankelijk via https://www.ema.europa.eu/en/news/covid-19-how-ema-fast-tracks-development-support-and-approval-medicines-and-vaccines

de resultaten van de toekomstige proeven met Coronavaccins. Aangezien beoordelingen door regelgevende instanties doorgaans een belangrijk knelpunt vormen in het ontwikkelingsproces van vaccins, heeft deze prioritering naar schatting ongeveer vier jaar ontwikkelingstijd bespaard.[57]

(c) Opvoeren van de productie in afwachting van goedkeuring door de regelgevende instanties

54. Voorts begon Pfizer op grote schaal met de productie van Comirnaty *voordat* er (voorwaardelijke) handelsvergunningen waren verkregen, om ervoor te zorgen dat er direct na het verkrijgen van de vergunning een groot aantal doses beschikbaar was.[58] Pfizer was bereid dit risico te nemen omwille van de mondiale volksgezondheid.

55. Samenvattend kan het succes van BioNTech en Pfizer om binnen een jaar een goedgekeurd vaccin aan miljoenen patiënten aan te bieden, dus alleen maar worden beschreven als een ongekende prestatie, die mogelijk werd gemaakt door de gezamenlijke inspanningen van de wetenschappelijke gemeenschap, bedrijven en regelgevende instanties over de hele wereld.

3.3.2 Het doel en de effecten van Comirnaty zijn consistent en transparant gecommuniceerd aan het publiek

56. In essentie beweren [redacted] e.a. dat (i) hun is verteld dat men zich niet alleen voor zijn/haar eigen veiligheid maar ook voor die van anderen moet laten vaccineren, (ii) dat dit misleidend was en (iii) zij zich niet zouden hebben laten vaccineren als zij naar behoren waren geïnformeerd over het feit dat Comirnaty de overdracht van het Coronavirus niet voorkomt.[59] Bourla zal deze onjuiste aantijgingen nu adresseren.

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57 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed

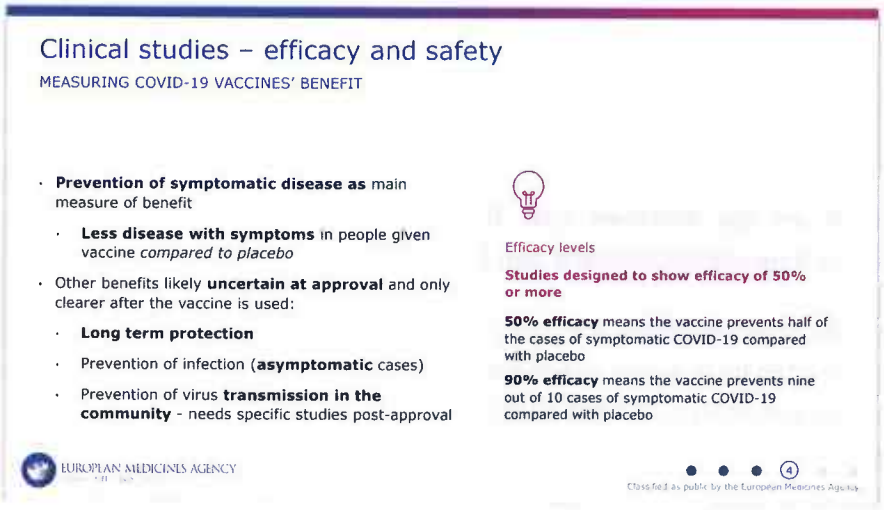
58 Zie Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021 (**Bourla-25**), toegankelijk via www.sciencenews.org/article/covid-coronavirus-vaccine-development-speed

59 Dagvaarding, nrs. 145 e.v. Tegelijkertijd heeft geen van de eiseressen gesteld dat zij schade hebben geleden doordat Comirnaty heeft nagelaten de overdracht van het Coronavirus van of naar een van de eiseressen te voorkomen.

Het primaire doel van Comirnaty

57. Het doel van Comirnaty was het voorkomen dat gevaccineerde mensen ernstig (symptomatisch) ziek zouden worden en om het aantal sterfgevallen als gevolg van COVID-19 te minimaliseren. Dit werd vanaf het begin duidelijk gemaakt door de regelgevende instanties die begin 2020 de oproep deden om zo snel mogelijk een COVID-19 vaccin te ontwikkelen.

58. In een presentatie over de ontwikkeling van COVID-19-vaccins van het EMA, staat bijvoorbeeld dat de "*main measure of benefit*" van een COVID-19-vaccin de "*prevention of symptomatic disease*" is. In diezelfde presentatie geeft het EMA aan dat het niet mogelijk is om vast te stellen, tegen de tijd dat een vaccin wordt goedgekeurd, of het de effecten van "*prevention of infection*" en "*prevention of virus transmission*" zal hebben.[60]



59. Talrijke academische bijdragen die werden gepubliceerd in de aanloop naar de toelating van Comirnaty legden op dezelfde manier

60 EMA, *How are COVID-19 vaccines developed* (**Bourla-29**), toegankelijk via ema.europa.eu/en/documents/presentation/presentation-how-are-covid-19-vaccines-developed-marco-cavaleri_en.pdf, p. 8.

uit dat het primaire eindpunt[61] van de klinische studies het vermogen van het vaccin is om *ernstige* gevallen van COVID-19 te voorkomen:

> "*The primary endpoint for all the phase 3 vaccine trials is amelioration of COVID-19 disease.*"[62]

60. Het voorkomen van overdracht was geen kenmerk van de COVID-19 vaccins (inclusief Comirnaty) dat getest en aangetoond moest worden voordat het vaccin op de markt kon worden gebracht.

61. Het was dus vanaf het begin duidelijk dat het primaire doel van Comirnaty was om de kans op een ernstige COVID-19 ziekte te verkleinen, en niet om de overdracht van het Coronavirus te voorkomen. Zoals uitgelegd in paragraaf 3.2 gaven de gegevens toentertijd aan dat Comirnaty 95% effectief was in het voorkomen van symptomatische COVID-19-ziekte, wat zonder twijfel kan worden beschouwd als het bereiken van voornoemd doel.

Publieke mededelingen over het doel en het effect van Comirnaty

62. Zoals gezegd stellen [redacted] e.a. onder meer door Bourla te zijn misleid doordat zij geloofden dat Comirnaty was ontwikkeld om te voorkomen dat gevaccineerde mensen het Coronavirus zouden oplopen en vervolgens zouden overdragen.

63. Bourla heeft [redacted] e.a. echter niet misleid. Al voordat Comirnaty op 21 december 2020 een voorwaardelijke handelsvergunning kreeg, was Bourla transparant over het feit dat het overdrachtspreventieve effect ervan niet was getest tijdens de klinische studies en niet bekend was.[63]

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61 Eenvoudig gezegd zijn eindpunten gerichte uitkomsten van een klinische studie die statistisch worden geanalyseerd om de werkzaamheid en veiligheid van de onderzochte therapie te helpen bepalen.

62 Zie bijvoorbeeld Nature, *Whither COVID-19 vaccines*, 28 september 2020 (**Bourla-30**), toegankelijk via www.nature.com/articles/s41587-020-0697-7

63 In een persbericht van 13 maart 2020 zei Bourla overigens het volgende: "*Many companies, including Pfizer, are working to develop antiviral therapies to help infected patients fight this emerging virus as well as new vaccines to prevent infection and halt the further spread of this disease.*" Het persbericht bevat echter ook een gedetailleerde disclaimer die zegt dat dit allemaal erg onzeker is en daarmee dat er geen rechten aan kunnen worden ontleend: "*This release contains forward-looking information about Pfizer's efforts to battle COVID-19 that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development (...). A further description*

64. In een interview met NBC News dat op 3 december 2020 is gepubliceerd, zegt Bourla bijvoorbeeld dat het onbekend is of mensen die gevaccineerd zijn nog steeds drager van het Coronavirus kunnen zijn en het op anderen kunnen overdragen:

> "*I think this is something that needs to be examined. We are not certain about that right now.*"[64]

65. In een interview met The Journal dat op 13 januari 2021 werd gepubliceerd, verklaarde Bourla opnieuw dat er weliswaar "*encouraging*" eerste gegevens waren over het vermogen van Comirnaty om de overdracht van het Coronavirus te voorkomen, maar dat deze gegevens "*not conclusive*" waren. Bourla waarschuwde verder dat Pfizer nog niet het bestaan van een overdrachtspreventief effect had bewezen:

> "*This is not conclusive yet. We know that in animals,* [there is] *significant protection from transferring the virus.... We haven't* [proven that in] *humans yet.*"[65]

66. Regelgevende instanties zijn even zo duidelijk geweest over het feit dat er geen tests zijn uitgevoerd, en dat er nog geen empirische gegevens zijn verzameld, over de vraag of Comirnaty een overdrachtspreventief effect heeft.

67. Zo publiceerde het EMA op 21 december 2020 een document bij zijn aanbeveling om Comirnaty een voorwaardelijke handelsvergunning te verlenen. Daarin legde het EMA uit dat Comirnaty voor 95% effectief was in het voorkomen van symptomatische COVID-19-ziekte, waarmee het aan zijn doel voldeed. Tegelijkertijd waarschuwde het EMA:

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of risks and uncertainties can be found in Pfizer's Annual Report on Form 10- K for the fiscal year ended December 31, 2019 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com." Zie Pfizer, *Pfizer Outlines Five-Point Plan to Battle COVID-19*, 13 maart 2020 (**Bourla-10**), toegankelijk via www.pfizer.com/news/press-release/press-release-detail/pfizer-outlines-five-point-plan-battle-covid-19

64 NBC News, *3 vaccine executives say that after approval, distribution will be the main challenge*, 3 december 2020 (**Bourla-31**), toegankelijk via www.nbcnews.com/news/us-news/3-vaccine-executives-say-after-approval-distribution-will-be-main-n1249928

65 The Journal, *Pfizer CEO says there is 'encouraging' data on whether its vaccine stops Covid transmission*, 13 januari 2021 (**Bourla-32**), toegankelijk via www.thejournal.ie/pfizer-ceo-5323949-Jan2021/

> "*The impact of vaccination with Comirnaty on the spread of the SARS-CoV-2 virus in the community is not yet known. It is not yet known how much vaccinated people may still be able to carry and spread the virus.*"[66]

68. Ook de Amerikaanse Food and Drug Administration ("**FDA**") verklaarde in een persbericht op 11 december 2020 dat "*at this time, [...] nor is there evidence that the vaccine prevents transmission of SARS-CoV-2 from person to person.*[67]

69. Hetzelfde geldt voor de WHO, die op 8 januari 2021 waarschuwde dat er "*not yet any evidence of the effect of the vaccine on virus transmission*" was. Zij heeft deze kwestie toen gemarkeerd als een aanbevolen gebied voor verder onderzoek.[68]

70. Het voorgaande maakt duidelijk dat tijdens een hoorzitting in het Europees Parlement op 10 oktober 2022 helemaal niet is "*onthuld*" dat de effecten van Comirnaty ter voorkoming van overdracht niet tijdens klinische proeven waren getest, zoals [redacted] e.a. suggereren.[69] Op dat moment was dit al bijna twee jaar een vaststaand en transparant gepubliceerd feit.

Werkelijk effect van Comirnaty ter voorkoming van overdracht

71. Tegelijkertijd heeft Comirnaty feitelijk wel bijgedragen aan de vermindering van de overdracht van ten minste de eerdere varianten van het Coronavirus die voorkwamen tijdens de eerste fases van de COVID-19 pandemie.[70]

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66 EMA, *Comirnaty, COVID-19 mRNA vaccine (nucleoside modified)*, 21 december 2020 (**Bourla-33**), toegankelijk via ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-comirnaty_en.pdf

67 FDA, *FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*, 11 december 2020 (**Bourla-34**), toegankelijk via www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19

68 WHO, *Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine*, 8 januari 2021 (**Bourla-35**), toegankelijk via iris.who.int/bitstream/handle/10665/338484/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1-eng.pdf?isAllowed=y&sequence=1#page=5, p. 5.

69 Dagvaarding, nr. 147.

70 Zie bijvoorbeeld Reuters, *Fact Check: Preventing transmission never required for COVID vaccines' initial approval* (**Bourla-36**), toegankelijk via www.reuters.com/article/factcheck-pfizer-vaccine-transmission/fact-check-preventing-transmission-never-required-for-covid-vaccines-initial-approval-pfizer-vax-did-reduce-transmission-of-early-variants-idUSL1N31F20E/

72. Het is duidelijk dat het vaccin heeft bijgedragen aan het vertragen van de verspreiding van het virus door de virale lading en (symptomatische) infecties bij gevaccineerde personen te verminderen, wat op zijn beurt leidt tot verminderde overdracht.[71]

73. Daarnaast hebben COVID-19 vaccins, waaronder Comirnaty, door het voorkomen van ernstige COVID-19-symptomen, bijgedragen aan het beheersen van de belasting van de nationale gezondheidszorgstelsels, waaronder die in Nederland.

74. COVID-19-vaccins hadden kortom tastbare positieve effecten op de volksgezondheid die verder gingen dan individuele bescherming. De herhaalde stellingen van [redacted] e.a. dat zij zijn misleid over het doel van Comirnaty zijn ongegrond.[72]

3.3.3 De chemische samenstelling van Comirnaty is al lang bekend

75. [redacted] e.a. beweren dat Comirnaty "*grafeenoxide*" bevat.[73] Dit is onjuist.

76. In werkelijkheid is de chemische samenstelling van Comirnaty al openbaar sinds de voorwaardelijke handelsvergunning is verleend in de EU, waaronder Nederland. De volledige lijst van ingrediënten in Comirnaty is bijvoorbeeld te allen tijde vermeld in de productinformatie (de samenvatting van de productkenmerken gericht op beroepsbeoefenaren in de gezondheidszorg en de bijsluiter voor patiënten die een vaccin ontvangen) die door het EMA is goedgekeurd en beschikbaar is gesteld vanaf de datum van verlening van de voorwaardelijke handelsvergunning op 21 december 2020.[74] Deze lijst van ingrediënten is ook gepubliceerd in talrijke andere media, en overheids- en academische bronnen, zoals door de FDA in haar Emergency Use Authorisation review memorandum van 11 december

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71 Zie bijvoorbeeld ECDC, *Risk of SARS-CoV-2 transmission from newly-infected individuals with documented previous infection or vaccination*, 29 maart 2021 (**Bourla-37**), toegankelijk via ecdc.europa.eu/en/publications-data/sars-cov-2-transmission-newly-infected-individuals-previous-infection

72 Zie ook conclusie van antwoord van de Staat e.a. van 10 januari 2024, nr. 6.2.

73 Dagvaarding, nrs. 150 e.v.

74 EMA, *Comirnaty product information* (selectie) (**Bourla-38**), toegankelijk via ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf, p. 345.

2020.[75] Informatie over de chemische samenstelling van Comirnaty was voor [redacted] e.a. dus vóór hun vermeende vaccinaties openbaar gemaakt en direct beschikbaar.

77. Voor de volledigheid volgt nu een korte beschrijving van elk van de ingrediënten in Comirnaty en hun rol in het waarborgen van de veiligheid, effectiviteit en productiekwaliteit van het vaccin.

De werkzame stof

78. De werkzame stof van Comirnaty heet Tozinameran. Simpel gezegd bestaat Tozinameran uit mRNA dat codeert voor het virale spike-eiwit van SARS-CoV-2.. Het zorgt ervoor dat cellen het "*spike*"-eiwit aanmaken, een eiwit dat aanwezig is op het oppervlak van het SARS-CoV-2 virus. Het eiwit zelf is niet besmettelijk of anderszins schadelijk. Het lichaam reageert er echter op als een "vreemd" eiwit. Op deze manier worden de cellen 'getraind' om antilichamen aan te maken wanneer ze het spike-eiwit van het Coronavirus tegenkomen, zodat de ontvanger van het vaccin beschermd is tegen infectie wanneer hij of zij aan het virus wordt blootgesteld.[76]

De lipiden (beschermende bolletjes)

79. Comirnaty bevat vier lipiden. Deze vormen kleine vettige bolletjes die het mRNA omhullen om het te beschermen tegen vernietiging voordat het de cellen binnenkomt. Deze beschermende bolletjes staan bekend als lipide-nanodeeltjes of LNP's.

80. De eerste lipide wordt meestal aangeduid met de codenaam ALC-0315.[77] Omdat ALC-0315 tijdens het productieproces geïoniseerd kan worden, dat wil zeggen een positieve lading krijgt, kan het aan het mRNA "kleven", dat een negatieve lading heeft. Hierdoor kan ALC-0315 het mRNA inkapselen en dus beschermen.. De vetbolletjes

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75 FDA, *Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum*, 20 november 2020 (**Bourla-39**), toegankelijk via www.fda.gov/media/144416/download, p. 11.

76 Zie ook randnummer 45 hiervoor.

77 De volledige wetenschappelijke naam van de verbinding ALC-0315 is *((4-hydroxybutyl)azaandiyl)bis(hexaan-6,1-diyl)bis(2-hexyldecanoaat)*.

brengen de werkzame stof, het mRNA, vervolgens via de celwand in het cytoplasma van de cel.[78]

81. De tweede lipide wordt meestal aangeduid met de codenaam ALC-0159.[79] De belangrijkste functie van ALC-0159 is het vormen van een beschermende laag rond het LNP. Dit verhoogt de stabiliteit van het mRNA en dus de bewaarbaarheid van Comirnaty.[80]

82. De derde en vierde lipiden in Comirnaty zijn cholesterol en DSPC.[81] Dit zijn conventionele lipiden die worden gebruikt in tal van toegelaten geneesmiddelen en dienen om de stabiliteit van het LNP verder te vergroten.[82]

Andere ingrediënten

83. Tot slot bevat Comirnaty nog verschillende andere ingrediënten, die allemaal heel gebruikelijk zijn. Ten eerste bevat Comirnaty sacharose, een gewone suiker. De functie ervan is ervoor te zorgen dat LNP's niet aan elkaar plakken wanneer ze worden ingevroren.[83] Ten tweede bevat Comirnaty een mengsel van zouten (waaronder natriumchloride of keukenzout) dat algemeen bekend staat als fosfaatgebufferde zoutoplossing, of trometamol, een veelgebruikte buffer voor een betere stabiliteit.[84] Het doel van deze zouten is ervoor te zorgen dat de zuurgraad van het vaccin vergelijkbaar is met die van het menselijk

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78 Zie Gov.UK, *Summary of the Public Assessment Report COVID-19 Vaccine*, december 2020 (**Bourla-40**), toegankelijk via bijvoorbeeld www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

79 De volledige wetenschappelijke naam van de verbinding ALC-0159 is *2-[(polyethyleenglycol)-2000]-N,N-ditetradecylacetamide.*

80 Zie bijvoorbeeld Gov.UK, *Summary of the Public Assessment Report COVID-19 Vaccine*, december 2020 (**Bourla-40**), toegankelijk via www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

81 De volledige wetenschappelijke naam van DSPC is *1,2-Distearoyl-sn-glycero-3-foscholine.*

82 Zie bijvoorbeeld Gov.UK, *Summary of the Public Assessment Report COVID-19 Vaccine*, december 2020 (**Bourla-40**), toegankelijk via www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

83 MIT Technology Review, *What are the ingredients of Pfizer's covid-19 vaccine*, 9 december 2020 (**Bourla-41**), toegankelijk via www.technologyreview.com/2020/12/09/1013538/what-are-the-ingredients-of-pfizers-covid-19-vaccine/

84 Specifiek zijn deze zouten: kaliumchloride, monobasisch kaliumfosfaat, natriumchloride, dibasisch natriumfosfaat dihydraat. Zie FDA, *Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum*, 20 november 2020 (**Bourla-39**), toegankelijk via www.fda.gov/media/144416/download, p. 11.

lichaam. Ten derde bevat Comirnaty water, omdat het vaccin een waterige oplossing is.

84. De lijst van ingrediënten die in de voorgaande paragrafen wordt beschreven, is uitputtend: Comirnaty bevat geen andere bestanddelen, waaronder "*grafeenoxide*". Dit is keer op keer bevestigd door het EMA en andere autoriteiten.[85] Grafeenoxide wordt niet gebruikt in het productieproces van Comirnaty en kan niet per ongeluk aanwezig zijn geweest in een dosis van Comirnaty. Dit is ook bevestigd door de Eurocommissaris voor Gezondheid en Voedselveiligheid, die op 8 maart 2022 verklaarde dat "*graphene oxide is not used in the manufacture or formulation of any of the COVID-19 vaccines or other medicines*".[86]

85. In de dagvaarding erkennen [redacted] e.a. dat een aantal onafhankelijke derden de bewering dat grafeenoxide in Comirnaty aanwezig zou zijn, hebben onderzocht. [redacted] e.a. hebben ook gelijk dat de uitkomst van deze *fact-checks* steeds hetzelfde was: Comirnaty bevat geen grafeenoxide.[87] [redacted] e.a. doen deze rapporten desondanks af als "*valselijk*", zonder enige onderbouwing aan te dragen.[88] Vervolgens refereren [redacted] e.a. aan "*videos en wetenschappelijke rapporten van zeer gerenommeerde personen*" waarin die "*aan de hand van bewijsmiddelen met grote precisie*" zouden verklaren "*dat het grafeen-oxide in alle mRNA injecties als hoofdbestanddeel aanwezig is*".[89] Het enige waar [redacted] e.a. in deze context naar verwijzen is een videofragment van een aflevering van een Amerikaans onlineprogramma genaamd "*The Stew Peters Show*".[90] In dit fragment suggereert een gast – mevrouw Karen Kingston – dat alle mRNA-vaccins, waaronder Comirnaty, grafeenoxide bevatten. Ze probeert

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85 Zie bijvoorbeeld EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 26 oktober 2021 (**Bourla-42**), toegankelijk via www.europarl.europa.eu/doceo/document/P-9-2021-003980-ASW_EN.html#ref1

86 87. EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 8 maart 2022 (**Bourla-43**), toegankelijk via www.europarl.europa.eu/doceo/document/P-9-2022-000303-ASW_EN.pdf

87 Dagvaarding, nr. 152. Enkele voorbeelden van dergelijke fact-checking: Reuters, *COVID-19 vaccines do not contain graphene oxide*, 23 juli 2021 (**Bourla-44**), toegankelijk via www.reuters.com/article/factcheck-grapheneoxide-vaccine-idUSL1N2OZ14F/ en AP, *Pfizer vaccine does not contain graphene oxide*, 8 juli 2021 (**Bourla-45**), toegnagelijk via apnews.com/article/fact-checking-430816913228

88 Dagvaarding, nr. 152.

89 Dagvaarding, nr. 153.

90 Dagvaarding, Productie 44.

deze conclusie te ondersteunen door op een misleidende manier te verwijzen naar een aantal octrooien, die geen van alle toebehoren aan Pfizer of een van zijn groepsbedrijven, en waarvan het verband met Comirnaty niet wordt begrepen en in ieder geval wordt betwist.

86. Er bestaat geen enkele aanwijzing dat mevrouw Kingston deskundige kennis heeft van de chemische samenstelling, het ontwikkelingsproces, de effecten of enig ander aspect van Comirnaty, laat staan dat zij een"zeer gerenommeerd persoon" is. Mevrouw Kingston is een voormalig werknemer van Pfizer. Zij was echter niet betrokken bij het onderzoek, de ontwikkeling of de productie van Comirnaty. Hoe dan ook bevat Comirnaty simpelweg geen grafeenoxide.

87. De stelling van [redacted] e.a. dat grafeenoxide aanwezig is in Comirnaty – zelfs "*als hoofdbestanddeel*" – is onjuist.[91] Hetzelfde geldt daarmee voor de stelling dat Bourla deze "*verkeerde voorstelling van zaken opzettelijk [liet] voortbestaan*".[92]

3.3.4 [redacted] e.a. interpreteren het rapport van Pfizer van 30 april 2021 fundamenteel verkeerd

88. In de dagvaarding verwijzen [redacted] e.a. maar liefst acht keer naar het rapport van Pfizer nr. FDA-CBER-2021-5683-0000054 van 30 april 2021 (het "**Pfizer-rapport**"). Zij presenteren het Pfizer-rapport als een "*smoking gun*" dat bewijst dat Comirnaty gevaarlijk is. Specifiek stellen [redacted] e.a. dat 42.086 mensen zouden hebben deelgenomen aan een Comirnaty proef ("*trial*") die liep van november 2020 tot februari 2021, en dat daarvan 1.223 mensen zouden zijn overleden en 11.361 mensen ernstig en blijvend letsel zouden hebben opgelopen.

89. Het Pfizer-rapport bewijst niets van dien aard.

90. Ten eerste heeft het Pfizer-rapport geen betrekking op een klinische proef. In plaats daarvan is het een geïntegreerde analyse van veiligheidsgegevens *na toelating* van Comirnaty, zoals het rapport zelf beschrijft.[93] Simpel gezegd registreert het Pfizer-rapport

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91 Dagvaarding, nr. 153.
92 Dagvaarding, nr. 152.
93 Productie 40, p. 5.

vermoedelijke bijwerkingen die gemeld zijn, meestal via nationale instanties, vóór de sluitingsdatum van 28 februari 2021. Het Pfizer-rapport is een Amerikaans rapport. Het equivalent in de EU-regelgeving voor geneesmiddelen is het Periodic Safety Update Report ("**PSUR**"). Dat is een rapport dat wordt opgesteld door de houder van de vergunning voor het in de handel brengen van een geneesmiddel en waarin de wereldwijde veiligheidservaringen daarmee op een bepaald moment na de toelating worden beschreven.[94]

91. Ten tweede verdraaien [redacted] e.a. de cijfers die in het Pfizer-rapport worden gepresenteerd. Tijdens de relevante periode meldden 42.086 ontvangers van Comirnaty bijwerkingen.[95] Om de veiligheid van Comirnaty ook maar enigszins zinnig te kunnen beoordelen, moet dit aantal worden afgezet tegen het totaal aantal mensen aan wie Comirnaty is toegediend. Dit bevestigt het sterke veiligheidsprofiel van Comirnaty: volgens het EMA werden tot 29 april 2021 wereldwijd meer dan 330 miljoen doses Comirnaty toegediend,[96] wat aangeeft dat slechts een zeer beperkt deel van de vaccinaties resulteerde in een melding van een vermeende bijwerking.[97]

92. Ten derde geven [redacted] e.a. een onjuiste voorstelling van de betekenis van de gerapporteerde bijwerkingen die in het Pfizer-rapport worden geanalyseerd. In het rapport wordt niet gesuggereerd dat deze bijwerkingen werden *veroorzaakt* door Comirnaty. Het Pfizer-rapport vermeldt alleen dat dergelijke bijwerkingen zich op een bepaald

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94 Het Engelse origineel luidt als volgt: "*A report prepared by the marketing-authorisation holder describing the worldwide safety experience with a medicine at a defined time after its authorisation.*" Zie EMA, *Periodic safety update report* (**Bourla-46**), toegankelijk via www.ema.europa.eu/en/glossary/periodic-safety-update-report#:~:text=A%20report%20prepared%20by%20the,reports%3A%20questions%20and%20answers%27. Zie bijvoorbeeld EMA, *Comirnaty periodic safety update report assessment 19 June 2022 to 18 December 2022* (selectie) (**Bourla-47**) vindbaar via www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2022-18-december-2022_en.pdf

95 Productie 40, p. 8.

96 EMA, Assessment report on the annual renewal of the conditional marketing authorisation (Comirnaty), 2021 (**Bourla-48**), toegankelijk via www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-r-0046-epar-assessment-report-renewal_en.pdf, p. 16.

97 Hoewel de periode in het EMA-rapport langer is dan de periode waarop het door [redacted] e.a. genoemde rapport ziet (29 april 2021 respectievelijk 28 februari 2021), laat dit zien dat het aantal gemelde overlijdens en het aantal gemelde personen met ernstig blijvend lichamelijk letsel – afgezet tegen het totaal aantal doses – zeer beperkt is, en ook significant kleiner dan [redacted] e.a. doen voorkomen.

moment *na* de injectie zouden hebben voorgedaan.[98] Daarmee is nog niet gezegd dat de bijwerkingen vermeld in het rapport ook daadwerkelijk komen *door* vaccinatie. Dat geldt te meer nu in de beginperiode van de vaccinatie – waar dit rapport op ziet – met name ouderen en kwetsbaren werden gevaccineerd. [redacted] e.a. maken een fundamentele fout door correlatie te verwarren met causaliteit, terwijl het ene het andere niet bewijst of zelfs maar noodzakelijkerwijs suggereert. In plaats daarvan worden dit soort rapporten gewoonlijk gebruikt als onderdeel van geneesmiddelenbewaking na toelating om vast te stellen of er veiligheidssignalen zijn die nader onderzoek rechtvaardigen.

93. Ten vierde geven [redacted] e.a. zelfs de meest elementaire statistische en demografische gegevens in het rapport verkeerd weer.

- Zij suggereren bijvoorbeeld dat 2.990 kinderen "*deelnamen*" aan de analyse. In werkelijkheid wordt er in het Pfizer-rapport gesproken over 2.990 personen van wie het geslacht niet werd vermeld in het bijwerkingenrapport.[99] Bovendien wordt vermeld dat er 175 personen jonger dan 18 jaar waren voor wie bijwerkingen werden gerapporteerd.[100]

- Daarnaast stellen [redacted] e.a. bijvoorbeeld dat 11.361 personen ernstig blijvend lichamelijk letsel zouden hebben opgelopen. Niets in het rapport wijst op ernstig blijvend letsel, of zelfs maar op de fysieke aard van een bijwerking.

94. Ook de stelling dat het rapport door Bourla "*verborgen*" zou zijn gehouden is onjuist, net als de datum waarop het rapport publiek zou zijn vrijgegeven.[101] Farmaceutische bedrijven, waaronder Pfizer, geven hun rapporten niet uit aan het publiek, maar aan de relevante regelgevende instanties. Voor alle duidelijkheid: Bourla noch Pfizer heeft stappen ondernomen om de uiteindelijke publicatie van het

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98 De FDA heeft bevestigd dat "*In fact, reviews by FDA and CDC have determined that the vast majority of the deaths reported are not directly attributable to the vaccines. FDA requires healthcare providers to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause.*" Zie Reuters, *Pages of suspected side effects released about Pfizer's COVID-19 vaccine [...]*, 17 maart 2022 (**Bourla-49**), toegankelijk via www.reuters.com/article/factcheck-coronavirus-pfizer-idUSL2N2VK1G1/.

99 Productie 40, p. 7.

100 Productie 40, p. 7.

101 Dagvaarding, nr. 144.

Pfizer-rapport in het kader van de Freedom of Information Act-procedure in de VS te voorkomen.[102] Bovendien is het analoge document in de EU – het PSUR – openbaar beschikbaar op de website van het EMA.[103]

3.3.5 De vage opmerkingen van [redacted] e.a. over vermeend verschillende kwaliteiten van batches vaccins zijn irrelevant en onjuist

95. [redacted] e.a. beweren dat Pfizer geen consistente productiekwaliteit heeft gehandhaafd voor de verschillende batches van Comirnaty.[104] Specifiek verwijzen zij naar batch EM0477 als een "*bijzonder dodelijk[e]*" variant.[105] Deze stellingen zijn onjuist.

96. Vooropgesteld, [redacted] e.a. hebben niet gesteld dat ze zijn gevaccineerd tegen COVID-19, laat staan welke batch Comirnaty ze zouden hebben ontvangen.[106] Zij hebben evenmin gesteld dat hun vaccinaties afkomstig waren van een batch die zij van mindere kwaliteit achten. De stellingen van [redacted] e.a. over de vermeend verschillende kwaliteiten van batches vaccins houden dus kennelijk geen verband met de gevorderde schadevergoeding, en zijn daarom irrelevant. Daarnaast hebben [redacted] e.a. niet deugdelijk onderbouwd dat batch EM0477 verschilde van andere batches Comirnaty.[107]

97. Belangrijker is dat een groot deel van het verhaal van [redacted] e.a. berust op een onjuiste interpretatie van een wetenschappelijk rapport van. Peter Riis Hansen ("**Hansen**"),[108] en de daaropvolgende vraag van een Europarlementariër aan de Europese Commissie waarin wordt verwezen naar het rapport van Hansen.[109] [redacted] e.a. beweren ten onrechte dat het rapport van Hansen bewijst "*[d]at er zeer grote verschillen in dodelijkheid en bijwerkingen van Pfizer Covid-19*

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102 Verzoeken onder de Amerikaanse Freedom of Information Act zijn vergelijkbaar met verzoeken onder de Wet open overheid (Woo) in Nederland.
103 Zie hierboven, nr. 90.
104 Dagvaarding, nrs. 245 e.v.
105 Dagvaarding, nr. 246.
106 De enige uitzondering is mevrouw [redacted] ten aanzien van wie op pagina 7 van productie 91 is vermeld dat zij Comirnaty-doses kreeg toegediend uit batches FC3143 en FF0688.
107 Dagvaarding, nrs. 245 e.v.
108 Productie 83, tweede document. Hansen is overigens één van de drie auteurs.
109 Productie 83, eerste document.

injectiebatches [bestaan]." In werkelijkheid is de conclusie van Hansen:

> "*In conclusion, the results suggest the existence of a batch-dependent safety signal for the BNT162b2 vaccine, and more studies are warranted to explore this preliminary observation and its consequences.*"[110]

98. Het rapport van Hansen weerspiegelt ook het basale wetenschappelijke inzicht dat analyses van bijwerkingen niet bedoeld zijn om een oorzakelijk verband vast te stellen tussen het vaccin en gezondheidsproblemen. Dit is des te meer het geval als het gaat om zelfrapportagesystemen, die per definitie gevoelig zijn voor vertekeningen in de rapportage en tekortkomingen in de gegevens. Hansen erkent terecht dat het doel van dergelijke systemen, en van zijn rapport, is om een potentieel veiligheidssignaal voor nader onderzoek te identificeren:

> "*The present preliminary findings must be interpreted in the light of several limitations. The DKMA-managed spontaneous SAE reporting system in Denmark is a passive surveillance system [...], and reports from these systems are subject to reporting biases, with potential for both under- and over-reporting, as well as incomplete data and variable quality of the reported information. Owing to these inherent limitations, signals detected by these systems must be considered to be hypothesis-generating and generally cannot be used to establish causality. In addition, in the present study, the SAE case history of prior COVID-19 was unknown, and specific SAE types [...] were not examined. Notably, to our knowledge, the Danish Serum Institute has not issued recalls of BNT162b2 vaccine batches.*"[111]
> (onderstrepingen toegevoegd, advocaat)

99. Naast het verkeerd voorstellen van deze voorlopige conclusie van Hansen als bewijs van de vermeende "*dodelijkheid*" van Comirnaty, negeren [redacted] e.a. dat er door de relevante Europese autoriteiten nader onderzoek is verricht naar de Deense partijen die Hansen noemt. Dit volgt uit het antwoord van de Eurocommissaris voor Gezondheid en Voedselveiligheid[112] op de vraag van een Europarlementariër, aan welke *vraag* [redacted] e.a. zoals gezegd wel

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110 Productie 83, tweede document, p. 3.
111 Productie 83, tweede document, p. 3.
112 Dat antwoord kwam op 3 juli 2023. Dat is vóór de datum waarop de dagvaarding is uitgebracht.

refereren.[113] Uit dat antwoord blijkt dat er geen verhoogd risico op bijwerkingen voor specifieke partijen is aangetoond:

> "*As regards literature monitoring, if various sources of information point to a potential issue more in-depth review is initiated. This was not the case for the mentioned Danish study.*
>
> *In addition to the limitations mentioned in the study, analyses performed by the European Medicines Agency on the batches reported in suspected AR cases did not reveal an increased risk of side effects for specific batches.*"[114]

100. De Europese Commissie herhaalde verder dat elke batch aan een strenge kwaliteitstest wordt onderworpen voordat die op de EU-markt wordt gebracht. Elke batch wordt eerst zorgvuldig getest door de fabrikant. En daarna voert de nationaal bevoegde autoriteit een extra onafhankelijke controle uit, de zogenaamde Official Control Authority Batch Release-test:

> "*As for any other medicinal products authorised in the EU, once a COVID-19 vaccine has received approval, each vaccine batch can only be released following quality control testing to confirm that the product is in line with the specifications that were approved as part of the respective marketing authorisation.*
>
> *This control is carried out by the manufacturer. However, for most centrally authorised vaccines, the EU legislation requires that a Member State Official Medicines Control Laboratory performs an additional independent control for each batch before it is put on the EU market.*
>
> *This independent control is referred to as Official Control Authority Batch Release testing and includes testing of agreed quality parameters and a compliance check of the manufacturer's own test results.*"[115]

101. Zoals vermeld in de vraag van de Europarlementariër zijn zowel vaccinfabrikanten als regelgevende instanties uiterst streng als het gaat om het waarborgen van een consistent hoge productiekwaliteit

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113 Dagvaarding, nr. 248, met verwijzing naar productie 83, eerste document.

114 EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 3 juli 2023 (**Bourla-50**), toegankelijk via www.europarl.europa.eu/doceo/document/E-9-2023-001537-ASW_EN.html

115 EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 3 juli 2023 (**Bourla-50**), toegankelijk via www.europarl.europa.eu/doceo/document/E-9-2023-001537-ASW_EN.html; zie ook EMA, *COVID-19 vaccines: development, evaluation, approval and monitoring* (**Bourla-51**), toegankelijk via www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-public-health-emergency-international-concern-2020-23/covid-19-vaccines-development-evaluation-approval-and-monitoring

van vaccins. In één situatie werden bijvoorbeeld 1,6 miljoen doses teruggeroepen door Moderna omdat in slechts 39 doses een vreemde substantie werd aangetroffen.[116]

102. Daarnaast vertonen de gegevens en de methodologie die voor het rapport van Hansen zijn gebruikt, ernstige tekortkomingen, zoals een vertegenwoordiger van de Deense nationale bevoegde autoriteit – het Deense Serum Instituut – in een ingezonden brief heeft opgemerkt. In die brief wordt uitgelegd dat het rapport van Hansen geen rekening houdt met het feit dat sommige van de door hem onderzochte batches niet (of nauwelijks) zijn gebruikt, terwijl die batches logischerwijs geen of zeer weinig meldingen van vermoedelijke bijwerkingen hadden. Dat maakt de verschillende onderzochte batches onvergelijkbaar. Toen de eerste batches werden toegediend, werden behandelaars bovendien aangemoedigd om alle vermoedelijke bijwerkingen te melden; later in de pandemie moedigden de autoriteiten het melden van lichte bijwerkingen echter niet meer aan. Zoals uitgelegd in de brief van de vertegenwoordiger van het Deense Serum Instituut, houdt het rapport van Hansen hiermee ook geen rekening. Ook hierom kan het onderzoek geen zinvolle inzichten bieden in de variabiliteit van batches.[117]

103. Tegelijkertijd heeft het Deense Serum Instituut geen partijen Comirnaty teruggeroepen, zoals Hansen in zijn rapport bevestigt. Sterker nog, er zijn nergens in de EU, noch wereldwijd, partijen Comirnaty teruggeroepen om veiligheidsredenen. Dit is op zichzelf al voldoende om enige zinnige bezorgdheid over de kwaliteit van individuele batches weg te nemen.

104. Kortom, de beweringen van [redacted] e.a. voor wat betreft vermeende variaties in kwaliteit van de verschillende batches Comirnaty zijn irrelevant en onjuist.

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116 Productie 83, eerste document.

117 De brief is van Anders Hviid, ontvangen op 20 juni 2023 en geaccepteerd op 9 juli 2023. Zie Hviid, A., *Inaccurate representation of shipped vaccines as administered*, 20 juni 2023 (**Bourla-52**), toegankelijk via factreview.gr/wp-content/uploads/2023/07/Eur-J-Clin-Investigation-2023-Hviid-Inaccurate-representation-of-shipped-vaccines-as-administered.pdf

3.3.6 Onjuiste uitspraken over de verhouding met de Europese Commissie

105. [redacted] e.a. doen een aantal niet-onderbouwde en onjuiste uitspraken over de contractuele relatie tussen Pfizer en de Europese Commissie met betrekking tot Comirnaty.[118] [redacted] e.a. hebben ook niet uitgelegd wat hiervan de relevantie zou zijn voor hun vorderingen.

106. [redacted] e.a. beweren dat de Europese Commissie Comirnaty heeft gekocht voor EUR 71 miljard. Dit is onjuist. Dit bedrag vertegenwoordigt de waarde van de bestellingen van de EU voor vaccins bij acht fabrikanten. Bovendien omvat dit bedrag aankoop*opties* die niet zijn gelicht en die zien op bijna de helft van de 4,6 miljard wel aangekochte doses.[119] [redacted] e.a. stellen ook dat de EU-lidstaten hoofdelijk aansprakelijk zijn als borg voor deze vermeende betaling. Dat is eveneens onjuist. Tot slot stellen [redacted] e.a. dat de EU, vertegenwoordigd door de Europese Commissie, Pfizer niet heeft betaald voor de vaccins. Ook dat is onjuist.

3.3.7 Comirnaty is geen gentherapie

107. [redacted] e.a. stellen herhaaldelijk dat Comirnaty "*op gentherapie gebaseerd*" is.[120] Zij onderbouwen deze stelling niet. Deze stelling is bovendien onjuist.

108. De term gentherapie heeft een bepaalde en gevestigde betekenis volgens de EU-wetgeving. Bijlage I van Richtlijn 2001/83/EG definieert een "*geneesmiddel voor gentherapie*" als volgt:

> "*a) het geneesmiddel bevat een werkzame stof die geheel of gedeeltelijk bestaat uit recombinant nucleïnezuur dat bij de mens wordt gebruikt of aan de mens wordt toegediend om een genetische sequentie te reguleren, te repareren, te vervangen, toe te voegen of te verwijderen;*
>
> *b) de therapeutische, profylactische of diagnostische werking van het geneesmiddel houdt rechtstreeks verband met de erin opgenomen*

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118 Dagvaarding, nrs. 165 e.v.

119 ECA, *Special report, EU COVID-19 vaccine procurement: Sufficient doses secured after initial challenges, but performance of the process not sufficiently assessed*, 2022 (**Bourla-53**), vindbaar via www.eca.europa.eu/Lists/ECADocuments/SR22_19/SR_EU_COVID_vaccine_procurement_EN.pdf

120 Dagvaarding, nrs. 131 e.v., nr. 169.

recombinante nucleïnezuursequentie of met het genetische expressieproduct van die sequentie.

Vaccins tegen infectieziekten worden niet als geneesmiddelen voor gentherapie beschouwd." (onderstreping toegevoegd door advocaat)

109. Comirnaty valt niet onder deze definitie, omdat het de gensequentie van gevaccineerden niet regelt, repareert, vervangt, toevoegt of verwijdert – en dat ook niet kan. Het mRNA in het vaccin komt niet in de celkern, waar het menselijk genoom, dat wil zeggen DNA, zich bevindt. In plaats daarvan wordt het mRNA snel afgebroken door het lichaam van de gevaccineerde.[121] Bovendien sluit de definitie vaccins tegen infectieziekten uitdrukkelijk uit.

4 [redacted] E.A. HEBBEN GEEN ENKEL ELEMENT VAN EEN ONRECHTMATIGE DAAD VASTGESTELD

110. [redacted] e.a. vragen uw rechtbank om de schade op te maken bij staat.[122] Dit betekent dat in deze procedure moet komen vast te staan dat Bourla toerekenbaar onrechtmatig heeft gehandeld jegens [redacted] e.a. en dat aannemelijk is dat laatstgenoemden daardoor mogelijk schade hebben geleden.

111. Aan geen van deze vereisten is voldaan. Bourla heeft [redacted] e.a. niet misleid, laat staan opzettelijk. Comirnaty is, overigens net zoals de andere COVID-19 vaccins, ontwikkeld gedurende het gebruikelijke zorgvuldige proces en voldoet aan de wettelijke normen voor veiligheid, werkzaamheid en productiekwaliteit (zie paragraaf 3.2).

112. Voorzover de stellingen van [redacted] e.a. zouden neerkomen op een (afgeleide) aansprakelijkheid van Bourla in zijn hoedanigheid als CEO van Pfizer, ontbreekt elke relevante stelling over vermeende aansprakelijkheid van Pfizer. Daar stuiten die vorderingen al op af. Voor zover Bourla in andere hoedanigheid wordt aangesproken door [redacted] e.a., voert Bourla hieronder verweer.

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121 Zie bijvoorbeeld Reuters, *mRNA vaccines are distinct from gene therapy*, 10 augustus 2021 (**Bourla-54**), toegankelijk via www.reuters.com/article/idUSL1N2PH16N.

122 Zie randnummer 7 voor de vordering van [redacted] e.a.

4.1 Geen onrechtmatig handelen

4.1.1 Geen foltering of wrede, onmenselijk of vernederende behandeling of bestraffing op grond van artikel 7 IVBPR

113. Bourla begrijpt de stellingen van [redacted] e.a. over artikel 7 IVBPR zo dat alleen de Staat daarop een inbreuk zou hebben gepleegd. De Staat zou namelijk haar burgers hebben gefolterd, of aan wrede, onmenselijke of vernederende behandeling of bestraffing hebben onderworpen, door hen te onderwerpen aan een voortdurend medisch en wetenschappelijk (gedrags-)experiment.[123] Ondanks dat Bourla door [redacted] e.a. kennelijk niet wordt aangesproken op schending van artikel 7 IVBPR, wenst hij hierover het volgende op te merken.

114. Comirnaty kwalificeert niet als medisch of wetenschappelijk *experiment*.[124] Hoewel het ontwikkelingsproces is versneld, heeft het vaccin alle reguliere ontwikkelings- en testfasen, inclusief die van klinische studies, doorlopen. Het vaccin is bovendien pas in de handel gebracht na verlening van een voorwaardelijke goedkeuring door de Europese Commissie in december 2020.[125] Het begrip "*voorwaardelijke* goedkeuring" zou tot misverstanden kunnen leiden, maar betekent niets anders dan dat het vaccin aan alle eisen voldoet voor wat betreft veiligheid, effectiviteit en productiekwaliteit, maar dat nog aanvullende gegevens moeten worden verstrekt (zie de randnummers 19-20 en 50-55).[126]

115. Ook is geen sprake van foltering of onmenselijke of vernederende behandeling of bestraffing. De overheid heeft haar burgers de mogelijkheid geboden zich te laten vaccineren. Van geweld is geen sprake, van vrijheidsbeneming is geen sprake en [redacted] e.a. hebben de keuze gehad om zich wel of niet te laten vaccineren tegen COVID-19.

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123 Dagvaarding, nr. 254-255.

124 Zie aldus ook Rb. Den Haag 5 maart 2021, ECLI:NL:RBDHA:2021:1920, r.o. 4.7 jo. 4.5 en bevestigd in hoger beroep door hof Den Haag 22 juni 2021, ECLI:NL:GHDHA:2021:1094, r.o. 5.6.

125 In oktober 2022 werd de voorwaardelijke handelsvergunning die aan Comirnaty was verleend, omgezet in een standaard handelsvergunning; zie nr. 33 hierboven.

126 Zie ook CBG-MEB, *Column 'Over medicijnen': Coronavaccins experimenteel?*, 2 juni 2021 (**Bourla-55**), toegankelijk via www.cbg-meb.nl/actueel/nieuws/2021/06/02/column-over-medicijnen-coronavaccins-experimenteel.

4.1.2 Geen schending van een wettelijke verplichting

Artikel 97a Sr - steun vragen in buitenland voor omwenteling

116. [redacted] e.a. stellen kennelijk dat Bourla, net zoals de andere gedaagden, het oogmerk had om de vermeende belangen van Schwab en het WEF bij The Great Reset te steunen.[127] Daarmee zou hij artikel 97a Sr hebben overtreden.[128] Dat raakt kant noch wal.

117. Artikel 97a Sr beoogt de Nederlandse grondwettige regeringsvorm en de orde van troonopvolging te beschermen tegen onwettige verandering of vernietiging.[129] Waarom van een dergelijke omwenteling sprake zou zijn, wat de rol van Bourla daarin zou zijn, en waarom overtreding van deze bepaling een grondslag zou vormen voor het vergoed krijgen van vermeend geleden schade als gevolg van een COVID-19 vaccin, hebben [redacted] e.a. in het geheel niet toegelicht.

Artikel 300 Sr - eenvoudige mishandeling

118. [redacted] e.a. stellen bovendien dat Bourla zich heeft schuldig gemaakt aan mishandeling in de zin van artikel 300 Sr.[130] Dat is onjuist.

119. Mishandeling bestaat in het opzettelijk toebrengen van lichaamspijn of lichamelijk letsel zonder dat daarvoor een rechtvaardigingsgrond bestaat.[131] Mishandeling vooronderstelt de wederrechtelijkheid van de gedraging. Zoals eerder toegelicht, voldoet Comirnaty aan de wettelijke normen voor veiligheid, werkzaamheid en productiekwaliteit (paragraaf 3.2) en zijn het doel en de effecten van het vaccin consistent en transparant gecommuniceerd aan het grote publiek (paragraaf 3.3.2). [redacted] e.a. hebben bovendien toestemming verleend voor hun vaccinatie, voor zover ze inderdaad gevaccineerd

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127 Zie hierover ook randnummer 6.
128 Dagvaarding, nr. 58-59 jo. 155.
129 Van der Woude, *T&C Strafrecht*, commentaar op artikel 97a Sr, onder 1 (online, bijgewerkt t/m 1 augustus 2023). Zie ook artikel 80bis Sr waaruit blijkt dat onder "*omwenteling*" wordt verstaan "*het vernietigen of op onwettige wijze veranderen van de grondwettige regeringsvorm of de orde van troonopvolging.*"
130 Dagvaarding, nr. 277.
131 C.P.M. Cleiren, in: *T&C Strafrecht*, art. 300 Sr, aant. 1 en 9 (online, bijgewerkt t/m 1 augustus 2023).

zijn. Daarmee kwalificeert het toedienen van een vaccin ook in algemene zin niet als mishandeling.

120. Zelfs al zou het toedienen van COVID-19 vaccinaties kwalificeren als mishandeling (*quod non*), kan dit handelen niet aan Bourla worden toegerekend. Bourla heeft zelf geen COVID-19 vaccinaties toegediend. Overigens kunnen [redacted] en [redacted] in ieder geval niet zijn mishandeld in de zin van artikel 300 Sr, aangezien zij reeds naar eigen zeggen geen klachten hebben overgehouden aan de vaccinaties.[132]

Artikel 308 Sr - zwaar lichamelijk letsel door schuld

121. [redacted] e.a. stellen dat Bourla schuldig zou zijn aan het veroorzaken van zwaar lichamelijk letsel bij [redacted] en [redacted] in de zin van artikel 308 Sr.[133] Ook dat is onjuist. Zelfs al zouden zij een medische aandoening hebben (lees: Parkinson of een TIA), dan hebben zij niet onderbouwd dat deze is ontstaan door Bourla's handelen (zie nader paragraaf 4.3 over causaal verband), althans dat deze aan zijn schuld te wijten is.

Artikel 3 WIM - genocide

122. [redacted] e.a. stellen verder dat het "*aannemelijk*" is dat Bourla (en de andere gedaagden) zich schuldig hebben gemaakt aan overtreding van artikel 3 lid 1 sub b en c Wet op de Internationale Misdrijven.[134] Dit is lariekoek en bovendien niet nader toegelicht.

4.1.3 Geen handelen in strijd met hetgeen volgens ongeschreven recht in het maatschappelijk verkeer betaamt

123. [redacted] e.a. stellen verder dat de farmaceutische industrie heeft meegewerkt aan de uitvoering van The Great Reset en de daarvoor benodigde wijdverbreide misleiding van burgers, waardoor die industrie hun vertrouwen op grove wijze heeft geschonden. Dit gedrag

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132 Zij hebben geen materiële schade geleden (zie paragraaf 4.2.2). De vermeend geleden immateriële schade is kennelijk slechts het gevolg van de vermeende misleiding en niet van de vaccinaties zelf, en onbekendheid met de precieze gevolgen van de vaccinaties is geen schade (zie randnummer 134).

133 Dagvaarding, nr. 278.

134 Dagvaarding, nr. 280-281.

zou in strijd komen met hetgeen volgens ongeschreven recht in het maatschappelijk verkeer betaamt.[135] Waarom Bourla het handelen van de gehele "farmaceutische industrie" kan worden toegerekend, wordt niet toegelicht. Reeds daarom dienen de vorderingen van [redacted] e.a. op deze grond te worden afgewezen.

124. Van onrechtmatig handelen is overigens ook geen sprake. Zoals eerder benoemd, gaan [redacted] e.a. uit van een complottheorie rondom The Great Reset (zie randnummer 6) die niet op enige waarheid is gebaseerd. Bovendien heeft noch Bourla, noch de farmaceutische industrie zich schuldig gemaakt aan misleiding. Zie hiervoor de paragrafen 3.2-3.3, waarin onder meer is toegelicht dat Comirnaty uitgebreid is getest en veilig en werkzaam is bevonden.

4.2 Geen schade

125. Voor verwijzing naar de schadestaatprocedure dient de mogelijkheid van schade aannemelijk te zijn (en dient de grondslag voor aansprakelijkheid komen vast te staan).[136] Dat klinkt in eerste instantie niet als een zware drempel. Tjong Tjin Tai maakt echter duidelijk dat de drempel ook weer niet te laag mag zijn. De omvang van de schade hoeft nog niet geheel duidelijk te zijn, maar wel moet duidelijk zijn dát er schade is geleden.[137] Die drempel halen [redacted] e.a. niet.

4.2.1 Grafeen-oxide vormt geen onderdeel van de COVID-19 vaccins

126. [redacted] e.a. stellen door de COVID-19 vaccins te zijn geïnjecteerd met "*het giftige grafeen-oxide*", waarvan het "*aannemelijk*" zou zijn dat het bij mensen blijvend nadelige consequenties voor de gezondheid veroorzaakt.[138] Reeds hierdoor zou aannemelijk zijn dat [redacted] e.a. schade lijden. Deze stelling van [redacted] e.a. is echter onjuist. Zoals in paragraaf 3.3.3 toegelicht, bevatten de COVID-19 vaccinaties geen grafeen-oxide.

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135 Dagvaarding, nr. 284.
136 Zie ook dagvaarding, nr. 268.
137 T.F.E. Tjong Tjin Tai, *De schadestaatprocedure*, Deventer: Kluwer 2012, nr. 422-423.
138 Dagvaarding, nr. 265.

4.2.2 [redacted] e.a. voldoen niet aan hun stelplicht; de meerderheid van hen geeft bovendien toe dat zij geen materiële schade hebben geleden[139]

127. Twee van de zes eiseressen stellen zwaar lichamelijk letsel te hebben geleden.[140] De overige vier eiseressen stellen geen zwaar lichamelijk letsel te hebben geleden, maar zouden wel minder vergaande klachten hebben.[141] Ook zou aannemelijk zijn dat de gezondheid van eiseressen op de lange termijn onder de COVID-19 injecties zou lijden.[142]

128. Waaruit het zwaar lichamelijk letsel, de minder vergaande klachten en de langetermijneffecten bestaan, is niet gesteld. Er is slechts bloot verwezen naar productie 91, waarin "*diagnosen*" door "*medisch specialisten*" zouden zijn opgenomen. Die "*diagnosen*" kunnen echter niet neutraal, objectief, betrouwbaar en deskundig worden geacht en dienen daarom buiten beschouwing te worden gelaten.

Verklaringen van Van Walraven

129. Productie 91 bevat zeven verklaringen van bedrijfsarts A.H. van Walraven ("**Van Walraven**"), die in grote mate identiek zijn.[143]

130. Van Walraven aarzelt in zijn "*diagnosen*" niet om ook zijn eigen mening over de COVID-19 vaccinaties en het gevoerde overheidsbeleid te ventileren en hangt kennelijk dezelfde theorieën aan als [redacted] e.a.[144] Zo zegt hij dat [redacted] e.a. zich *terecht* misleid voelen door de overheid, suggereert hij dat de overheid niet het beste met haar mensen voor heeft, zou er nooit een noodsituatie zijn geweest, en zou het sterftecijfer van corona conform griep zijn geweest en dit cijfer op zichzelf geen enkele door de overheid genomen maatregel rechtvaardigen. Dergelijke passages horen niet

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139 [redacted] e.a. baseren deze vordering kennelijk op artikel 6:106 sub b BW.
140 [redacted] en [redacted] volgens de "diagnose" in productie 91).
141 [redacted] en [redacted]
142 Dagvaarding, nr. 265.
143 Die van [redacted] en [redacted] zijn zelfs volledig identiek.
144 Zie eventueel ook het Manifest van Van Walraven aan alle artsen in Nederland; te vinden via www.youtube.com/watch?v=sOpfIZOaqmU

thuis in medische verklaringen en vormen op zichzelf voldoende grond om deze buiten beschouwing te laten.

131. Daarnaast zijn de stellingen van Van Walraven zowel medisch als juridisch onvoldoende om een causaal verband aan te nemen. Ten eerste gooit Van Walraven correlatie en causaal verband erg eenvoudig op één hoop. Hij zou als arts beter moeten weten.Uit de "*diagnosen*" van Van Walraven volgt dat [redacted] Parkinson zou hebben opgelopen en [redacted] een TIA. Volgens Van Walraven kunnen deze ziektes aan de COVID-19 vaccinatie worden toegeschreven, omdat (i) de klachten (kort) na de vaccinatie zijn ontstaan (in de situatie van [redacted] en (ii) andere oorzaken niet zijn gevonden (in de situaties van [redacted] en [redacted] Voor [redacted] is überhaupt niet gesteld dat zijn klachten *na* een COVID-19 vaccinatie zijn ontstaan. Desondanks concludeert Van Walraven ten aanzien van [redacted] dat sprake is van "*een vaccinbijwerking tot het tegendeel bewezen is*". Dat is onjuist – en leidt enkel tot devalidatie van alle door Van Walraven ingenomen stellingen. De stelling dat de klachten kort na de vaccinaties zijn ontstaan, is slechts een ingangsvereiste, maar geen onderbouwing van de stelling dat de vermeende klachten *door* de vaccinatie zijn ontstaan.[145] Bourla betwist dit dan ook. Ten tweede zijn de verklaringen van Van Walraven veelal niet (nader) onderbouwd en daarom oncontroleerbaar. Zie bijvoorbeeld de stelling ten aanzien van [redacted] dat geen andere oorzaken zijn gevonden en de stellingen ten aanzien van [redacted] over de negatieve familieanamnese en het snelle beloop. Voor dergelijke ziektebeelden zijn overigens vaak geen oorzaken te vinden, dus het enkele gebrek aan een "*andere*" oorzaak geldt op geen enkele wijze als indicatie dat de ziektebeelden dan dus maar door een vaccin zijn veroorzaakt.

132. Voorts blijkt Van Walraven ondeskundig ten aanzien van de bijwerkingen van Comirnaty. Hij wijst erop dat Parkinson en stollingsproblemen waaronder TIA's op de bijwerkingenlijst van de

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145 Dit is ook een bekende drogreden: *post hoc ergo propter hoc.*

vaccins staan, maar dat is onjuist, zo blijkt uit de bijwerkingenlijsten die zijn gepubliceerd op de websites van het EMA en het Lareb.[146]

133. Overigens, zelfs al zou een bijwerking op de bijwerkingenlijst staan, dan nog steeds geldt niet noodzakelijkerwijs dat het vaccin die bijwerking veroorzaakt. En zelfs als kan worden aangetoond dat een bijwerking wordt veroorzaakt door het vaccin, leidt dat nog steeds niet tot aansprakelijkheid indien het vaccin voldoet aan de voorgeschreven veiligheidsnormen en niet gebrekkig is. Veiligheid is geen absoluut begrip, vooral niet bij geneesmiddelen, aangezien die altijd zowel risico's als voordelen met zich meebrengen en uitdrukkelijk worden toegelaten op basis van bewijs dat de verhouding daartussen gunstig is. Comirnaty voldoet aan de toepasselijke veiligheidsnormen. Dit blijkt uit de verlening van de vergunning voor het in de handel brengen nadat het EMA had bevestigd dat de afweging van de voordelen en risico's van Comirnaty gunstig was, en uit de geneesmiddelenbewaking na toelating. [redacted] e.a. hebben daar niets tegen ingebracht: zij hebben niet gesteld, noch toegelicht, dat de vermeend toegediende vaccins op enigerlei wijze gebrekkig waren.

4.2.3 Vermeend geleden immateriële schade komt niet voor vergoeding in aanmerking

134. Naast materiële schade, stellen [redacted] e.a. immateriële schade te hebben geleden. Deze zou bestaan uit (i) het geestelijk ervaren nadeel als gevolg van de door gedaagden teweeggebrachte misleiding (gevoelens van pijn, leed, schaamte, machteloosheid en onzekerheid over hun gezondheid) en (ii) het onbekend zijn met de precieze gevolgen van de vaccinaties.[147]

135. [redacted] e.a. baseren deze vorderingen kennelijk ten eerste op artikel 6:106 sub b BW. Geestelijk letsel valt namelijk onder de daarin genoemde categorie *aantasting in zijn persoon op andere wijze*.[148]

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146 EMA, *Comirnaty product information* (selectie) (**Bourla-38**), toegankelijk via www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_nl.pdf respectievelijk LAREB, *Bijwerkingen coronavaccins* (**Bourla-56**), toegankelijk via www.lareb.nl/bijwerkingen-coronavaccins#pfizer

147 Dagvaarding, nr. 266.

148 S.D. Lindenbergh, in: *T&C BW*, art. 6:106 BW, aant. 3 (online, bijgewerkt t/m 1 september 2023).

136. Uit de wetsgeschiedenis blijkt dat geestelijk letsel "*voldoende ernstig*" dient te zijn om voor vergoeding in aanmerking te komen.[149] Meer of minder sterk psychisch onbehagen is onvoldoende, wat ook vaste rechtspraak is.[150] Reeds hierom dienen de vorderingen van [redacted] e.a. te worden afgewezen. De Hoge Raad heeft bovendien overwogen dat degene die zich beroept op "*aantasting in zijn persoon op andere wijze*", voldoende concrete feiten zal moeten aanvoeren waaruit kan volgen dat in verband met de omstandigheden van het geval psychische schade is ontstaan, waartoe nodig is dat naar objectieve maatstaven het bestaan van geestelijk letsel kan worden vastgesteld.[151] [redacted] e.a. hebben dat niet gedaan. De blote stelling dat zij geestelijk nadeel ervaren en onbekend zijn met de precieze gevolgen van de vaccinaties is hiervoor onvoldoende. Voor zover [redacted] e.a. ook in de context van immateriële schade zouden verwijzen naar productie 91, verwijst Bourla naar randnummer 128 en verder waarin is uitgelegd dat deze verklaringen niet neutraal, objectief, betrouwbaar en deskundig zijn.

137. [redacted] e.a. doen ten tweede kennelijk een beroep op artikel 6:106 sub a BW. Zij stellen namelijk "*gemotiveerd [te] hebben gesteld dat bij gedaagden het oogmerk heeft bestaan om hen nadeel toe te brengen*".[152] [redacted] e.a. hebben dit echter nergens gesteld, laat staan gemotiveerd. Deze stelling is ongefundeerd en incorrect.[153] Ten derde refereren [redacted] e.a. aan artikel 6:106 sub c BW en stellen dat enkele eisers getrouwd zijn.[154] De relevantie wordt niet duidelijk uit de dagvaarding.

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149 Parl. Gesch. BW Boek 6 1981 p. 389 (EV I).

150 S.D. Lindenbergh, "Smartengeld wegens spanning, frustratie, ergernis en (ander) onbehagen? Over het begrip 'persoonsaantasting' buiten lichamelijk en geestelijk letsel", *NTBR* 2019/20, p. 122-130, p. 124, onder verwijzing naar HR 13 januari 1995, *NJ* 1997/366, m.nt. C.J.H. Brunner (*Ontvanger/B.*) en HR 21 februari 1997, *NJ* 1999/145, m.nt. C.J.H. Brunner (*Wrongful birth*).

151 HR 15 maart 2019, ECLI:NL:HR:2019:376, *NJ* 2019/162 (*EBI*).

152 Dagvaarding, nr. 267.

153 [redacted] e.a. miskennen met deze stelling bovendien dat het oogmerk moet zijn gericht op het toebrengen van specifiek de *immateriële* schade. De enkele omstandigheid dat iemand opzettelijk een situatie heeft geschapen - waarvan overigens ook geen sprake is - waardoor ander nadeel dan vermogensschade is toegebracht, kan de gevolgtrekking dat deze het oogmerk had zodanig nadeel toe te brengen niet dragen. (Zie HR 26 mei 2020, ECLI:NL:HR:2020:868, *NJ* 2020/231, r.o. 2.3.2-2.4. Zie aldus ook S.D. Lindenbergh, in: *T&C BW*, art. 6:106 BW, aant. 2 (online, bijgewerkt t/m 1 september 2023)). Het toepassingsbereik van deze bepaling is in de praktijk dan ook beperkt.

154 Dagvaarding, nr. 267.

4.3 Geen causaal verband

138. [redacted] e.a. hebben niet gesteld dat:

(a) zij eens of vaker Comirnaty hebben genomen;[155]

(b) zij zonder de vermeende misleiding die vaccinaties niet hadden genomen (lees: welke informatie voor hen leidend is geweest bij het nemen van de vaccins);

(c) Comirnaty kan leiden tot de vermeend geleden schade (generieke causaliteit); en

(d) Comirnaty bij [redacted] e.a. heeft geleid tot de vermeend geleden schade (specifieke causaliteit).

139. Bourla wijst er nogmaals op dat de stellingen van Van Walraven zowel medisch als juridisch onvoldoende zijn om (specifieke) causaliteit aan te nemen (zie randnummers 128 en verder) en de stellingen die Van Walraven kennelijk bereid is in te nemen ook overigens maakt dat de bewijswaarde van zijn verklaringen zeer gering tot nihil is.

140. Ook de vermeend geleden immateriële schade - wat zoals toegelicht überhaupt geen schade is die voor vergoeding in aanmerking komt (zie paragraaf 4.2.3) - staat niet in causaal verband met Comirnaty of een van de andere COVID-19 vaccins. [redacted] e.a. hebben hierover geen stellingen ingenomen. Bovendien is algemeen bekend dat psychische klachten ook kunnen worden - en zelfs op grote schaal zijn - veroorzaakt door de corona*crisis*, en niet zozeer door de corona*vaccins*.[156]

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155 Met uitzondering van [redacted]

156 Zie bijvoorbeeld Trimbos Instituut, *Voortdurende coronacrisis leidt tot toename psychische klachten en behoefte aan perspectief*, 25 februari 2021 (**Bourla-57**), toegankelijk via www.trimbos.nl/actueel/nieuws/voortdurende-coronacrisis-leidt-tot-toename-psychische-klachten-en-behoefte-aan-perspectief/#:~:text=gezondheid%20van%20volwassenen.-,Toename%20psychische%20klachten,jaar%20hebben%20de%20meeste%20klachten en Nederlands Jeugdinstituut, *Onderzoek naar corona en mentaal welbevinden* (**Bourla-58**), toegankelijk via www.nji.nl/coronavirus/onderzoek-naar-corona-en-mentaal-welbevinden

4.4 Geen groepsaansprakelijkheid (artikel 6:166 BW)

141. Ook de vermeende vorderingen ingesteld op basis van artikel 6:166 BW falen. Voor een succesvol beroep op artikel 6:166 BW hadden [redacted] e.a dienen te stellen en bewijzen:

(a) dat Bourla heeft deelgenomen aan;

(b) gedragingen in groepsverband;

(c) waarvan de kans op het aldus toebrengen van schade de deelnemers had behoren te weerhouden;

(d) dat diens deelneming aan deze gedragingen hem kan worden toegerekend; en

(e) dat één van de deelnemers aan die gedragingen de benadeelde onrechtmatig schade heeft toegebracht.[157]

142. Zoals toegelicht heeft Bourla niet onrechtmatig gehandeld (zie paragraaf 4.1). Dat geldt ook voor de andere gedaagden. Bourla en de andere gedaagden hebben [redacted] e.a. evenmin schade berokkend (zie paragraaf 4.2). Reeds daarom kan Bourla ook niet (hoofdelijk) aansprakelijk worden gesteld op grond van artikel 6:166 BW.

5 BEWIJSAANDRAAGPLICHT EN BEWIJSAANBOD

143. Ter staving van de gronden van zijn verweer beschikt Bourla over de volgende bewijsmiddelen:

Nummer	Omschrijving
Bourla-1	WHO, *WHO Director-General's opening remarks at the media briefing on COVID-19* , 11 maart 2020
Bourla-2	EMA, *COVID-19 medicines*
Bourla-3	WHO, *Statement on the fifteenth meeting of the IHR (2005)*, 5 mei 2023
Bourla-4	The Lancet, *Global impact of the first year of COVID-19*, 23 juni 2022
Bourla-5	EMA, *Conditional marketing authorisation*
Bourla-6	EMA, *Good pharmacovigilance practices*
Bourla-7	EMA, *Comirnaty risk management plan*, oktober 2023 (selectie)
Bourla-8	EMA, Periodic safety update reports (PSURs)

[157] R.J.B. Boonekamp, *Stelplicht & Bewijslast*, commentaar op art. 6:166 BW (online, bijgewerkt t/m 2 oktober 2017).

Bourla-9 EMA, *COVID-19 vaccines development, evaluation, approval and monitoring*
Bourla-10 Pfizer, *Pfizer Outlines Five-Point Plan to Battle COVID-19*, 13 maart 2020
Bourla-11 Pfizer, *Pfizer and BioNTech to Co-Develop Potential COVID-19 Vaccine*, 17 maart 2020
Bourla-12 Pfizer, *Pfizer and BioNTech Announce Further Details on Collaboration to Accelerate*, 9 april 2020
Bourla-13 ClinicalTrials.gov, *A Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-2019 in Healthy and Immunocompromised Adults*, 13 januari 2022
Bourla-14 ClinicalTrials.gov, *Study to Describe the Safety, Tolerability, Immunogenicity [...]*, 28 februari 2023
Bourla-15 EMA, *Comirnaty Assessment report*, 19 februari 2021
Bourla-16 EMA, *EMA starts second rolling review of a COVID-19 vaccine*, 6 oktober 2020
Bourla-17 OJEU, 24 december 2020
Bourla-18 EMA, *Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines*
Bourla-19 Watson O. e.a., *Global impact of the first year of COVID-19 vaccination: a mathematical modelling study*, 23 juni 2022
Bourla-20 Gezondheidsraad, *Advies-COVID-19 vaccinatie BioNTech-Pfizer*, 24 december 2020
Bourla-21 Lewis, L.M. e.a., *The Race to Develop the Pfizer-BioNTech COVID-19 Vaccine: From the Pharmaceutical Scientists' Perspective*, 18 september 2022
Bourla-22 Institut Pasteur, *Discovery of messenger RNA in 1961*, 15 februari 2021
Bourla-23 BioNTech, *The History of BioNTech - The Road to a New Era of Immunotherapy*
Bourla-24 Press release *The Nobel Prize in Physiology or Medicine 2023*, 2 oktober 2023
Bourla-25 Science News, *How COVID-19 vaccines were made so quickly without cutting corners*, 29 juni 2021
Bourla-26 Bettini, E., *SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond*, 2021
Bourla-27 Wadhwa et al., *Opportunities and Challenges in the Delivery of mRNA-Based Vaccines*, januari 2020
Bourla-28 EMA, *COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines*, 4 mei 2020
Bourla-29 EMA, *How are COVID-19 vaccines developed*
Bourla-30 Nature, *Whither COVID-19 vaccines*, 28 september 2020
Bourla-31 NBC News, *3 vaccine executives say that after approval, distribution will be the main challenge*, 3 december 2020

Bourla-32 The Journal, *Pfizer CEO says there is 'encouraging' data on whether its vaccine stops Covid transmission*, 13 januari 2021
Bourla-33 EMA, *Comirnaty, COVID-19 mRNA vaccine (nucleoside modified)*, 21 december 2020
Bourla-34 FDA, *FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*, 11 december 2020
Bourla-35 WHO, *Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine*, 8 januari 2021
Bourla-36 Reuters, *Fact Check: Preventing transmission never required for COVID vaccines' initial approval*
Bourla-37 ECDC, *Risk of SARS-CoV-2 transmission from newly-infected individuals with documented previous infection or vaccination*, 29 maart 2021
Bourla-38 EMA, *Comirnaty product information* (selectie)
Bourla-39 FDA, *Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum*, 20 november 2020
Bourla-40 Gov.UK, S*ummary of the Public Assessment Report COVID-19 Vaccine*, december 2020
Bourla-41 MIT Technology Review, *What are the ingredients of Pfizer's covid-19 vaccine*, 9 december 2020
Bourla-42 EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 26 oktober 2021
Bourla-43 87. EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 8 maart 2022
Bourla-44 Reuters, *COVID-19 vaccines do not contain graphene oxide*, 23 juli 2021
Bourla-45 AP, *Pfizer vaccine does not contain graphene oxide*, 8 juli 2021
Bourla-46 EMA, *Periodic safety update report*
Bourla-47 EMA, *Comirnaty periodic safety update report assessment 19 June 2022 to 18 December 2022* (selectie)
Bourla-48 EMA, Assessment report on the annual renewal of the conditional marketing authorisation (Comirnaty), 2021
Bourla-49 Reuters, *Pages of suspected side effects released about Pfizer's COVID-19 vaccine [...]*, 17 maart 2022
Bourla-50 EU Parliament, *Answer given by Ms Kyriakides on behalf of the European Commission*, 3 juli 2023
Bourla-51 EMA, *COVID-19 vaccines: development, evaluation, approval and monitoring*
Bourla-52 Hviid, A., *Inaccurate representation of shipped vaccines as administered*, 20 juni 2023
Bourla-53 ECA, *Special report, EU COVID-19 vaccine procurement: Sufficient doses secured after initial challenges, but performance of the process not sufficiently assessed*, 2022
Bourla-54 Reuters, *mRNA vaccines are distinct from gene therapy*, 10 augustus 2021

Bourla-55	CBG-MEB, *Column 'Over medicijnen': Coronavaccins experimenteel?*, 2 juni 2021
Bourla-56	LAREB, *Bijwerkingen coronavaccins*
Bourla-57	Trimbos Instituut, *Voortdurende coronacrisis leidt tot toename psychische klachten en behoefte aan perspectief*, 25 februari 2021
Bourla-58	Nederlands Jeugdinstituut, *Onderzoek naar corona en mentaal welbevinden*

144. Bourla wil met het vorenstaande niet geacht worden onverplicht enige bewijslast op zich te hebben genomen die niet rechtens op Bourla rust.

145. Bourla stelt zich op het standpunt dat de bewijslast in deze procedure op [redacted] e.a. rust. Bourla biedt uitdrukkelijk tegenbewijs aan.

146. Voor zover de bewijslast van enige stelling naar het oordeel van de rechtbank op Bourla mocht rusten, biedt Bourla daarvan bewijs aan door alle middelen rechtens, in het bijzonder door het horen van getuigen.

OP DEZE GRONDEN CONCLUDEERT BOURLA:

dat de rechtbank bij vonnis, voor zover rechtens mogelijk uitvoerbaar bij voorraad:

(a) [redacted] e.a. in hun vorderingen niet-ontvankelijk zal verklaren, althans hen deze vorderingen zal ontzeggen;

(b) [redacted] e.a. hoofdelijk zal veroordelen in de kosten van het geding, alsmede in de gebruikelijke nakosten (zowel zonder als met betekening), te vermeerderen met de wettelijke rente als bedoeld in artikel 6:119 BW vanaf veertien dagen na de datum van het vonnis, des de ene eiser betalende de andere eisers zullen zijn bevrijd.

advocaat loco N. Vonk

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Productie 1

World Health Organization

WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020

11 March 2020

العربية | 中文 | Français | Русский | Español

Good afternoon.

In the past two weeks, the number of cases of COVID-19 outside China has increased 13-fold, and the number of affected countries has tripled.

There are now more than 118,000 cases in 114 countries, and 4,291 people have lost their lives.

Thousands more are fighting for their lives in hospitals.

In the days and weeks ahead, we expect to see the number of cases, the number of deaths, and the number of affected countries climb even higher.

WHO has been assessing this outbreak around the clock and we are deeply concerned both by the alarming levels of spread and severity, and by the alarming levels of inaction.

We have therefore made the assessment that COVID-19 can be characterized as a pandemic.

Pandemic is not a word to use lightly or carelessly. It is a word that, if misused, can cause unreasonable fear, or unjustified acceptance that the fight is over, leading to unnecessary suffering and death.

Describing the situation as a pandemic does not change WHO's assessment of the threat posed by this virus. It doesn't change what WHO is doing, and it doesn't change what countries should do.

We have never before seen a pandemic sparked by a coronavirus. This is the first pandemic caused by a coronavirus.

And we have never before seen a pandemic that can be controlled, at the same time.

WHO has been in full response mode since we were notified of the first cases.

And we have called every day for countries to take urgent and aggressive action.

We have rung the alarm bell loud and clear.

===

As I said on Monday, just looking at the number of cases and the number of countries affected does not tell the full story.

Of the 118,000 cases reported globally in 114 countries, more than 90 percent of cases are in just four countries, and two of those – China and the Republic of Korea - have significantly declining epidemics.

81 countries have not reported any cases, and 57 countries have reported 10 cases or less.

We cannot say this loudly enough, or clearly enough, or often enough: all countries can still change the course of this pandemic.

If countries detect, test, treat, isolate, trace, and mobilize their people in the response, those with a handful of cases can prevent those cases becoming clusters, and those clusters becoming community transmission.

Even those countries with community transmission or large clusters can turn the tide on this virus.

Several countries have demonstrated that this virus can be suppressed and controlled.

The challenge for many countries who are now dealing with large clusters or community transmission is not whether they **can** do the same – it's whether they **will**.

Some countries are struggling with a lack of capacity.

Some countries are struggling with a lack of resources.

Some countries are struggling with a lack of resolve.

We are grateful for the measures being taken in Iran, Italy and the Republic of Korea to slow the virus and control their epidemics.

We know that these measures are taking a heavy toll on societies and economies, just as they did in China.

All countries must strike a fine balance between protecting health, minimizing economic and social disruption, and respecting human rights.

WHO's mandate is public health. But we're working with many partners across all sectors to mitigate the social and economic consequences of this pandemic.

This is not just a public health crisis, it is a crisis that will touch every sector – so every sector and every individual must be involved in the fight.

I have said from the beginning that countries must take a whole-of-government, whole-of-society approach, built around a comprehensive strategy to prevent infections, save lives and minimize impact.

Let me summarize it in four key areas.

First, prepare and be ready.

Second, detect, protect and treat.

Third, reduce transmission.

Fourth, innovate and learn.

I remind all countries that we are calling on you to activate and scale up your emergency response mechanisms;

Communicate with your people about the risks and how they can protect themselves – this is everybody's business;

Find, isolate, test and treat every case and trace every contact;

Ready your hospitals;

Protect and train your health workers.

And let’s all look out for each other, because we need each other.

===

There’s been so much attention on one word.

Let me give you some other words that matter much more, and that are much more actionable.

Prevention.

Preparedness.

Public health.

Political leadership.

And most of all, people.

We’re in this together, to do the right things with calm and protect the citizens of the world. It’s doable.

I thank you.

Productie 2

← Coronavirus disease (COVID-19)

COVID-19 medicines

Human COVID-19

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Authorised COVID-19 vaccines

The table below lists the **COVID-19 vaccines** that are authorised for use in the EU, including originally authorised and **adapted vaccines**.

Adapted vaccines are intended to provide broader protection against different **virus variants** following initial vaccination.

Companies marketing **originally authorised vaccines** can apply to change the marketing authorisation to include an adapted version, which is shown in italics in the table below.

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Vaccine	Marketing authorisation holder	Key milestones	More information
Bimervax (previously COVID-19 Vaccine HIPRA)	HIPRA Human Health S.L.U.	Marketing authorisation issued: 30/03/2023	Latest news Product information
Comirnaty (developed by BioNTech and Pfizer)	BioNTech Manufacturing GmbH	Comirnaty Omicron XBB.1.5 (adapted) authorised: 31/08/2023 Standard marketing authorisation issued: 10/10/2022 Comirnaty Original/Omicron BA.4-5 (adapted) authorised: 12/09/2022 Comirnaty Original/Omicron BA.1 (adapted) authorised: 01/09/2022 Annual renewal issued: 03/11/2021 Conditional marketing authorisation issued: 21/12/2020	Latest news Product information Clinical data (login required)

Paediatric investigation plan

Jcovden (previously COVID-19 Vaccine Janssen)

Janssen-Cilag International NV

Standard marketing authorisation issued: 10/01/2023

Annual renewal issued: 03/01/2022

Conditional marketing authorisation issued: 11/03/2021

Latest news

Product information
Clinical data (login required)

Paediatric investigation plan

Nuvaxovid

Novavax CZ, a.s.

Nuvaxovid XBB.1.5 (adapted) authorised: 31/10/2023

Standard marketing authorisation issued: 04/07/2023

Annual renewal issued: 03/10/2022

Conditional marketing authorisation issued: 20/12/2021

Latest news

Product information

Clinical data (login required)

Spikevax (previously COVID-19 Vaccine Moderna)

Moderna Biotech Spain S.L.

Spikevax XBB.1.5 (adapted) authorised: 15/09/2023

Spikevax bivalent Original/Omicron BA.4-5 (adapted) authorised: 20/10/2022

Standard marketing authorisation issued: 03/10/2022

Spikevax bivalent Original/Omicron BA.1 (adapted) authorised: 01/09/2022

Annual renewal issued: 04/10/2021

Conditional marketing authorisation issued: 06/01/2021

Latest news

Product information
Clinical data (login required)
Paediatric investigation plan

Vaxzevria (previously COVID-19 Vaccine AstraZeneca)

AstraZeneca AB

Standard marketing authorisation issued: 31/10/2022

Annual renewal issued: 09/11/2021

Conditional marketing authorisation issued: 29/01/2021

Latest news

Product information
Clinical data (login required)
Paediatric investigation plan

VidPrevtyn Beta

Sanofi Pasteur

Marketing authorisation issued: 10/11/2022

Latest news

Product information

For more information on how EMA evaluated these **vaccines**, see:

- COVID-19 vaccines: Scientific evaluation and approval

Authorised COVID-19 treatments

The following **treatments** can be used in the EU to treat COVID-19:

Show 25 entries

Search:

Treatment	Status	More information
Evusheld (tixagevimab / cilgavimab)	Marketing authorisation granted: 25/03/2022	Latest news
Kineret (anakinra)	Marketing authorisation granted: 17/12/2021	Latest news
Paxlovid (PF-07321332 / ritonavir)	Conditional marketing authorisation granted: 28/01/2022	Latest news Paediatric investigation plan
Regkirona (regdanvimab)	Marketing authorisation granted: 12/11/2021	

Latest news

Paediatric investigation plan

RoActemra

Marketing authorisation for COVID-19 indication granted: 07/12/2021

Latest news

Ronapreve (casirivimab / imdevimab)

Marketing authorisation granted: 12/11/2021

Latest news

Veklury (remdesivir)

Marketing authorisation granted: 08/08/2022

Conditional marketing authorisation granted: 03/07/2020

Latest news

Clinical data (login required)

Paediatric investigation plan

Xevudy (sotrovimab)

Marketing authorisation granted: 17/12/2021

Latest news

Showing 1 to 8 of 8 entries

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For more information on how EMA fast-tracks its evaluation of promising potential COVID-19 medicines, see:

- COVID-19 guidance: assessment and marketing authorisation

COVID-19 vaccines: strains, use and age ranges

The overview below summarises the characteristics of the COVID-19 vaccines authorised in the EU:

- Platforms - the type of technology used to develop the vaccine
- Strains - the type of virus the vaccine targets, i.e. 'wild-type' (original), a variant or a sub-variant of the virus
- Use - whether the vaccine is for primary or for booster vaccination
- Population - which age groups the vaccine is used in

This overview also details the composition of COVID-19 vaccines and the milestones for authorisation of adapted vaccines.

Overview of authorised COVID-19 vaccines

Vaccine	Platform*	Strain	Population ≥6 months	≥5 years	≥12 years	≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain				✓
Jcovden (Janssen)	Adenoviral vector	Original strain				✓
Nuvaxovid (Novavax)	Protein	Original strain			✓	✓
		Omicron XBB.1.5 variant (adapted**)			✓	✓
VidPrevtyn Beta (Sanofi Pasteur)	Protein	Beta variant***				✓
Bimervax (HIPRA Human Health S.L.U.)	Protein	Alpha + Beta variants***			✓ 16-18 years	✓

* Available platforms: See Figure 1 below

** Milestones for adapted vaccines: See Figure 2 below

*** Only used as boosters

Figure 1: Available platforms

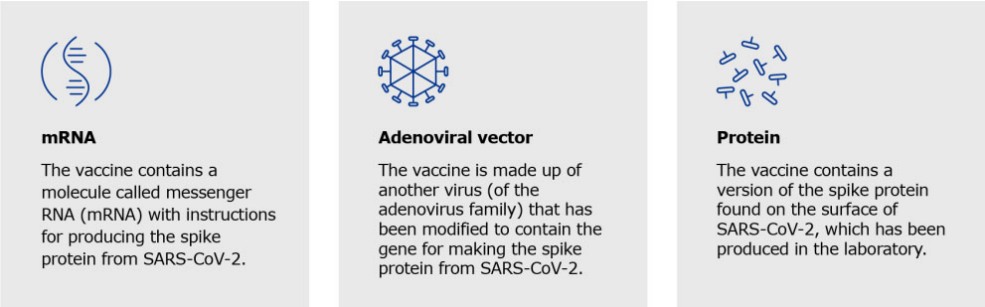
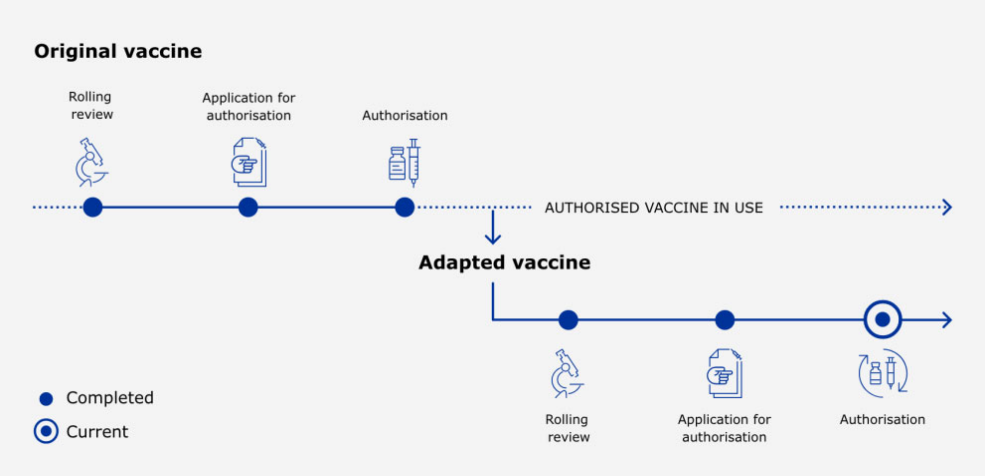


Figure 2: Milestones for adapted COVID-19 vaccines



Safety information for authorised COVID-19 vaccines

EMA monitors the safety of COVID-19 vaccines authorised in the EU extremely carefully. This enables the detection of any **rare side effects** that may emerge once many millions of people are vaccinated.

Safety information on each COVID-19 vaccine is available:

- Safety of COVID-19 vaccines

Ongoing clinical trials

Information on ongoing clinical trials for COVID-19 treatments in the European Economic Area (EEA) is available in the EU Clinical Trials Register (EU CTR):

- EU CTR: COVID-19 treatments

Users can find information on:

- phase II to phase IV **adult clinical trials** for COVID-19 treatments where the investigator sites are in the EEA;
- any **clinical trials in children** with investigator sites in the EU and any trials that form part of a paediatric investigation plan, including those where the investigator sites are outside the EU.

Phase I clinical trials conducted solely in adults are not made publicly available in the EU CTR.

For more information on the EU CTR and how clinical trials are authorised and overseen in the EEA, see:

- Clinical trials in human medicines.

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Productie 3

World Health Organization

Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic

5 May 2023 | Statement | Reading time: 7 min (1792 words)

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The WHO Director-General has the pleasure of transmitting the Report of the fifteenth meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, held on Thursday 4 May 2023, from 12:00 to 17:00 CET.

During the deliberative session, the Committee members highlighted the decreasing trend in COVID-19 deaths, the decline in COVID-19 related hospitalizations and intensive care unit admissions, and the high levels of population immunity to SARS-CoV-2. The Committee's position has been evolving over the last several months. While acknowledging the remaining uncertainties posted by potential evolution of SARS-CoV-2, they advised that it is time to transition to long-term management of the COVID-19 pandemic.

The WHO Director-General concurs with the advice offered by the Committee regarding the ongoing COVID-19 pandemic. He determines that COVID-19 is now an established and ongoing health issue which no longer constitutes a public health emergency of international concern (PHEIC).

The WHO Director-General considered the advice provided by the Committee regarding the proposed Temporary Recommendations and issued them as per the below statement. The WHO Director-General will convene an IHR Review Committee to advise on Standing Recommendations for the long-term management of the SARS-CoV-2 pandemic, taking into account the 2023-2025 COVID-19 Strategic Preparedness and Response Plan. During this transition, States Parties are advised to continue following the issued Temporary Recommendations. The Director-General expressed his sincere gratitude to the Chair, the Members, and the Advisors of the Committee for their engagement and advice during the last three years.

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Proceedings of the meeting

The WHO Director-General, Dr Tedros Adhanom Ghebreyesus, welcomed Members and Advisors of the Emergency Committee, who were convened by videoconference. He noted that the number of weekly reported deaths and hospitalizations continue to decrease, but expressed concern that surveillance reporting to WHO has declined significantly, that there continues to be inequitable access to life-saving interventions, and that pandemic fatigue continues to grow. The Director-General announced the publication of the 2023-2025 COVID-19 Strategic Preparedness and Response Plan which is designed to guide countries in transitioning to long-term management of COVID-19. This plan outlines important actions for countries to consider for five areas: collaborative surveillance, community protection, safe and scalable care, access to countermeasures, and emergency coordination. The Director-General thanked Professor Houssin for his leadership in guiding the Committee over the last three years and each of the Committee Members and Advisors for their expertise, dedication, and commitment.

The Office of Legal Counsel's representative briefed the Committee Members and Advisors on their roles, responsibilities, and mandate under the relevant articles of the IHR. The Ethics Officer from the Department of Compliance, Risk Management, and Ethics reminded Members and Advisers of their duty of confidentiality as to the meeting discussions and the work of the Committee, as well as their individual responsibility to disclose to WHO in a timely manner any interests of a personal, professional, financial, intellectual, or commercial nature that may give rise to a perceived or direct conflict of interest. No conflicts of interest for the attending Members and Advisors were identified.

The Chair of the Emergency Committee, Professor Didier Houssin, introduced the objectives of the meeting: to provide views to the WHO Director-General on whether the COVID-19 pandemic continues to constitute a PHEIC and to review Temporary Recommendations to States Parties.

While the global risk assessment remains high, there is evidence of reducing risks to human health driven mainly by high population-level immunity from infection, vaccination, or both; consistent virulence of currently circulating SARS-CoV-2 Omicron sub-lineages compared to previously circulating Omicron sub-lineages; and improved clinical case management. These factors have contributed to a significant global decline in the weekly number of COVID-19 related deaths, hospitalizations, and admissions to intensive care units since the beginning of the pandemic. While SARS-CoV-2 continues to evolve, the currently circulating variants do not appear to be associated with increased severity.

WHO provided updates on the status of global vaccination and considerations of implications for the potential termination of a PHEIC. The Committee was informed that, globally, 13.3 billion doses of COVID-19 vaccines have been administered. Currently, 89% of health workers and 82% of adults over 60 years have completed the primary series (the initial one or two doses recommended as per the vaccine schedule), although coverage in these priority groups varies in different regions.

As requested by the Committee, the WHO Secretariat provided overviews of the status of integration of COVID-19 surveillance into the Global Influenza Surveillance and Response System and opportunities to streamline this; the process for issuing Standing Recommendations under the IHR; and the potential regulatory implications for Emergency Use Listed (EUL) when a PHEIC is terminated. As the Director-General will continue to authorize the use of EUL procedure, the termination of the PHEIC should not affect access to vaccines and diagnostics that have already received an EUL. States Parties will still be able to access these vaccines and diagnostics (provided the manufacturers continue production). COVAX will also continue to provide funded doses and delivery support throughout 2023 in line with demand. This continuity can enable a smooth transition from EUL to prequalification of vaccines and diagnostics. As the large majority of therapeutics used to treat COVID-19 are repurposed medicines already licensed for other indications, the termination of a PHEIC should not affect their regulatory status.

Deliberative Session on the Status of the PHEIC

The Committee considered the three criteria of a PHEIC: whether COVID-19 continues to constitute 1) an extraordinary event, 2) a public health risk to other States through the international spread, and 3) potentially requires a coordinated international response. They discussed the current status of the COVID-19 pandemic. They acknowledged that, although SARS-CoV-2 has been and will continue circulating widely and evolving, it is no longer an unusual or unexpected event. The Committee recognized that the Director-General may decide to convene an IHR Emergency Committee on COVID-19 in the future if the situation requires.

The COVID-19 PHEIC has prompted countries to enhance their functional capacities, particularly related to emergency coordination, collaborative surveillance, clinical care, and risk communications and communication engagement. The world has made significant and impressive global progress since the declaration of the PHEIC in January 2020. Reaching the point where COVID-19 can be considered as no longer constituting a PHEIC should be seen as accolade to international coordination and commitment to global health.

As it has during past meetings, the Committee deliberated the potential benefits and issues posed by maintaining the PHEIC. While the PHEIC has been a valuable instrument to support the global response to COVID-19, the Committee agreed that the time is right to move towards the long-term management of SARS-CoV-2 as an ongoing health issue.

Moving forward, the Committee suggested that the Director-General consider convening an IHR Review Committee to advise on Standing Recommendations to for long-term risks posed by SARS-CoV-2 taking into account the 2023-2025 COVID-19 Strategic Preparedness and Response Plan. At the same time, the Committee recognized that Member States are currently negotiating the Pandemic Prevention, Preparedness, and Response Accord, discussing amendments to the IHR, and considering the ten proposals to build a safer world together by strengthening the Global Architecture for Health Emergency Preparedness, Response, and Resilience (HEPR).

They thanked the WHO Secretariat and States Parties for their sustained commitment and technical expertise, and emphasized that this is not the time to stop work or dismantle systems. The Committee stressed that it will be critical to address the gaps recognised during the pandemic. They highlighted the need to strengthen health systems, continue active risk communications and community engagement, implement a One Health approach to preparedness and response, and integrate COVID-19 surveillance and response activities into

routine health programmes. The Committee advocated that WHO, partners, and States Parties dedicate sustained attention and resources to preparedness and resilience for emerging threats.

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Temporary Recommendations issued by the WHO Director-General to all States Parties

1. Sustain the national capacity gains and prepare for future events to avoid the occurrence of a cycle of panic and neglect. States Parties should consider how to improve country readiness for future outbreaks. In alignment with WHO guidance, States Parties should update respiratory pathogen pandemic preparedness plans incorporating learnings from national and sub-national After Action Reviews. States Parties should continue to restore health programmes adversely affected by the COVID-19 pandemic.

- Preparedness and resilience for Emerging Threats;
- Strengthening pandemic preparedness planning for respiratory pathogens: policy brief;
- WHO COVID-19 policy briefs;
- Emergency Response Reviews

2. Integrate COVID-19 vaccination into life course vaccination programmes. States Parties should maintain efforts to increase COVID-19 vaccination coverage for all people in the high-priority groups (as defined by the SAGE Roadmap of April 2023) with WHO recommended vaccines and continue to actively address vaccine acceptance and demand issues with communities.

- Global COVID-19 Vaccination Strategy in a Changing World (July 2022 update);
- SAGE Roadmap (Updated March 2023);
- Good practice statement on the use of variant-containing COVID-19 vaccines;
- Continued collaboration with IVAC and others to summarise VE studies, Behavioural and social drivers of vaccination: tools and practical guidance for achieving high uptake.

3. Bring together information from diverse respiratory pathogen surveillance data sources to allow for a comprehensive situational awareness. States Parties should maintain reporting of mortality and morbidity data as well as variant surveillance information to WHO. Surveillance should incorporate information from an appropriate mix of representative sentinel populations, event-based surveillance, human wastewater surveillance, sero-surveillance, and surveillance of selected animal populations known to be at risk of SARS-

COV-2. States Parties should leverage the Global Influenza Surveillance and Response System (GISRS) and support the establishment of the WHO Global Coronavirus Laboratory Network (CoViNet).

- Public health surveillance for COVID-19

4. Prepare for medical countermeasures to be authorized within national regulatory frameworks to ensure long-term availability and supply. States Parties should strengthen their regulatory authorities to support long-term authorization and use of vaccines, diagnostics, and therapeutics.

- Therapeutics and COVID-19: living guideline;
- COVID-19 Clinical Care Pathway;
- Emergency Use Listing procedures;
- Prequalification procedures for vaccines;
- Prequalification procedures for in vitro diagnostics

5. Continue to work with communities and their leaders to achieve strong, resilient, and inclusive risk communications and community engagement (RCCE) and infodemic management programmes. State Parties should adapt RCCE and infodemic management strategies and interventions to local contexts.

6. Continue to lift COVID-19 international travel related health measures, based on risk assessments, and to not require any proof of vaccination against COVID-19 as a prerequisite for international travel.

- Interim position paper: considerations regarding proof of COVID-19 vaccination for international travellers;
- Policy considerations for implementing a risk-based approach to international travel in the context of COVID-19

7. Continue to support research to improve vaccines that reduce transmission and have broad applicability; to understand the full spectrum, incidence and impact of post COVID-19 condition and the evolution of SARS-COV-2 in immunocompromised populations; and to develop relevant integrated care pathways.

Productie 4

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

Oliver J Watson, Gregory Barnsley*, Jaspreet Toor, Alexandra B Hogan, Peter Winskill, Azra C Ghani*

Summary

Background The first COVID-19 vaccine outside a clinical trial setting was administered on Dec 8, 2020. To ensure global vaccine equity, vaccine targets were set by the COVID-19 Vaccines Global Access (COVAX) Facility and WHO. However, due to vaccine shortfalls, these targets were not achieved by the end of 2021. We aimed to quantify the global impact of the first year of COVID-19 vaccination programmes.

Methods A mathematical model of COVID-19 transmission and vaccination was separately fit to reported COVID-19 mortality and all-cause excess mortality in 185 countries and territories. The impact of COVID-19 vaccination programmes was determined by estimating the additional lives lost if no vaccines had been distributed. We also estimated the additional deaths that would have been averted had the vaccination coverage targets of 20% set by COVAX and 40% set by WHO been achieved by the end of 2021.

Findings Based on official reported COVID-19 deaths, we estimated that vaccinations prevented 14·4 million (95% credible interval [CrI] 13·7–15·9) deaths from COVID-19 in 185 countries and territories between Dec 8, 2020, and Dec 8, 2021. This estimate rose to 19·8 million (95% CrI 19·1–20·4) deaths from COVID-19 averted when we used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19·8 million of 31·4 million) during the first year of COVID-19 vaccination. In COVAX Advance Market Commitment countries, we estimated that 41% of excess mortality (7·4 million [95% CrI 6·8–7·7] of 17·9 million deaths) was averted. In low-income countries, we estimated that an additional 45% (95% CrI 42–49) of deaths could have been averted had the 20% vaccination coverage target set by COVAX been met by each country, and that an additional 111% (105–118) of deaths could have been averted had the 40% target set by WHO been met by each country by the end of 2021.

Interpretation COVID-19 vaccination has substantially altered the course of the pandemic, saving tens of millions of lives globally. However, inadequate access to vaccines in low-income countries has limited the impact in these settings, reinforcing the need for global vaccine equity and coverage.

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See Comment page 1254

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Introduction

The first COVID-19 vaccine was delivered outside of a clinical trial setting on Dec 8, 2020.[1] By Dec 8, 2021, 55·9% of the global population was estimated to have received at least one dose of a COVID-19 vaccine, 45·5% estimated to have received two doses, and 4·3% estimated to have received a booster dose.[2] Despite the incredible speed with which COVID-19 vaccines were developed in 2020 and subsequently distributed during 2021, more than 3·5 million deaths due to COVID-19 have been reported globally since the first vaccine was administered.[2]

Understanding the global impact of vaccination on the course of the COVID-19 pandemic is challenging given the heterogeneous access to vaccines coupled with different levels of transmission and ongoing non-pharmaceutical interventions across countries. In the early months of 2021, the impact of vaccination would have been minimal because of the delay in developing the infrastructure for a widespread vaccination campaign, the need for a delayed two-dose regimen in some jurisdictions to ensure maximum protection,[3] and the delay in the development of antibodies following vaccination. Additionally, as vaccine supply was constrained, most countries opted to prioritise vaccination in high-risk populations, including health-care workers and older people. Such strategies would have generated direct protection but would have had comparatively less impact on SARS-CoV-2 transmission. However, from mid-2021 onwards those countries with access to plentiful vaccine supply opted for mass vaccination of the adult population, later including children and subsequent boosting to maintain high levels of protection given the waning in vaccine efficacy and the emergence of new variants of

Research in context

Evidence before this study

We searched PubMed up to April 26, 2022, without any date limits or language restrictions, using the search terms "vaccin* AND impact AND (death* OR live*) AND (estimat* OR evaluat*) AND (COVID-19 OR SARS-CoV-2)". We found eight published studies that estimated the impact of COVID-19 vaccination, including deaths averted from vaccination. None of the studies considered the global impact of COVID-19 vaccination, focusing instead on specific regions (Italy, California, North Carolina, Stockholm, subsets of states in the USA, New York City, and the WHO European Region). Furthermore, the study focusing on the WHO European region only quantified the direct impact of vaccination and did not estimate the indirect effects (ie, decreasing infection risk of both vaccinated and unvaccinated susceptible individuals).

Added value of this study

This mathematical modelling study advances previous work both in terms of scale (number of regions modelled) and in terms of quantifying both the direct and indirect impact of COVID-19 vaccination globally. We estimated the impact of vaccination up to Dec 8, 2021, by fitting COVID-19 transmission models to both reported deaths and excess mortality during the pandemic as a proxy for deaths due to COVID-19. This study is, to the best of our knowledge, the first to use excess mortality estimates in this way, allowing for the impact of COVID-19 vaccination to be estimated more accurately in countries with weaker surveillance systems.

Implications of all the available evidence

The results highlight the substantial impact that vaccination has had on the trajectory of the COVID-19 pandemic. They also illustrate the broader impact of COVID-19 vaccination in terms of allowing countries with high vaccine coverage to relax interventions. Furthermore, the findings highlight the importance of equitable access to vaccines, particularly in low-income regions, where substantially more lives could have been saved if the vaccination targets set out by the COVID-19 Vaccines Global Access (COVAX) Facility (20% coverage in COVAX Advance Market Commitment countries by the end of 2021) and WHO (40% coverage in each country by the end of 2021) had been reached.

concern. This approach has resulted in vast inequalities in global vaccine distribution.[4]

To reduce inequality, a fair allocation mechanism for COVID-19 vaccines was developed through the COVID-19 Vaccines Global Access (COVAX) facility, with a key target of achieving 20% vaccine coverage for the countries covered by its Advance Market Commitment (AMC) through COVAX-secured doses by the end of 2021.[5] WHO expanded this target by setting a global strategy to achieve 70% coverage in all countries by mid-2022, with an interim target of 40% coverage by the end of 2021.[7] However, as a result of numerous challenges, particularly the constrained vaccine supply to COVAX (exacerbated by some countries obtaining a greater proportion of the global vaccine supply, pharmaceutical companies not meeting their contractual obligations to COVAX, and unpredictable delays in supply including vaccines with brief expiry windows), these targets were not reached in many lower-middle-income countries and low-income countries.[6] Vaccine uptake has also been suboptimal in many countries because of vaccine hesitancy.[7] This considerable heterogeneity in vaccination coverage has resulted in continued reliance on non-pharmaceutical interventions for pandemic management in some countries[8] but concomitantly enabled other nations to relax interventions as a route out of the pandemic.[9]

Quantifying the impact of vaccination is further challenged by the incomplete picture of the COVID-19 pandemic that is obtained from reported deaths. In many countries, vital registration systems are incomplete and therefore only a fraction of deaths are routinely reported. However, even in countries with complete vital registration systems, it is difficult to accurately define the cause of death in individuals who present with multiple morbidities. Excess all-cause mortality (the difference between the observed and expected number of deaths in non-pandemic years) has therefore been used to quantify the impact of the COVID-19 pandemic.[10] Although the exact contribution of COVID-19 to excess mortality is unknown, the strong temporal correlation observed globally between reported COVID-19 mortality and excess mortality provides evidence that excess mortality is an informative indicator of pandemic-related mortality.[11] Robust vital registration systems do not exist in many parts of the world, with WHO estimating that 40% of global deaths that occurred in 2020 were unregistered,[12] and therefore data on excess mortality are not available for every country. Model-based estimates have therefore been developed to obtain a more complete estimate of the pandemic to date. One set of estimates produced by *The Economist* uses a range of socioeconomic and epidemiological data to infer excess mortality.[13] Although the precise estimates differ between research groups[14] and WHO,[15] they all suggest a substantially larger number of COVID-19 deaths than have been reported to date.

We aimed to quantify the global impact of the first year of COVID-19 vaccination and estimate the number of deaths from COVID-19 averted in 185 countries and territories, both from the direct protection of vaccinated individuals and from the indirect protection of all individuals living in vaccinated environments due to the reduction in risk of infection. Additionally, we aimed to quantify the impact that a more equitable global vaccination campaign, meeting the vaccination targets set by COVAX of 20% vaccination coverage of the eligible population by the end of 2021, could have had in COVAX

AMC countries. We also aimed to quantify the impact of achieving the WHO target of 40% coverage by the end of 2021 in all countries.

Methods

Transmission model fitting

For this mathematical modelling study, we used a previously published COVID-19 transmission model[16,17] and fitting framework[18] to obtain profiles of the COVID-19 pandemic in each country and thus estimate the counterfactual scenario in which vaccines are not delivered. Briefly, the model is a population-based, age-structured susceptible-exposed-infectious-recovered-susceptible (SEIRS) model, which explicitly captures disease severity, passage through different indicated health-care levels, and the roll-out of vaccination. We incorporated country-level data on demography, age-based mixing patterns, and health-care capacity. We fit the model to officially reported COVID-19 deaths in each country, resulting in an inferred time-varying level of transmission, R_t, denoting the mean number of secondary infections in the absence of both infection-induced and vaccine-derived immunity. By fitting directly to mortality, we indirectly captured the impact that non-pharmaceutical interventions have had over the course of the COVID-19 pandemic.

Vaccination rates for first and second doses in each country were taken from Our World in Data[2] and the WHO dashboard. We assumed a vaccination strategy that first targets those most at risk (including health-care workers) and then iteratively distributes vaccines in descending age order. Vaccination was assumed to confer protection against SARS-CoV-2 infection and the development of severe disease requiring hospital admission,[3] and to reduce transmission from vaccine breakthrough infections (ie, we assumed vaccinated individuals who develop infection would be less infectious than unvaccinated individuals).[19] We inferred vaccine efficacy for each country on the basis of vaccine types known to be predominantly used in each country. We explicitly modelled the emergence of the delta (B.1.617.2) variant and its impact on vaccine efficacy, hospital admissions, and immune escape.[20,21] Any epidemiological differences associated with previous variants were assumed to be reflected by their effects on mortality,[22] which were subsequently captured by the estimated R_t trend. We fit the model to COVID-19 mortality in a Bayesian framework using a Metropolis-Hastings Markov Chain Monte Carlo-based sampling scheme. We used the resulting fit to estimate the time-varying reproductive number, R_t, and its associated uncertainty.

Complete details of the model, vaccination, variants, and model fitting are given in the appendix (pp 2–10). No ethical concerns were noted for this study, with all mortality data used based on nationally aggregated statistics; all datasets used were publicly available.

Excess mortality and COVID-19 mortality data

Because of the heterogeneity in death registration and certification worldwide, we also fit the model to all-cause excess mortality. For countries and time periods for which excess mortality had not been reported, we used model-based estimates of all-cause excess mortality, first produced by *The Economist*.[13] More details of the methodology are given in the appendix (p 2). Given the wide uncertainty in these model-based estimates of excess mortality in many parts of the world, we also presented the deaths averted as estimated by fitting to official reported COVID-19 deaths from the Johns Hopkins University COVID-19 Data Repository (appendix p 2). Importantly, these estimates based on official reported COVID-19 deaths represent the lower bound of deaths averted at the global level due to the considerable levels of under-reporting of COVID-19 mortality documented worldwide.[23]

For the **Johns Hopkins University COVID-19 Data Repository** see https://coronavirus.jhu.edu/map.html

Estimating deaths averted due to vaccination

The first vaccination outside a clinical trial setting was given on Dec 8, 2020. We introduced vaccination from this point onwards in the model and explored the impact of the first year of vaccination up to Dec 8, 2021. To quantify the impact of vaccination and its associated uncertainty, we took 100 draws from the estimated distribution of R_t and vaccine efficacy estimates for each country and simulated a counterfactual scenario in which no vaccines are available and the epidemic in each country follows the same R_t trend since the start of the pandemic; a counterfactual in which vaccines are delivered but there are no indirect effects (ie, they do not reduce SARS-CoV-2 transmission); and the observed scenario in which vaccines were delivered at the rates reported. The third scenario generated an estimate of the trajectory of the epidemic for our fitted model and hence closely matched reported COVID-19 or excess deaths or estimated excess deaths in each country. We calculated the deaths averted as a result of vaccination by subtracting the estimated COVID-19 deaths from the simulation with vaccines included (the observed scenario) from the estimated COVID-19 deaths under the first counterfactual scenario. This process is illustrated in the appendix (p 18), which shows the estimated deaths averted for the USA. Because of the difficulty in predicting how governments and populations would have responded, and how viral evolution would have progressed if vaccines had not been available, we made no attempt to adjust the R_t trends for further non-pharmaceutical interventions, changes in mobility, or development of variants that probably would have occurred differently in the absence of vaccination. To explore the impact of key model parameters on estimates of deaths averted, we did additional sensitivity analyses. These included characterising the effects of the assumed relationship between the infection fatality ratio (IFR) and age (appendix p 10), as well as the assumed degree of immune evasion exhibited by the delta variant (appendix p 7).

For the **WHO dashboard** see https://covid19.who.int/

See **Online** for appendix

	Total COVID-19 deaths	Vaccination coverage (%)	Estimated deaths averted by vaccinations		
			Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	5 469 000 (5 339 000–5 613 000)	38·30%	14 400 000 (13 650 000–15 900 000)	22·81 (21·63–25·18)	25·99 (24·64–28·69)
World Bank income group					
High-income countries	1 956 000 (1 892 000–2 032 000)	68·80%	6 353 000 (6 105 000–6 604 000)	52·6 (50·54–54·67)	36·67 (35·23–38·11)
Upper-middle-income countries	2 287 000 (2 220 000–2 355 000)	50·10%	2 914 000 (2 785 000–3 047 000)	25·6 (24·47–26·77)	23·36 (22·33–24·43)
Lower-middle-income countries	1 188 000 (1 099 000–1 302 000)	29·80%	5 083 000 (4 379 000–6 628 000)	15·27 (13·16–19·91)	20·39 (17·57–26·59)
Low-income countries	36 520 (33 390–40 410)	3·57%	20 380 (17 680–23 870)	0·3188 (0·2766–0·3733)	2·965 (2·572–3·472)
WHO region					
African region	153 800 (145 100–164 700)	5·48%	97 190 (88 420–107 400)	0·8677 (0·7894–0·9589)	5·958 (5·420–6·584)
Region of the Americas	2 492 000 (2 418 000–2 576 000)	58·30%	3 813 000 (3 624 000–3 987 000)	37·46 (35·6–39·17)	29·28 (27·83–30·62)
Eastern Mediterranean region	318 700 (307 200–331 500)	28·10%	639 200 (581 600–707 700)	8·746 (7·958–9·684)	13·50 (12·28–14·95)
European region	1 628 000 (1 589 000–1 673 000)	56·50%	4 334 000 (4 214 000–4 487 000)	46·77 (45·48–48·42)	39·52 (38·43–40·92)
South-East Asian region	713 800 (635 900–807 000)	35·40%	3 913 000 (3 234 000–5 491 000)	19·61 (16·21–27·52)	21·63 (17·88–30·36)
Western Pacific region	149 000 (120 100–234 400)	62·40%	1 574 000 (1 267 000–1 839 000)	30·14 (24·26–35·21)	22·58 (18·18–26·38)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Vaccination coverage is the proportion of the population with a full dose in the modelled countries by Dec 8, 2021. Total deaths are all modelled deaths in the presence of vaccinations when fitted to reported deaths from the start of the pandemic up to Dec 8, 2021.

Table 1: **Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to officially reported COVID-19 deaths**

We also explored the impact of increasing vaccine distribution to meet WHO and COVAX targets. We modelled two scenarios in which the targets set by WHO to fully vaccinate 40% of the eligible population in each country and administrative region, and by COVAX to fully vaccinate 20% of the eligible population in AMC countries, by the end of 2021 had been reached. To do so, for countries in which these targets had not been met, we scaled the roll-out of vaccines across the year by a constant factor such that exactly the targeted amount of the population had received their second vaccine dose by our end date (Dec 8, 2021).

Statistical analysis

All analyses were done with R software (version 4.1.3), with all data, code, packages, and versions used available online at GitHub. This analysis covered 185 countries and territories with a population greater than 90 000 as reported in *World Population Prospects 2019*,[24] and that reported at least one death due to COVID-19 or 1 week of positive estimated excess mortality. We excluded China from our estimates because of its unique position as the origin of the detected epidemic and its large influence on estimates of deaths averted stemming from its population size.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Based on our model fit to officially reported COVID-19 deaths, we estimated that 18·1 million (95% credible interval [CrI] 17·4–19·7) deaths due to COVID-19 would have occurred without vaccinations worldwide during the first year of the COVID-19 vaccination programme (Dec 8, 2020, to Dec 8, 2021). Of these, we estimated that vaccination prevented 14·4 million (95% CrI 13·7–15·9) deaths due to COVID-19, representing a global reduction of 79% of deaths (14·4 million of 18·1 million) during the first year of COVID-19 vaccination (table 1). These estimates of vaccine impact do not account for the potential under-ascertainment of deaths related to COVID-19.

Using our model fit to predicted and reported excess mortality (appendix p 23), we estimated that 31·4 million (95% CrI 30·6–32·1) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination, with 19·8 million (95% CrI 19·1–20·4) deaths averted, corresponding to 63% (19·8 million of 31·4 million) of total deaths (table 2). The difference between vaccine impact estimates based on excess mortality and official deaths due to COVID-19 was greatest in low-income regions, with approximately ten times more deaths estimated to have been averted in low-income countries when relying on excess mortality estimates (appendix pp 13, 19).

Using our model fit to excess mortality, we estimated that most deaths averted were due to the high levels of individual-level direct protection conferred by vaccination, with 79% (15·5 million of 19·8 million) of deaths averted through direct protection (figure 1A). Vaccine impact was also conferred through reducing the levels of burden placed on health-care systems, reducing the number of days that health-care capacity would have been exceeded and therefore contributing to an overall lower fatality rate from infection (appendix p 20). Throughout 2021, vaccine impact changed over time and space. Vaccine impact was

	Total excess deaths	Estimated deaths averted by vaccinations		
		Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	17 990 000 (17 610 000–18 530 000)	19 810 000 (19 130 000–20 380 000)	31·21 (30·14–32·1)	35·68 (34·47–36·71)
World Bank income group				
High-income countries	2 503 000 (2 412 000–2 609 000)	8 004 000 (7 644 000–8 438 000)	66·18 (63·20–69·77)	46·14 (44·07–48·64)
Upper-middle-income countries	4 717 000 (4 611 000–4 827 000)	4 230 000 (4 051 000–4 384 000)	36·97 (35·40–38·31)	33·71 (32·28–34·94)
Lower-middle-income countries	9 688 000 (9 329 000–10 170 000)	7 401 000 (6 841 000–7 655 000)	22·23 (20·55–23·00)	29·69 (27·44–30·71)
Low-income countries	1 087 000 (1 068 000–1 106 000)	180 300 (171 400–188 900)	2·711 (2·576–2·840)	26·23 (24·93–27·48)
WHO region				
African region	1 614 000 (1 580 000–1 652 000)	466 400 (446 300–487 000)	4·164 (3·985–4·348)	28·59 (27·36–29·85)
Region of the Americas	3 354 000 (3 260 000–3 456 000)	4 469 000 (4 233 000–4 728 000)	43·89 (41·57–46·43)	34·31 (32·50–36·29)
Eastern Mediterranean region	2 310 000 (2 248 000–2 376 000)	992 800 (938 800–1 066 000)	13·58 (12·85–14·59)	20·97 (19·83–22·52)
European region	3 448 000 (3 347 000–3 568 000)	5 811 000 (5 551 000–6 187 000)	62·30 (59·51–66·33)	52·63 (50·28–56·04)
South-East Asian region	6 741 000 (6 398 000–7 247 000)	5 658 000 (5 114 000–5 858 000)	27·99 (25·3–28·98)	31·29 (28·28–32·39)
Western Pacific region	518 700 (489 200–547 800)	2 429 000 (2 266 000–2 617 000)	46·31 (43·21–49·91)	34·74 (32·42–37·44)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Total deaths are all modelled deaths in the presence of vaccinations when fitted to excess mortality from the start of the pandemic up to Dec 8, 2021.

Table 2: **Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality**

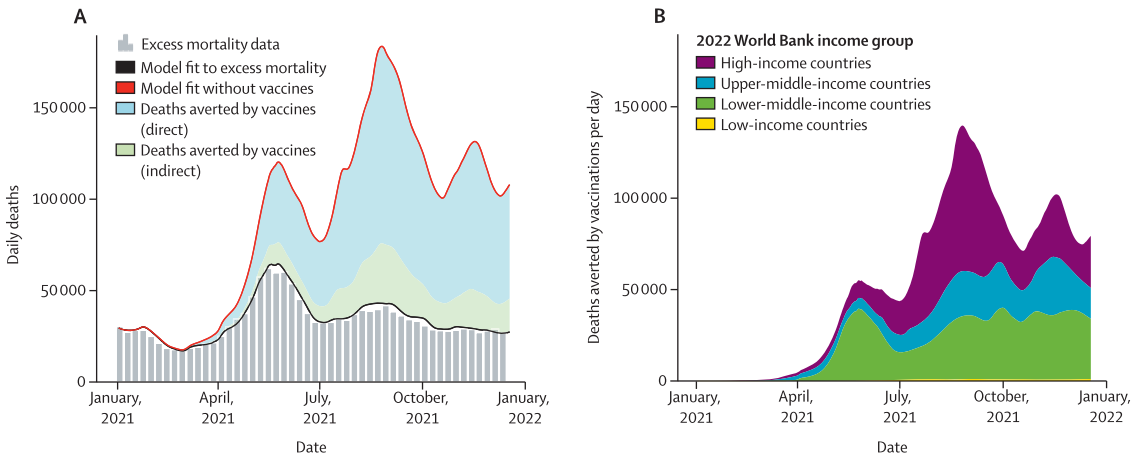

Figure 1: **Global COVID-19 deaths averted due to vaccination based on excess mortality**

(A) Median number of daily COVID-19 deaths based on excess mortality estimates (grey vertical bars) in the first year of vaccination. The baseline estimate of daily COVID-19 deaths from the model fit to excess mortality is plotted with the solid black line and the counterfactual scenario without vaccines is plotted with a red line. The gap between the red and black line indicates the deaths averted due to vaccination, with the proportion of total deaths averted by direct protection conferred by vaccination shown in blue and indirect protection shown in green. (B) Median number of daily deaths averted per day as per 2022 World Bank income group.

initially concentrated in lower-middle-income countries (figure 1B), resulting from the significant epidemic wave in India as the delta variant emerged. This was subsequently followed by vaccine impact being concentrated in high-income countries that were then either able to relax interventions due to high vaccination coverage (eg, the UK), or that did not implement further restrictions despite the spread of the more virulent delta variant in the second half of 2021.

Overall, estimated deaths averted per capita were highest in high-income countries, reflecting the earlier and wider roll-out of vaccination campaigns (table 2, figure 2; appendix p 13). We estimated that substantially more deaths were averted in the WHO European region. This was due to both the greater number of vaccinations administered in these regions and the higher levels of vaccine coverage achieved before the arrival of the delta variant.

The estimated number of deaths averted per vaccine administered was notably higher in high-income countries and upper-middle-income countries, in part due to greater access to the more efficacious mRNA vaccines (table 2;

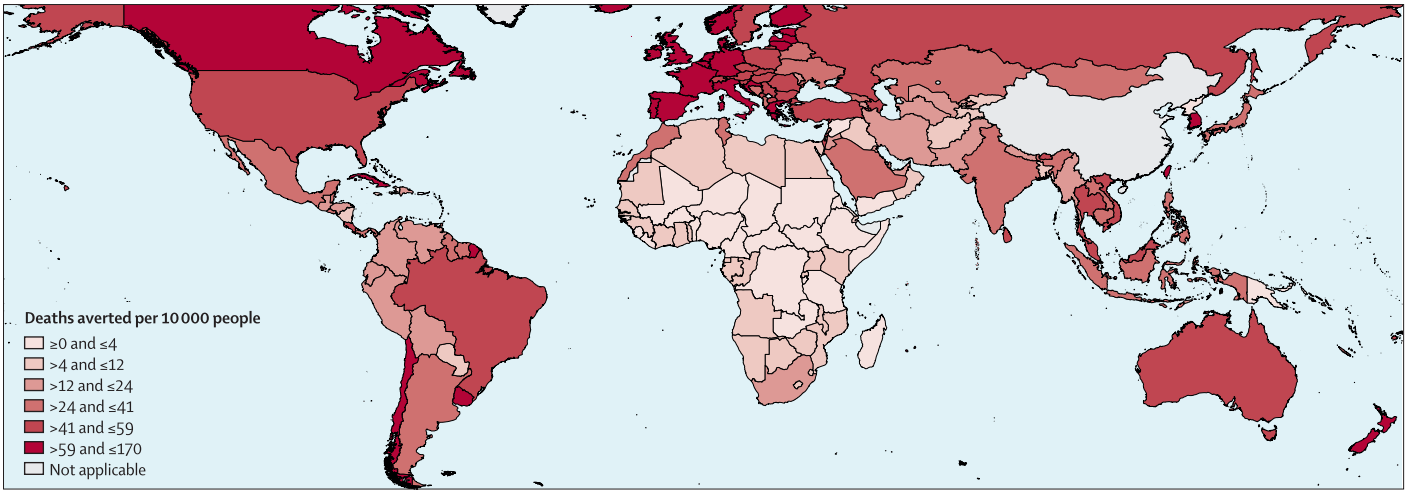

Figure 2: **Median deaths averted by vaccinations per 10 000 people by country in the first year of COVID-19 vaccination**
Estimates of deaths averted were based on model fits to excess mortality and were binned within seven equal quantiles starting at 0 deaths averted. Deaths averted listed as not applicable for China because of its exclusion from our analysis, due to its unique position as the origin of the detected epidemic and large influence on estimates of deaths averted stemming from its population size.

appendix p 14). Across the geographical regions, the estimated number of deaths averted per vaccine administered was estimated to be significantly higher in the European region and significantly lower in the Eastern Mediterranean region, reflecting disparities in access to different vaccine types (appendix p 14) coupled with very high predicted excess mortality in several countries in the Eastern Mediterranean region (table 2). The disparity in the number of deaths averted per vaccine between the European region and the Western Pacific region, despite access to similar vaccine types, reflects the zero-COVID strategy adopted by some countries in the Western Pacific region, such as New Zealand, which resulted in smaller epidemics predicted in the no-vaccine counterfactual (table 2; appendix p 13). Conversely, we estimated the greatest vaccine impact to have occurred in high-income countries that did not pursue a zero-COVID strategy (appendix p 13), reflecting how maximising vaccination coverage was leveraged to re-open the economy, resulting in increased transmission and subsequently higher inferred R_t trends. When viewed across income strata, a linear log–log relationship was observed between per-capita deaths averted and vaccines administered (figure 3), with low-income countries estimated to have a lower vaccine impact resulting from lower vaccine coverage. This relationship was weakest within high-income countries, as all high-income countries had high levels of vaccinations per capita, with the variation in deaths averted explained by other heterogeneities in their epidemics, such as pursuing zero-COVID strategies.

For the 83 COVAX AMC countries modelled, using our model fit to excess mortality, we estimated that 17·9 million (95% CrI 17·2–18·5) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination. We estimated that vaccinations averted 7·4 million (95% CrI 6·8–7·7) deaths, 41% (7·4 million of 17·9 million) of the deaths that would have occurred in COVAX AMC countries. Notably, the shortfall of the COVAX target in several regions was estimated to have resulted in an additional 156 900 (95% CrI 147 800–165 400) deaths (table 3). Although these deaths constituted a small proportion of the total deaths averted globally, these avertable deaths were concentrated in 25 low-income countries, which we predict would have averted an additional 81 750 (95% CrI 75 430–88 200) deaths across low-income countries by reaching 20% coverage, representing an additional 45% of deaths averted (table 3).

We found that 96 countries and administrative regions were below the WHO target of 40% vaccination coverage by the end of 2021. Had this target been met, we estimated that 599 300 (95% CrI 577 700–622 400) additional deaths would have been averted (table 3). The majority of these deaths occurred in lower-middle-income countries and the African and Eastern Mediterranean regions, although the largest proportional increase was seen in low-income countries, with the averted deaths making up a 111% increase in estimated deaths averted by vaccinations (table 3).

Our vaccine impact estimates were dependent on the assumed level of immune escape shown by the delta variant and the assumed relationship between age and the IFR. In the scenario in which the epidemic wave caused by the delta variant was comparable to previous waves and neither reached herd immunity nor resulted in health-system capacity being breached, our estimates of vaccine impact were unchanged regardless of the assumed level of immune evasion associated with the delta variant (appendix p 21). However, in scenarios in which the introduction of the delta variant produced a significantly larger wave that resulted in herd immunity being reached in the counterfactual, increased immune escape associated with the delta variant resulted in an

increased number of averted deaths due to the larger effective size of the susceptible population. In sensitivity analyses in which the relationship between age and IFR was changed, we estimated that vaccine impact would be greater in scenarios with higher IFRs, reflecting the higher number of deaths that could be averted by vaccination (appendix p 22).

Discussion

The high individual-level protection against severe disease and mortality due to COVID-19, as well as the population-level benefit afforded by mild protection against SARS-CoV-2 infection (before the emergence of the omicron [B.1.1.529] variant), conferred by vaccination, has fundamentally altered the course of the COVID-19 pandemic. Directly measuring the impact of vaccination programmes on COVID-19 mortality is not possible as the counterfactual (ie, without vaccinations) cannot be observed. Mathematical models are a valuable tool for quantifying the impact of vaccination campaigns on epidemic dynamics.[25] We evaluated the impact of the first year of COVID-19 vaccination, revealing how vaccinations have more than halved the potential global death toll due to COVID-19, with an estimated 19·8 million deaths from COVID-19 averted as a result of vaccination, based on excess mortality estimates of the impact of the pandemic. These reductions were concentrated in high-income countries that relied on their vaccination programmes to relax interventions and allow SARS-CoV-2 transmission to increase as they moved into a new stage of the pandemic.

In low-income countries, particularly countries that did not reach the 20% targets set out by COVAX, vaccine impact was substantially lower, with vaccine impact estimated to have been almost doubled if the targets had been reached. If the 40% target, per country, from WHO had been met, we estimated a further increase in deaths averted, mainly focused in lower-middle-income countries and low-income countries. A limitation of our assessment of the COVAX and WHO targets is the timeframe of our analysis, as these targets were set to be reached by the end of 2021, whereas our modelling endpoint was Dec 8, 2021, to align with 1 year since the start of public vaccination. Hence, some countries might have moved closer to achieving the targets, or achieved them, by the end of the year. However, any recent vaccination drives would have had consequently negligible impact given the delay in developing protection and insufficient impact on COVID-19 dynamics.

Deriving estimates of vaccine impact is heavily dependent on the counterfactual scenario chosen. In our counterfactual, we assumed the same time-varying levels of SARS-CoV-2 transmission as estimated in our model fits. Consequently, the largest impact was observed in countries that delivered the most vaccinations to date and simultaneously relaxed interventions, allowing SARS-CoV-2 transmission to increase. However, several countries with slower vaccination roll-out as well as countries adopting a zero-COVID strategy maintained stronger interventions to suppress transmission and thus observed smaller impacts of their vaccination programmes as a result. As these countries start to reopen, we predict that vaccine impact estimates would increase in line with increasing levels of SARS-CoV-2 transmission.

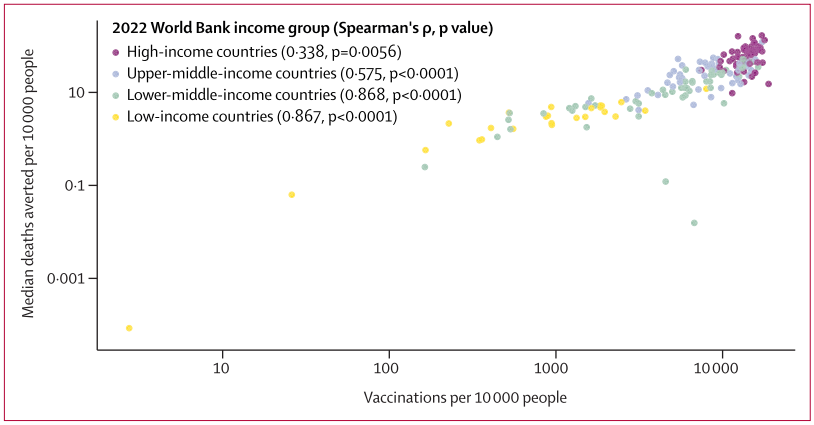

Figure 3: **Median deaths averted by vaccinations per 10 000 against vaccinations per 10 000 for each country**
All measures are on the log-scale. Spearman's rank correlation coefficient (Spearman's ρ) is also given for each income group with a p value based on the Z score against a null hypothesis of no correlation. Countries that did not deliver any vaccinations or had no deaths averted are not included.

Under-ascertainment of COVID-19 mortality is a known issue that has hindered our understanding of the pandemic.[23] In this analysis, we consequently focused on fitting to all-cause excess mortality, which provides a more complete description of the pandemic.[15] However, even when relying on model fits based on reported COVID-19 deaths, we estimated that more than 14 million deaths were averted by COVID-19 vaccination. The discrepancy between vaccine impact estimates based on excess mortality and COVID-19 deaths was concentrated in settings with lower death registration and certification. This substantial discrepancy underpins the crucial need for continued investment in civil registration and vital statistics to prevent biases in mortality reporting further minimising the perceived impact and necessity of vaccination in settings with lower reporting of deaths. In countries with more complete reporting systems, our estimates were broadly comparable to other endeavours focused on officially reported COVID-19 deaths and on understanding the direct impact of vaccination on people older than 60 years in Europe.[26] We identified one study that estimated both the indirect and direct impact of vaccination, which again yielded estimates for vaccine impact in the USA that were similar to our impact estimates based on reported COVID-19 deaths.[27]

In our effort to provide impact estimates globally, we introduced various assumptions into our model. We were hindered by the global disparities in SARS-CoV-2 genomic surveillance and the absence of detailed vaccination data for the majority of countries. Consequently, key model

	COVAX target (20% of eligible population in COVAX Advance Market Commitment countries fully dosed)				WHO target (40% of eligible population fully dosed)			
	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)
Worldwide	41	4·15%	156 900 (147 800–165 400)	0·792% (0·744–0·843)	96	27·8%	599 300 (577 700–622 400)	3·03% (2·89–3·17)
World Bank income group								
High-income countries	..	..	..	..	1	0·00191%	20 (20–30)	0·000298% (0·000243–0·000342)
Upper-middle-income countries	..	..	..	..	27	6·1%	51 110 (47 860–66 690)	1·21% (1·12–1·58)
Lower-middle-income countries	16	4·28%	75 540 (68 640–80 380)	1·02% (0·923–1·13)	41	39·7%	347 500 (330 300–363 300)	4·71% (4·43–5·11)
Low-income countries	25	253%	81 750 (75 430–88 200)	45·2% (42·0–49·3)	27	1060%	200 000 (187 900–211 900)	111% (105–118)
WHO region								
African region	31	134%	132 700 (123 800–141 300)	28·4% (26·5–30·4)	44	631%	348 900 (330 200–370 000)	74·9% (70·7–78·8)
Region of the Americas	1	0·248%	1080 (850–1390)	0·0241% (0·0186–0·0308)	14	1·66%	6330 (5870–6840)	0·141% (0·129–0·155)
Eastern Mediterranean region	6	5·56%	20 850 (18 860–22 710)	2·09% (1·86–2·32)	13	61·6%	126 800 (118 900–134 600)	12·7% (11·6–13·7)
European region	..	..	..	..	13	3·05%	41 760 (38 110–46 160)	0·715% (0·644–0·799)
South-East Asian region	1	0·586%	1410 (50–2960)	0·0254% (0·000914–0·0532)	7	17·5%	70 420 (64 300–75 890)	1·25% (1·15–1·39)
Western Pacific region	2	0·302%	900 (610–1200)	0·0366% (0·0250–0·0492)	5	2·59%	4990 (4390–5730)	0·205% (0·178–0·237)

Data are n (95% credible interval [CrI]) or % (95% CrI). All percentages are reported to 3 significant figures. Increased vaccination coverage is defined as the percentage increase in the proportion of the population with a full dose in all modelled countries when meeting the respective targets. Countries are grouped by 2022 World Bank income group and WHO region. COVAX=COVID-19 Vaccines Global Access.
*In proportion to total deaths averted by vaccines, as shown in table 2.

Table 3: **Estimated increase in deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality had all countries met either of the COVAX or WHO vaccination targets**

inputs had to be created from working assumptions on which vaccines were delivered, how they were delivered, and when new variants of concern spread worldwide. We also assumed that the relationship between age and IFR was the same for each country. These assumptions would have affected our estimates of deaths averted, with sensitivity analyses showing that higher overall IFRs will increase the number of deaths that could be averted by vaccination. Our impact estimates were also limited by the inherent uncertainty in model-based estimates of excess mortality.[13] These estimates are likely to have underestimated or overestimated COVID-19 death tolls in many countries. Notably, our model fits were unable to recreate excess mortality death tolls in recent epidemic waves in Iraq and Sudan because of the depletion of the susceptible population. These discrepancies could have been due to multiple reasons, including overestimated excess mortality, proportions of excess mortality not due to COVID-19,[28] higher infection fatality rates by age in low-income settings than those estimated from high-income countries,[29] and lower vaccine effectiveness than assumed in our framework. Last, our impact estimates were dependent on the assumed degree of immune escape that each variant of concern exhibits.[20] If immune escape was higher than we assumed, more of the population would have been susceptible to re-infection and consequently more deaths from COVID-19 could have been averted by vaccination.

More broadly, our estimates should be considered in light of the considerable uncertainty inherent in estimating vaccine impact. Uncertainty in the true death toll of the pandemic, the circulating variants of concern and their immunological phenotypes, and the vaccines themselves administered in many countries vastly complicate efforts to derive accurate estimates of the impact of COVID-19 vaccines. However, the results of this analysis still provide a comprehensive and thorough assessment of the impact of COVID-19 vaccination, revealing the substantial impact that vaccines have had and the millions of lives that are likely to have been saved during the first year of vaccination. Despite this, more lives could have been saved if vaccines had been distributed more rapidly to many parts of the world and if vaccine uptake could have been strengthened worldwide. Reaching vaccination coverage targets and improving vaccine coverage globally is dependent on multiple factors and not solely dependent on improving

vaccine donations.[30] Vaccine intellectual property needs to be shared more quickly in the future, with more open technology and knowledge transfer surrounding vaccine production and allocation. Vaccine distribution and delivery infrastructure also needs to be scaled up worldwide and misinformation combatted to improve vaccine demand. Improvements must be made in all these areas to reach current vaccine targets and help ensure that vaccines are more equitably distributed in the future.

Contributors

OJW and ACG conceived the study with input from GB, ABH, PW, and JT. OJW and GB led the model fitting and counterfactual simulation analyses for the estimation of deaths averted. OJW and GB produced the first draft of the manuscript and have accessed and verified the underlying data. All authors read, contributed to, and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ACG has received personal consultancy fees from HSBC, GlaxoSmithKline, and WHO related to COVID-19 epidemiology and from The Global Fund to Fight AIDS, Tuberculosis and Malaria for work unrelated to COVID-19. ACG is a non-remunerated member of scientific advisory boards for Moderna and the Coalition for Epidemic Preparedness. ABH and PW have received personal consultancy related to COVID-19 work from WHO. All other authors declare no competing interests.

Data sharing

All data, codes, and supplementary tables used and generated by this study are available in a GitHub repository (version 1.0.1) or the Zenodo open repository. All estimates of deaths averted from vaccination are available in the appendix (p 13).

Acknowledgments

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Productie 5

← Marketing authorisation

Conditional marketing authorisation

Human | Early access

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The European Medicines Agency (EMA) supports the development of medicines that address unmet medical needs. In the interest of public health, applicants may be granted a conditional marketing authorisation for such medicines on less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

Medicines for human use are eligible if they are intended for treating, preventing or diagnosing seriously debilitating or **life-threatening diseases.** This includes **orphan medicines.**

Its use is also intended for a **public health emergency** (e.g. a pandemic). For these medicines, less comprehensive pharmaceutical and non-clinical data may also be accepted.

The legal basis is Article 14-a of Regulation (EC) No 726/2004. The provisions for granting a conditional

marketing authorisation are further elaborated in Regulation (EC) No 507/2006.

Criteria and conditions

EMA's CHMP may grant a conditional marketing authorisation for a medicine if it finds that all of the following **criteria** are met:

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are **valid for one year** and can be renewed annually.

Once a conditional marketing authorisation has been granted, the marketing authorisation holder must fulfil **specific obligations** within defined timelines.

These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.

EMA publishes the conditions of the marketing authorisation in the medicine's European public assessment report.

The marketing authorisation can be converted into a **standard marketing authorisation** (no longer subject to specific obligations) once the marketing authorisation holder fulfils the obligations imposed and the complete data confirm that the medicine's benefits continue to outweigh its risks. Initially, this is valid for 5 years. It can then be renewed for unlimited validity.

As for any medicine, if new data show that the medicine’s benefits no longer outweigh its risks, EMA can take

regulatory action, such as suspending or revoking the marketing authorisation.

EMA can also take regulatory action if the company does not comply with the imposed obligations.

Did you know..?

Conditional marketing authorisation is a pragmatic tool for the **fast-track approval** of a medicine that fulfils an unmet medical need. Despite earlier approval, it guarantees that the medicine meets rigorous EU standards for safety, efficacy and quality and that comprehensive data is still generated post-approval.

It offers a robust post-authorisation regulatory framework based on legally binding obligations, safeguards and controls.

These include:

- full prescribing information and package leaflet with detailed instructions for safe use and conditions for storage;
- a robust risk-management and safety monitoring plan;
- manufacturing controls including official batch controls for vaccines, as required;
- legally binding post-approval obligations (i.e. conditions) for the marketing authorisation holder and a clear legal framework for the evaluation of emerging efficacy and safety data;
- an paediatric investigation plan.

Guidance for applicants

EMA advises applicants to discuss their development plans with the Agency via scientific advice or protocol assistance early in the development process.

Involving **health technology assessment bodies** early is also encouraged, which is possible via EMA's parallel consultations procedure.

The applicant should indicate a request for conditional marketing authorisation in their notification of intention to submit a marketing authorisation application. They should submit this 6 to 7 month before submitting the application.

EMA also encourages applicants to further discuss their plans with EMA as part of a **pre-submission meeting**.

For products deemed suitable for a conditional marketing authorisation, EMA encourages applicants to also consider requesting accelerated assessment.

Applicants should include a formal request for a conditional marketing authorisation in their marketing authorisation application. The CHMP will assess this request together with the application.

For **detailed guidance**, see:

- Pre-authorisation guidance: Question 1.9 - 'Could my application qualify for a conditional marketing authorisation?'
- Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

See also:

- Obtaining an EU marketing authorisation, step-by-step
- Accelerated assessment
- Guidance for medicine developers and other stakeholders on COVID-19 (for COVID-19 treatments and vaccines)

Distinction from authorisation under exceptional circumstances

EMA may also grant a marketing authorisation in absence of comprehensive data under exceptional circumstances.

Unlike conditional marketing authorisation, where marketing approval is granted in the likelihood that the sponsor will provide such data within an agreed timeframe, EMA can grant authorisation under exceptional circumstances when comprehensive data cannot be obtained even after authorisation.

This authorisation route normally does not lead to a standard marketing authorisation.

For more information and comparison between these authorisation routes, see:

- Pre-authorisation guidance: Question 1.10 - 'Is my medicinal product eligible for approval under exceptional circumstances?'

Latest statistics

The **latest statistics** on the conditional marketing authorisations granted by EMA are available in the Agency's annual reports.

10-year review (2006-2016)

Conditional marketing authorisation - Report on ten years of experience at the European Medicines AgencyEMA's 10-year report on the conditional marketing authorisation provides a detailed analysis and review of the Agency's experience with this type of authorisation in its first 10 years

of application. It covers data collected between 2006 and 2016:

- Conditional marketing authorisation - Report on ten years of experience at the European Medicines Agency
- Conditional marketing authorisation - Report on ten years of experience at the European Medicines Agency
  - Annex 1 - Detailed information on conditional marketing authorisations
- Annex 1 - Detailed information on conditional marketing authorisations
  - Annex 2 - Detailed information on unsuccessful conditional marketing authorisations
- Annex 2 - Detailed information on unsuccessful conditional marketing authorisations

The report shows that conditional marketing authorisation can help speed up patient access to new medicines.

It also calls for further improvements, including wider use of early dialogue between EMA and applicants and engaging further stakeholder groups, such as health-technology-assessment bodies.

Use during COVID-19 pandemic

During the COVID-19 pandemic, the conditional marketing authorisation procedure has been used to expedite the approval of safe and effective COVID-19 treatments and vaccines in the EU.

This is in line with EU legislation which foresees that conditional marketing authorisation is used as the **fast-track authorisation** during public health emergencies to speed up approval and save lives.

It allows regulators to grant a marketing authorisation as soon as sufficient data becomes available to demonstrate that the medicine's benefits outweigh its risks, with robust safeguards and controls in place post-authorisation.

In a **public health emergency**, it can also be combined with a rolling review of data during the development of a promising medicine, to further expedite the evaluation.

Conditional marketing authorisation has been the most appropriate tool to grant access to **COVID-19 vaccines** to all EU citizens at the same time and to underpin mass vaccination campaigns.

For information on authorised COVID-19 medicines, see:

- COVID-19 medicines

Related information materials

Visual guide: 10-year report highlights

Conditional Marketing Authorisation - How early access to medicines has helped patients from 2006 to 2016

Related content

- Support for early access
- Pre-authorisation guidance

Related EU legislation

- Regulation (EC) No 726/2004
- Regulation (EC) No 507/2006

Related documents

- Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004

Publications

- The Lancet: The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines

Topics

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What we do

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Productie 6

← Pharmacovigilance

Good pharmacovigilance practices

Human | Regulatory and procedural guidance | Pharmacovigilance

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Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to marketing-authorisation holders, the European Medicines Agency (EMA) and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

Guideline on GVP

The guideline on GVP was a key deliverable of the 2010 pharmacovigilance legislation.

Each chapter and revisions are developed by a team consisting of experts from EMA and from EU Member States.

The guideline on GVP is divided into chapters that fall into two categories:

- modules covering major pharmacovigilance processes;
- product- or population-specific considerations.

Modules covering major pharmacovigilance processes

GVP modules I to XVI cover major pharmacovigilance processes and the development of this set of guidance is concluded. The module numbers XI, XII, XIII and XIV stay void, as their planned topics have been addressed by other guidance documents on the Agency's website (see bullet points below Final GVP modules table).

Product- or population-specific considerations

The **chapters on product- or population-specific considerations** are available for vaccines, biological medicinal products and the paediatric population. EMA plans one more consideration chapter as follows:

Chapter number	Preliminary chapter title	Date of release for public consultation
P V	Geriatric population	To be announced

GVP modules and considerations are regularly reviewed for revision needs and schedules.

Archives of documents

- Archive of development of GVP
- Superseded pharmacovigilance guidance documents

Also on this topic

- Archive of development of good pharmacovigilance practices
- Superseded pharmacovigilance guidance documents

Introduction

Guidelines on good pharmacovigilance practices (GVP): Introductory cover note, last updated with release of Addendum III of Module XVI on pregnancy prevention programmes for public consultation

First published:

14/03/2022
Reference Number:

EMA/95595/2022

English (EN) (201.43 KB - PDF)

View

Final GVP modules

Guideline on good pharmacovigilance practices: Module I – Pharmacovigilance systems and their quality systems

Adopted
First published:

25/06/2012
Last updated:

25/06/2012
Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/541760/2011
Legal effective date:

02/07/2012

English (EN) (213.14 KB - PDF)

View

Guideline on good pharmacovigilance practices: Module II – Pharmacovigilance system master file (Rev. 2)

Adopted
First published:

25/06/2012
Last updated:

30/03/2017
Reference Number:

EMA/816573/2011
Legal effective date:

31/03/2017

English (EN) (340.71 KB - PDF)
View

Guideline on good pharmacovigilance practices: Module III – Pharmacovigilance inspections

Adopted
First published:

13/12/2012
Last updated:

15/09/2014
Reference Number:

EMA/119871/2012 Rev 1
Legal effective date:

16/09/2014

English (EN) (189.47 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP) - Module IV – Pharmacovigilance audits (Rev. 1)

Adopted
First published:

12/12/2012
Last updated:

11/08/2015
Reference Number:

EMA/228028/2012 Rev 1

English (EN) (154.02 KB - PDF)
View

Guideline on good pharmacovigilance practices: Module V – Risk management systems (Rev. 2)

Adopted
First published:

25/06/2012
Last updated:

30/03/2017
Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/838713/2011
Legal effective date:

31/03/2017

English (EN) (568.8 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)

Adopted
First published:

25/06/2012
Last updated:

02/08/2017
Reference Number:

EMA/873138/2011 Rev. 2
Legal effective date:

22/11/2017

English (EN) (2.02 MB - PDF)
View

Guideline on good pharmacovigilance practices (GVP) - Module VI Addendum I – Duplicate management of suspected adverse reaction reports

Adopted
First published:

28/07/2017
Last updated:

02/08/2017
Reference Number:

EMA/405655/2016
Legal effective date:

22/11/2017

English (EN) (359.92 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report

Adopted
First published:

25/06/2012
Last updated:

12/12/2013

Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/816292/2011 Rev.1*
Legal effective date:

13/12/2013

English (EN) (1.45 MB - PDF)
View

Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev. 3)

Adopted
First published:

25/06/2012
Last updated:

12/10/2017
Reference Number:

EMA/813938/2011
Legal effective date:

13/10/2017

English (EN) (235.42 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP): Module VIII Addendum I - Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev. 3)

Adopted
First published:

23/06/2020
Reference Number:

EMA/395730/2012 Rev. 3

English (EN) (86.49 KB - PDF)

View

Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management (Rev. 1)

Adopted

First published:

25/06/2012

Last updated:

12/10/2017

Reference Number:

EMA/827661/2011

Legal effective date:

22/11/2017

English (EN) (283.21 KB - PDF)

View

Guideline on good pharmacovigilance practices (GVP): Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

Adopted

First published:

12/10/2017

Last updated:

12/10/2017

Reference Number:

EMA/209012/2015

Legal effective date:

22/11/2017

English (EN) (133.95 KB - PDF)

View

Guideline on good pharmacovigilance practices: Module X – Additional monitoring

Adopted

First published:

25/04/2013

Last updated:

25/04/2013

Consultation dates:

27/06/2012 to 24/08/2012

Reference Number:

EMA/169546/2012

Legal effective date:

25/04/2013

English (EN) (271.91 KB - PDF)

View

Guideline on good pharmacovigilance practices: Module XV – Safety communication (Rev. 1)

Adopted

First published:

24/01/2013

Last updated:

12/10/2017

Reference Number:

EMA/118465/2012

Legal effective date:

13/10/2017

English (EN) (188.52 KB - PDF)

View

Guideline on good pharmacovigilance practices: Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev. 2)

Adopted
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Last updated:

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Reference Number:

EMA/204715/2012
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English (EN) (375.58 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP): Module XVI Addendum I – Educational materials

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15/12/2015
Last updated:

15/12/2015
Reference Number:

EMA/61341/2015
Legal effective date:

16/12/2015

English (EN) (81.66 KB - PDF)
View

- Where GVP chapters refer to Modules XI or XIV, consult the Agency's page on partners and networks.

- Where GVP chapters refer to Module XII, consult the Agency's page on post-marketing authorisation: regulatory and procedural guidance for human medicinal products.
- Where GVP chapters refer to Module XIII, consult the Agency's page on the incident management plan.
- Please note the document on

  - Reporting requirements of marketing authorisation holders in the European Union (EU) regarding suspected adverse reactions occurring with medicinal products they donate outside the EU to public health programmes against ...

  - Reporting requirements of marketing authorisation holders in the European Union (EU) regarding suspected adverse reactions occurring with medicinal products they donate outside the EU to public health programmes against ...

  .
- In relation to the GVP VII module please note that an

  - Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report - Explanatory note

  - Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report - Explanatory note

  and a

  - Questions and answers on PSUSA: Guidance document for assessors

  - Questions and answers on PSUSA: Guidance document for assessors

  have been developed to clarify certain aspects of the single assessment that are specific to nationally authorised products. These documents should be considered as interim guidance until the GVP VII module is revised as per the established process. Once the updated GVP module is published this guidance will be

removed. These documents can be found on the Periodic safety update reports: questions and answers page.

- Where GVP modules refer to the European Medicines Agency's and the Heads of Medicines Agencies' procedural advice on referral procedures for safety reasons, consult referral procedures page.

Final GVP product- or population-specific considerations

Guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases

Adopted
First published:

12/12/2013
Last updated:

12/12/2013
Reference Number:

EMA/488220/2012
Legal effective date:

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English (EN) (460.19 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations II: Biological medicinal products

Adopted
First published:

15/08/2016
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Reference Number:

EMA/168402/2014
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English (EN) (377.05 KB - PDF)
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Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations IV: Paediatric population

Adopted
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07/11/2018
Reference Number:

EMA/572054/2016
Legal effective date:

08/11/2018

English (EN) (206.02 KB - PDF)
View

- Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products

- Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products

Final GVP annex I - Definitions

Guideline on good pharmacovigilance practices: Annex I - Definitions (Rev. 4)

Adopted
First published:

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Last updated:

12/10/2017
Reference Number:

EMA/876333/2011
Legal effective date:

13/10/2017

English (EN) (295.69 KB - PDF)
View

Final GVP annex II - Templates

Guideline on good pharmacovigilance practices: Annex II – Templates: Cover page of periodic safety update report (PSUR)

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First published:

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Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/170043/2013
Legal effective date:

25/04/2013

English (EN) (176.08 KB - PDF)
View

Guideline on good pharmacovigilance practices: Annex II – Templates: Direct Healthcare Professional Communication (DHPC) (Rev. 1)

Adopted
First published:

24/01/2013
Last updated:

12/10/2017
Reference Number:

EMA/36988/2013
Legal effective date:

13/10/2017

English (EN) (61.21 KB - PDF)
View

Guideline on good pharmacovigilance practices (GVP): Annex II – Templates: Communication Plan for Direct Healthcare Professional Communication (CP DHPC)

Adopted
First published:

12/10/2017
Last updated:

12/10/2017
Reference Number:

EMA/334164/2015
Legal effective date:

13/10/2017

English (EN) (80.24 KB - PDF)
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For other templates developed outside the GVP process, see:

- Risk-management plans
- Pharmacovigilance: regulatory and procedural guidance

Final GVP annex III - Other pharmacovigilance guidance

These pharmacovigilance guidance documents were developed under the previous legal framework but are still valid in conjunction with GVP.

Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data

Adopted
First published:

14/11/2005
Last updated:

14/11/2005
Reference Number:

EMEA/CHMP/313666/2005
Legal effective date:

02/05/2006

English (EN) (277.32 KB - PDF)
View

Note for guidance: EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) (historical)

Adopted
First published:

03/08/2004
Last updated:

22/10/2010
Reference Number:

EMA/H/20665/04/Final Rev. 2
Legal effective date:

07/02/2011

English (EN) (840.18 KB - PDF)
View

Overview of comments received on draft note for guidance: EudraVigilance version 7.1 - Processing of safety messages and individual case safety reports (ICSRs)

First published:

20/11/2009
Last updated:

20/11/2009
Reference Number:

EMEA/183240/2008

English (EN) (215.05 KB - PDF)
View

Draft note for guidance: EudraVigilance Human version 7.1 - Processing of safety messages and individual case safety reports (ICSRs)

Draft: consultation closed
First published:

01/02/2008
Last updated:

01/02/2008
Reference Number:

EMEA/553390/2007

English (EN) (720.45 KB - PDF)
View

For other pharmacovigilance guidance developed outside the GVP process, see:

- Pharmacovigilance: regulatory and procedural guidance
- Consideration on core requirements for RMPs of COVID-19 vaccines
- Signal management
- EudraVigilance
- European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use - Revision 3
- Union reference dates and submission of periodic safety update reports
- Guideline on registry-based studies
- Standards and guidances of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

- Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products

- Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products

- Good practice guide on recording, coding, reporting and assessment of medication errors.

- Good practice guide on recording, coding, reporting and assessment of medication errors.

- Good practice guide on risk minimisation and prevention of medication errors

- Good practice guide on risk minimisation and prevention of medication errors

- Risk minimisation strategy for high-strength and fixed-combination insulin products, addendum to the good practice guide on risk minimisation and prevention of medication errors

- Risk minimisation strategy for high-strength and fixed-combination insulin products, addendum to the good practice guide on risk minimisation and prevention of medication errors

Also, note the

- PRAC rules of procedure

- PRAC rules of procedure

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Final GVP annex IV - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for

Human Use (ICH) guidelines for pharmacovigilance

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use topic E 2 A: Clinical safety data management: Definitions and standards for expedited reporting - Step...

Adopted
First published:

01/06/1995
Last updated:

01/06/1995
Reference Number:

CPMP/ICH/377/95
Legal effective date:

01/06/1995

English (EN) (177.91 KB - PDF)
View

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E2B (R3): Electronic transmission of individual case safety reports (ICSRs) - data elements ...

Adopted
First published:

01/09/2005
Last updated:

27/08/2013
Reference Number:

CHMP/ICH/287/1995
Legal effective date:

01/07/2013

English (EN) (1.49 MB - PDF)

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- E2C(R2)Implementation working group ICH E2C(R2) Guideline: Periodic benefit-risk evaluation report questions & answers

- ICH M1 Medical Dictionary for Regulatory Activites (MedDRA)
- MedDRA support documentation
- ICH M2 electronic standards for the transfer of regulatory information (ESTRI) is available on multidisciplinary guidelines.

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Productie 7

COMIRNATY, COMIRNATY ORIGINAL/OMICRON BA.1, COMIRNATY ORIGINAL/OMICRON BA.4-5, COMIRNATY OMICRON XBB.1.5 (COVID-19 mRNA VACCINE) RISK MANAGEMENT PLAN

RMP Version number: 11.0

Data lock point for this RMP: See below:

Age group[a]	Module SIII. Clinical Trial Exposure	Module SVII.3. Details of Important Risks
Bivalent Omicron (BA.4-5)		
12 years of age and older bivalent Omicron - (BA.4-5) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg) as primary series or 4th dose	12 October 2022 Cohort 2 31 Oct 2022 Cohort 3 Study C4591044	12 October 2022 Cohort 2 31 Oct 2022 Cohort 3 Pfizer Clinical Database - Study C4591044 15 November 2022 Pfizer Safety Database (non-CT dataset)
5-<12 years of age bivalent Omicron - (BA.4-5) modified vaccine (BNT162b2 + BNT162b2 OMI 10 µg) as primary series or 4th dose	25 November 2022 [C4591048 Substudy D (group 2)]	25 November 2022 Pfizer Clinical Database - Study C4591048 (SSD group 2) 15 November 2022 Pfizer Safety Database (non-CT dataset)
6 months to <5 years of age bivalent Omicron - (BA.4-5) modified vaccine (BNT162b2 + BNT162b2 OMI 3 µg) as primary series	25 November 2022 [C4591048 Substudy B, (group 2)]	25 November 2022 Pfizer Clinical Database - Study C4591048 (SSB group 2) 15 November 2022 Pfizer Safety Database (non-CT dataset)
Comirnaty original (monovalent) + Bivalent Omicron (BA.1) + Bivalent Omicron (BA.4-5)		
12 years of age and older booster dose of a bivalent Omicron - (BA.1 and BA.4-5) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg)	Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 C4591031 (Substudy E). 11 March 2022 C4591031 (Substudy D – Cohort 2).	Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 Pfizer Clinical Database - Study C4591031 (Substudy E). 11 March 2022 Pfizer Clinical Database - Study C4591031 (SSD – Cohort 2). 30 June 2022 Pfizer Safety Database (non-CT dataset)
Comirnaty original (monovalent)		
6 months to <5 years (Primary series)	16 July 2021 (Phase 1) 29 April 2022 (Phase 2/3)	29 April 2022 Pfizer Clinical Database – Study C4591007 (Phase 2/3) 15 April 2022 Pfizer Safety Database (non-CT dataset)
5 to <12 years of age (Primary series)	06 September 2021	06 September 2021 Pfizer Clinical Database

Booster (3rd) dose in 5 to <12 years of age	22 March 2022 (Phase 2/3)	22 March 2022 Pfizer Clinical Database Study C4591007 31 August 2022 Pfizer Safety Database (non-CT dataset)
12-15 years of age, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database)	30 September 2021 Pfizer Safety Database (CT dataset)
Booster (3rd) dose in 12-15 years of age (6 months post dose 3 data)	03 November 2022 (Study C4591001)	03 November 2022 Pfizer Clinical Database, Study C4591001 28 February 2022 Pfizer Safety Database (non-CT dataset)
Booster (3rd) dose in 12-17 years of age 1 month post dose 3	14 July 2022 (C4591031 Substudy C)	28 February 2022 Pfizer Safety Database (non-CT dataset)
16 years and older, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database) 23 October 2020 (BioNTech Clinical Database)	30 September 2021 Pfizer Safety Database (CT dataset)
Booster (3rd) dose in 16 years and older[b]	17 June 2021 (Study C4591001)	17 June 2021 Pfizer Clinical Database - Study C4591001 28 February 2022 Pfizer Safety Database (non-CT dataset)
SV Post-Authorization Experience: 18 June 2023		

a. Detailed language is included in the SmPC.
b. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Date of final sign off: 13 October 2023

Rationale for submitting an updated RMP (v 11.0): This Type II variation (EMEA/H/C/005735/II/0188/G) includes an updated comprehensive RMP (based on v 10.0) that includes the removal of studies/milestones from aPV activities of the following completed studies: C4591001, BNT-162-01 and WI235284 (Emory).

Summary of significant changes in the RMP versions:

RMP Part/Module	RMP 11.0 Major Changes
PART I PRODUCT(S) OVERVIEW	Aligned with the current SmPC. Editorial changes to include the new strain XBB.1.5 (as per procedure EMEA/H/C/005735/II/0183).
PART II.Module SI Epidemiology of the Indication(s) and Target Populations	Editorial changes to include the new strain XBB.1.5.
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes made.

RMP Part/Module	RMP 11.0 Major Changes
PART II.Module SIII Clinical Trial Exposure	No changes made.
PART II.Module SIV Populations Not Studied in Clinical Trials	No changes made.
PART II.Module SV Post-Authorisation Experience	Updated as of 18 June 2023 (aligned with PSUR # 5).
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.
PART II.Module SVII Identified and Potential Risks	No changes made.
PART II.Module SVIII Summary of the Safety Concerns	No changes made.
III.1 Routine Pharmacovigilance activities	Editorial changes to clean-up routine activities and remove PBS 30 mcg presentation from vial differentiation / potential medication error. Updated to add Comirnaty Omicron XBB.1.5 presentations.
III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	Studies C4591001, BNT162-01 and WI235284 are removed.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.
V.1 Routine Risk Minimisation Measures V.2 Additional Risk Minimisation Measures V.3 Summary of Risk Minimisation Measures	Updated based on the changes made in PART III.
PART VI I The Medicine and What It Is Used For II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	Editorial changes to include the new strain XBB.1.5. Updated based on the changes made in PART III and V.
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: removal of studies: C4591001, BNT-162-01 and WI235284 Annex 3: removal of studies: C4591001, BNT-162-01 and WI235284. Annex 8: Changes to reflect the updates and the RMP up version as a part of the closing sequence.

Other RMP versions under evaluation:

None.

Details of the currently approved RMP

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Approved with procedure numbers:

EMEA/H/C/005735/X/0176

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EMEA/H/C/005735/X/0180

Date of approval: 22 June 2023

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
ACIP	Advisory Committee on Immunisation Practices
AE	adverse event
AESI	adverse event of special interest
A:G	albumin:globulin
ALC-0315	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
aPV	Additional pharmacovigilance
ARDS	acute respiratory distress syndrome
BALB/c	bagg albino
BC	Brighton Collaboration
BEST	biologics effectiveness and safety
BMI	body mass index
BP	blood pressure
CD4, CD8	cluster of differentiation-4,8
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLL	chronic lymphocytic leukaemia
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CP	contractual party
CRF	Case report form
CRRT	continuous renal replacement therapy
CSR	clinical study report
CT	clinical trial
DART	developmental and reproductive toxicology
DCA	data capture aid
DHPC	Direct Healthcare Professional Communication
DLP	data-lock point
DoD	Department of Defense
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
ECDC	European Center for Disease Control
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EHR	electronic health records
EMA	European Medicines Agency
EUA	emergency use authorisation
EU	European Union
FDA	(US) Food and Drug Administration
GLP	good laboratory practice
HbA1c	glycated haemoglobin
HBV	hepatitis b virus
HCO	health care organization
HCP	health care professional
HCV	hepatitis c virus
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IFN	interferon

Abbreviation	Definition of Term
Ig E	immunoglobulin E
IL-4	interleukin 4
IM	intramuscular(ly)
IMD	index of multiple deprivation
IND	investigational new drug
IRR	incidence rate ratio
LAC	Los Angeles County
LNP	lipid nanoparticle
LSV	last subject visit
MAA	marketing authorization applicant
MAH	marketing authorisation holder
Mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome-coronavirus
MHS	Military Health System
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid
NCMD	national child mortality database
NCHS	national center for health statistics
NDA	new drug application
NHLBI	National Heart, Lung and Blood Institute
NHP	nonhuman primate
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIS	Non interventional study
NSCLC	non-small-cell lung carcinoma
OCS	oral corticosteroids
OMI	Omicron
PASS	post-authorisation safety study
PBS	Phosphate Buffered Saline
PC	product complaint
PCR	polymerase chain reaction
PD1, PD2,PD3	post dose 1, post dose 2, post dose 3
PK	Pharmacokinetic
PHN	Pediatric Heart Network
PRAC	Pharmacovigilance risk assessment committee
PSUR	periodic safety update report
RA	rheumatoid arthritis
RBC	red blood cell
RMP	risk management plan
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
siRNA	small-interfering RNA
SMQ	standardised MedDRA query
SmPC	summary of product characteristics
SMSR	summary monthly safety report
SPEAC	Safety Platform for Emergency vACcines

Abbreviation	Definition of Term
SSR	summary safety report
SSE	substudy E
Tdap	tetanus, diphtheria, and acellular pertussis
TESSy	The European Surveillance System
Th1	T helper cell type 1
Th2	T helper cell type 2
TME	targeted medical event
TNF	tumour necrosis factor
TRIS	Tromethamine Buffer or (HOCH2)3CNH
UK	United Kingdom
US	United States
V8	variant 8
V9	variant 9
VAC4EU	Vaccine monitoring Collaboration for Europe
VAED	vaccine-associated enhanced disease
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VAERD	vaccine-associated enhanced respiratory disease
VSD	Vaccine Safety Datalink
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of child-bearing potential
WT	Wild type

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Productie 8

← Pharmacovigilance

Periodic safety update reports (PSURs)

This page includes information on periodic safety update reports (PSURs), PSUR submission requirements, PSUR single assessment procedures (PSUSAs) and the European Union reference dates (EURD) list.

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PSURs are pharmacovigilance documents intended to provide an evaluation of the **risk-benefit balance** of a medicinal product at defined time points after its authorisation.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account **new or emerging safety information** in the context of cumulative information on risk and benefits

EMA and national competent authorities assess information in PSURs to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed.

A PSUR assessment can determine if further investigations on a specific issue are needed, or if an action is necessary to

protect public health (e.g. an update of the information provided to healthcare professionals and patients).

Marketing authorisation holders (MAHs) are legally required to submit PSURs, in line with current legislation.

Article 35 of the Commission Implementing Regulation describes the structure of PSURs. Guidance is available on the preparation, submission and assessment of PSURs. This format is a legal requirement for both nationally authorised products and centrally authorised products.

Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report

Adopted
First published:

25/06/2012
Last updated:

12/12/2013
Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/816292/2011 Rev.1*
Legal effective date:

13/12/2013

English (EN) (1.45 MB - PDF)
View

For more information, see:

- Regulation (EU) No 1235/2010
- Directive 2010/84/EU
- Commission Implementing Regulation (EU) No 520/2012

Preparation of PSURs

MAHs should consult the following information when preparing a PSUR:

Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report

Adopted
First published:

25/06/2012
Last updated:

12/12/2013
Consultation dates:

21/02/2012 to 18/04/2012
Reference Number:

EMA/816292/2011 Rev.1*
Legal effective date:

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English (EN) (1.45 MB - PDF)
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The Agency has also published an **explanatory note** to GVP module VII, which all MAHs should consult when preparing PSURs. It addresses specific challenges in the EU single assessment procedure for nationally authorised products, but the issues may also apply to centrally authorised products.

For more information on GVP modules, see Good pharmacovigilance practices.

Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report - Explanatory note

Adopted
First published:

06/04/2017

Last updated:

29/04/2020
Reference Number:

EMA/670256/2017 Rev.3

English (EN) (301.89 KB - PDF)
View

Specific guidance is available on preparing PSURs for **COVID-19 vaccines**:

- COVID-19 guidance: Periodic safety update reports for COVID-19 vaccines

Submission of PSURs

As of 13 June 2016, MAHs are required to submit all PSURs in the EU to the central PSUR repository using the eSubmission Gateway/ Web Client.

Use of the **PSUR repository is mandatory** for both centrally and nationally authorised medicines, whether they follow the EU single assessment or a purely national assessment procedure.

For more information on how to use the PSUR repository, see:

- Periodic Safety Update Report (PSUR) repository mandatory use: questions and answers

Further information on the PSUR repository, guidance on how to register and multimedia tutorials for MAHs on **how to submit** a PSUR in the correctly-structured electronic formats can be found on EMA's eSubmission website.

Submission requirements and EU reference dates: the EURD list

MAHs for active substances and combinations of active substances that are **subject to assessment at EU level** must submit the relevant PSURs according to the requirements set up in the list of EU reference dates (EURD) list:

List of European Union reference dates and frequency of submission of periodic safety update reports (PSURs)

First published:

01/10/2012

Last updated:

31/01/2024

Reference Number:

EMA/630645/2012 Rev. 134

English (EN) (943.63 KB - XLSX)

View

The list does not include substances assessed at **national level**, although their PSURs must nonetheless be submitted via the PSUR repository. For these active substances, the frequency of submission is established at national level. For more information, see:

- CMDh best practice guide

The EURD list provides the following information for each active substance/combination it contains:

- frequency of PSUR submission;
- data lock point;
- submission date;

- requirements for the submission of PSURs for generic, well-established use, homeopathic and traditional herbal products.

The EURD list is a **legally binding document** and MAHs are legally responsible for complying with its requirements. The list overrules the 'standard' PSUR submission cycle and any conditions related to the frequency of PSUR submission included in a marketing authorisation.

EMA **updates the EURD list every month**, following adoption by the Committee for Medicinal Products for Human Use (CHMP) and Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), after consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).

Any amendment to the EURD list becomes effective **six months after its publication**.

For more information on the EURD list and answers to frequently-asked-questions, see the following document:

Introductory cover note to the list of European Union reference dates and frequency of submission of periodic safety update reports

First published:

01/10/2012
Last updated:

17/07/2019
Reference Number:

EMA/606369/2012 Rev.17

English (EN) (142.13 KB - PDF)
View

MAHs and other stakeholders can **request amendments to the EURD list** by emailing eurdlist@ema.europa.eu with the

following information:

Template for a request for amendments of or addition of active substances or combinations of active substances to the European Union reference-date list

First published:

01/10/2012

Last updated:

17/07/2019

English (EN) (103.03 KB - DOCX)

View

- extract of the relevant active substances/combinations from the Article 57 database for which the addition/amendment is requested.

Before submitting a request, EMA encourages stakeholders to carefully consult the introductory cover note. There may be some delay before EMA is able to respond due to the high volume of requests and necessary processing time.

Assessment of PSURs

PSURs submitted in accordance with the EURD list are subject to the EU PSUR **single assessment** (PSUSA) procedure.

EMA carries out PSUSA procedures to assess PSURs of medicines containing the same active substances or combinations, even if they are subject to different marketing authorisations and are authorised in different EU Member States. This aims to harmonise and strengthen benefit-risk review of medicines across the European Economic Area.

For more information, see the questions-and-answers below and Periodic safety update report single assessments.

Post-authorisation procedural advice: questions and answers

1. What is a Periodic Safety Update Report (PSUR)?

2. What is the scope of PSUR assessment under the EU single assessment?

3. How shall I present my PSUR and in which format?

4. What is the List of European Union reference dates (EURD list) and frequency of submission of PSURs?

5. When do changes to the EURD list become legally binding?

6. How can I request to amend the list of EU reference dates? Rev. December 2019

7. Do I have to submit a PSUR if the active substance/combination of active substances of my medicinal product is not in the EURD list?

8. Do I have to submit a PSUR if the combination of active substances of my product is not in the EURD list but one or more individual components are listed?

9. Do I have to submit a PSUR if my medicinal product is not marketed?

10. Do I have to submit a PSUR if the marketing authorisation for my product has been granted on or after the data lock point (DLP) in the EURD list?

11. My company holds a Parallel Import Authorisation; do we have to submit PSUR for these product(s)? If a PSUR is submitted will it be assessed?

12. Do I have to submit a PSUR for my medicinal product if it is a generic, a product containing a well-established substance, a homeopathic or herbal medicinal product?

13. Do I have to submit a PSUR for my hybrid medicinal product?

14. Do I have to submit a PSUR if my medicinal product is authorised in accordance with Article 126(a) of Directive 2001/83/EC?

15. Will the withdrawal/non-renewal/revocation of the marketing authorisation of my product impact on the ongoing EU single PSUR assessment?

16. Will I have to submit PSUR after withdrawal/non-renewal/revocation of the marketing authorisation of my product? Rev. Apr 2021

17. Do PSURs need to contain case narratives and line listings?

18. How can I submit the proposed changes to the product information within the PSUR for NAPs which are part of an EU single assessment?

19. Can I submit a RMP update together with my PSUR?

20. Can I submit a clinical study report together with my PSUR? Rev. Aug. 2020

21. What are the timelines for the submission of PSURs?

22. What happens if I missed the submission deadline?

23. To whom should I submit my PSUR?

24. How to identify the official contact person for the PSUR?

25. What fee do I have to pay? Rev. Apr 2021

26. How will my PSUR submission be handled?

27. How shall I submit the response to a request for supplementary information during a PSUSA procedure?

28. How is the CHMP opinion/CMDh position structured and which annexes need to be translated? Re. Apr 2021

29. To whom should I submit follow-up data requested after the conclusion of a PSUSA procedure?

30. How can I know about the outcome of a PSUSA procedure?

31. How shall I implement the outcome of a PSUSA procedure?

32. Can PSURs still be submitted with renewal application?

33. Who should I contact if I have a question regarding the preparation of a PSUR submission and during the procedure?

34. Who should I contact if I have a technical issue with the submission of the PSUR?

35. Who should I contact if I have an issue related to the EURD list?

36. Who should I contact if I have an issue related to the payment of fee and QPPV advice notes? Rev. Apr 2021

Topics

Regulatory and procedural guidance

Pharmacovigilance

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Productie 9

← COVID-19 public health emergency of international concern (2020-23)

COVID-19 vaccines: development, evaluation, approval and monitoring

The European Medicines Agency (EMA) plays an important role in enabling the development, scientific evaluation, approval and monitoring of COVID-19 vaccines in the European Union (EU).

Human COVID-19 Vaccines

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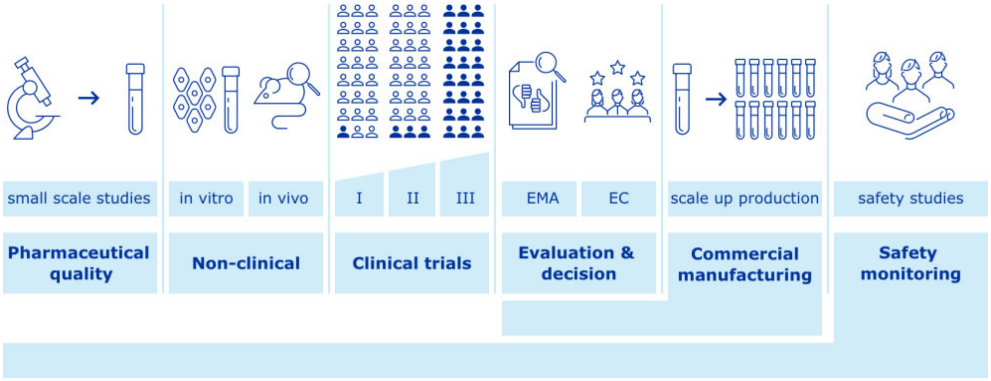
EMA published the information on this page for use during the COVID-19 public health emergency. EMA is no longer updating this page.

Vaccines for COVID-19 are developed, evaluated and approved according to current scientific knowledge and applicable regulatory guidelines and legal requirements.

Figure 1: Overview of vaccine development and approval stages



Development

Like all medicines, COVID-19 vaccines are first tested in the **laboratory** (e.g. studies on their pharmaceutical quality and studies to check first the effects in laboratory tests and animals).

Vaccines are then tested in human **volunteers** in studies called clinical trials. These tests help confirm how the vaccines work and, importantly, to evaluate their **safety** and protective **efficacy**.

Standard vaccine development

Standard vaccine development is a long process and studies are done in sequential steps.

Companies first make **small batches** and do small scale studies to characterise and optimise the production process. They perform studies to determinate a suitable formulation that can keep vaccine components **stable** to the end of its shelf life.

Then the company decides whether to continue development and scale up production. To assure that the vaccine meets its intended quality profile and complies with regulatory standards, the company develops a suitable and effective **quality control** strategy.

Studies on pharmaceutical quality look at the individual vaccine components, the final formulation to be used and at

the whole **manufacturing process** in detail.

The vaccine developer conducts more studies in laboratory models, using **in vitro** studies (e.g. cells in culture) or animal models (**in vivo** studies), to show how the vaccine triggers an immune response and works to prevent infection.

Finally, the vaccine developer studies the vaccine in three phases of **clinical trials**, with larger numbers of volunteers in each phase.

For approval, companies must also show that large scale **commercial manufacturing** consistently produces vaccines of the required quality.

Scaling up production and adaptations to commercial manufacturing can continue in the post-authorisation phase.

Did you know..?

Clinical trials in human medicines, including those for COVID-19 vaccines, are authorised and managed at national level in the EU. National competent authorities and **ethics committees** ensure that studies are scientifically sound and conducted in an ethical manner.

Human pharmacology studies (phase I trials) generally involve between 20 and 100 healthy volunteers to confirm if the medicine behaves as expected based on laboratory tests. This can establish:

- if the vaccine triggers the expected immune response;
- if the vaccine is safe to move into larger studies;
- which doses can be adequate.

Therapeutic exploratory studies (phase II trials) involve several hundred volunteers. The purpose of this phase is to study the best **doses** to use, the most common **side effects** and how many doses are needed.

These studies also check that the vaccine triggers a good immune response in a broader population. In certain cases, it could also provide some preliminary indications of how well the vaccine will work (efficacy).

Clinical efficacy and safety studies (phase III trials) include thousands of volunteers. This phase shows how **efficacious** the vaccine is at protecting against the infection compared with placebo (dummy) or alternative treatment and what are the less common side effects in those receiving the investigational vaccine.

The reduction in number of people with symptoms, severe disease or diagnosed with the infection can help to measure the efficacy of the vaccine.

For information on **ongoing COVID-19 clinical trials** in the European Economic Area (EEA), see:

- Clinical trials in human medicines
- Approval of vaccines in the European Union: European Vaccination Information Portal
- Authorisation of medicines

Fast-track vaccine development in a public health emergency

Vaccine development for COVID-19 vaccines continues to be fast-tracked globally. Development is compressed in time, applying the extensive knowledge on vaccine production gained with existing vaccines.

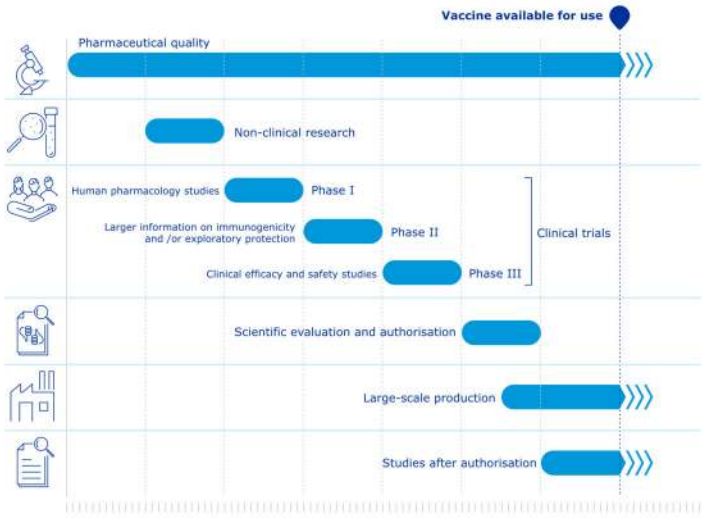
Early **scientific advice** from regulators helps speed up development. EMA additionally offers informal consultation with its COVID-19 Task Force (ETF) and rapid scientific advice. COVID-19 vaccine developers can receive prompt guidance and direction on the best methods and **study designs** to generate robust **data**. For more information, see:

- Early support for medicine and vaccine developers

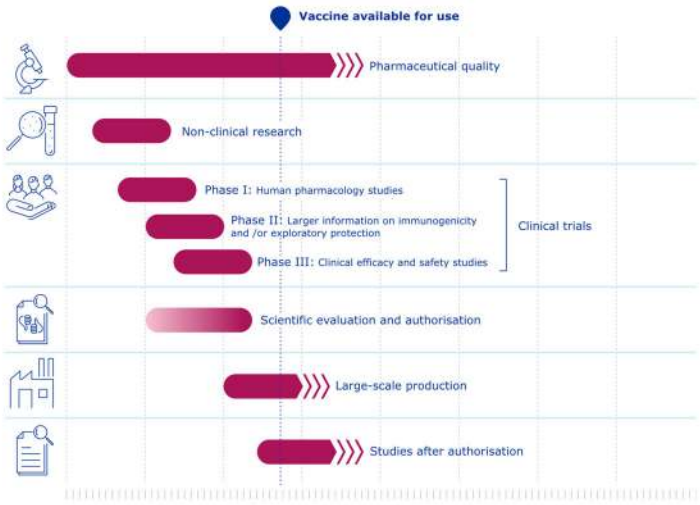
- COVID-19 medicines that have received EMA advice

Advising companies on regulatory requirements helps ensure that standards of **quality**, **safety** and **efficacy** are embedded early in the process and are taken into consideration when planning fast track development. Channeling resources and efforts at various levels ensures that high standards are maintained in the development and in the assessment of the dossiers.

Figure 2: Indicative timelines for COVID-19 vaccines compared with standard vaccines



Standard vaccines



COVID-19 vaccines

Vaccine manufacturers and academics use established **production systems** already used for **safe and effective vaccines**. In addition, they continuously research novel approaches to producing and developing vaccines, and some of the advances made to date are also applied to developing vaccines for COVID-19.

Some vaccines for COVID-19 are developed using **novel methods** intended to increase the **volume** and **speed of production** compared to other types of vaccines, enhance product stability and bring about strong immune responses.

Other vaccines are developed using existing methods used for vaccines for other diseases, making it easier to use **existing production facilities** to produce COVID-19 vaccines at a large scale.

EMA public stakeholder meeting COVID 19 - How are COVID 19 vaccines developed

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Companies may use various approaches to reduce **development timelines while ensuring high standards and adherence to legal requirements**, such as:

- mobilising more human resources simultaneously to analyse results from earlier studies more quickly and map out next steps in terms of resources, funding and regulatory strategy;
- combining clinical trial phases or conducting some studies in parallel where safe to do so.

Companies have also expanded **manufacturingcapacity** and large-scale production to facilitate **vaccine deployment** without delay once approved. In the EU, the European Commission has provided support to facilitate vaccine development and deployment as quickly as possible.

Some vaccine developers started **manufacturing** their COVID-19 vaccine before obtaining an EU marketing authorisation. This allowed them to be ready to **distribute** doses rapidly enough to meet demand once they were authorised.

Developers must still uphold the same **good manufacturing practice** (GMP) standards that apply in the EU to all vaccines.

All pharmaceutical manufacturers need a **manufacturing licence** from the national competent authority where they operate. National competent authorities carry out **GMP inspections** to check that manufacturers comply with EU

standards, the conditions of their licence and the marketing authorisation if obtained.

The European medicines regulatory network has sped up the approval of new **manufacturing lines** and **manufacturing sites** for COVID-19 vaccines. The EU's labelling and packaging requirements are also more flexible for COVID-19 vaccines to enable rapid roll-out.

For more information, see:

- COVID-19 medicines
- Good manufacturing practice
- COVID-19 guidance: assessment and marketing authorisation - Labelling flexibilities for COVID-19 vaccines
- European Commission - HERA Incubator to anticipate the threat of coronavirus variants

Figure 3: Key components of vaccine development - standard vaccines compared with COVID-19 vaccines

Regulatory standards

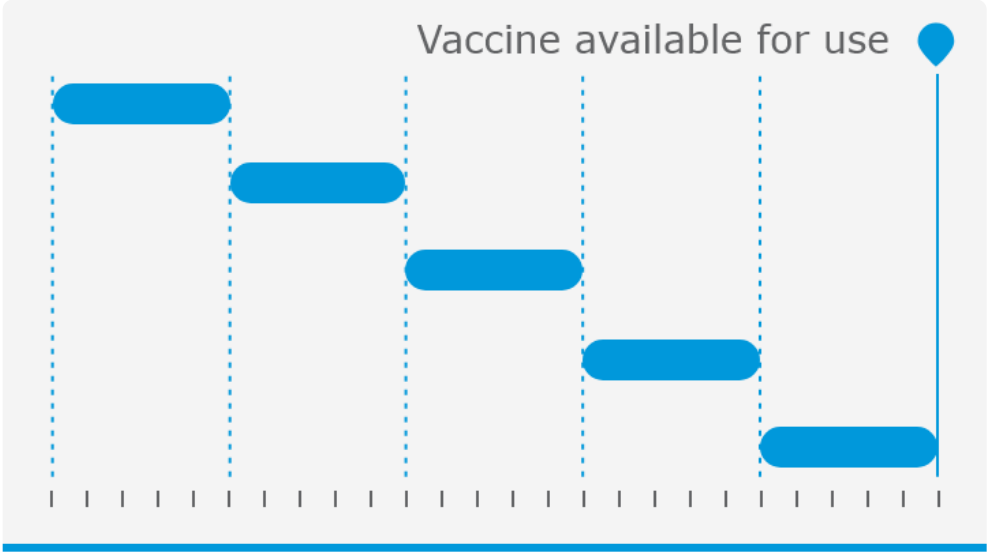
COVID-19 vaccines must be approved according to the same standards that apply to all medicines in the EU

Standard vaccines

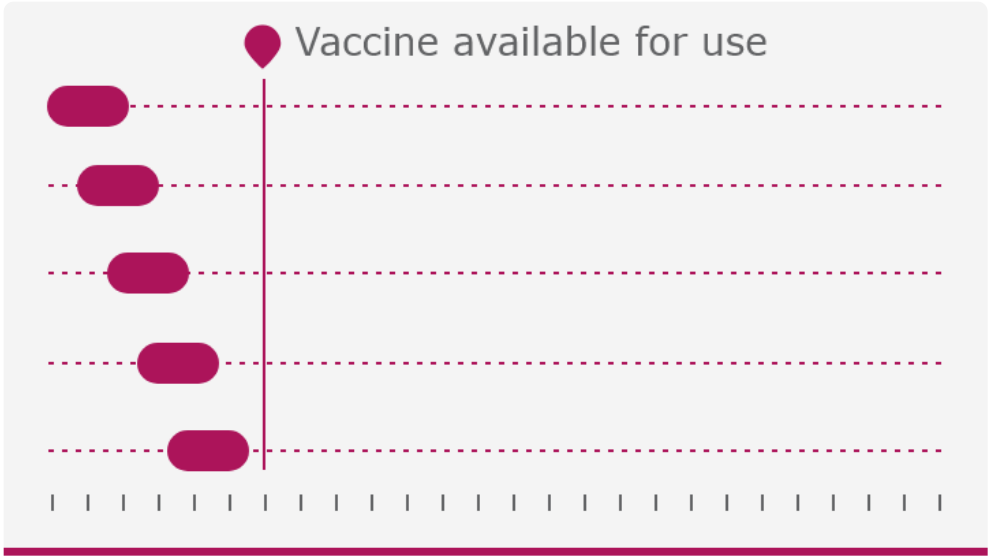
COVID-19 vaccines

Development

COVID-19 vaccine development is compressed in time, applying the extensive current knowledge on vaccine development.



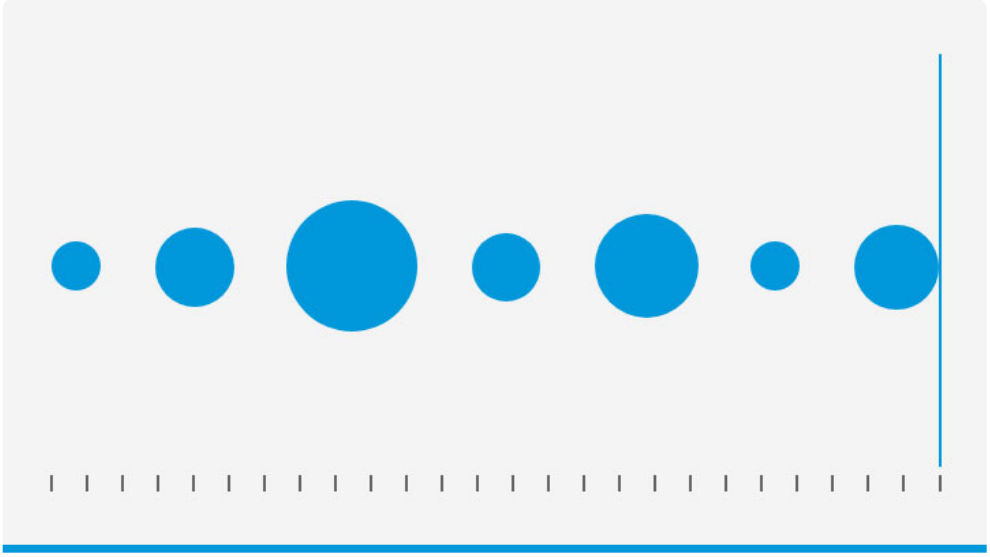
Standard vaccines



COVID-19 vaccines

Resources

COVID-19 vaccine development mobilises more resources simultaneously.



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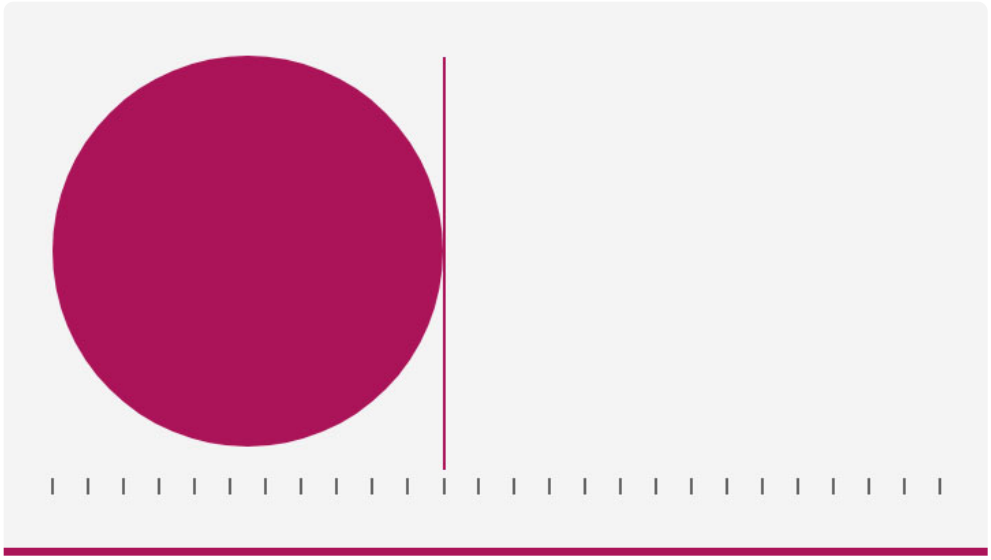
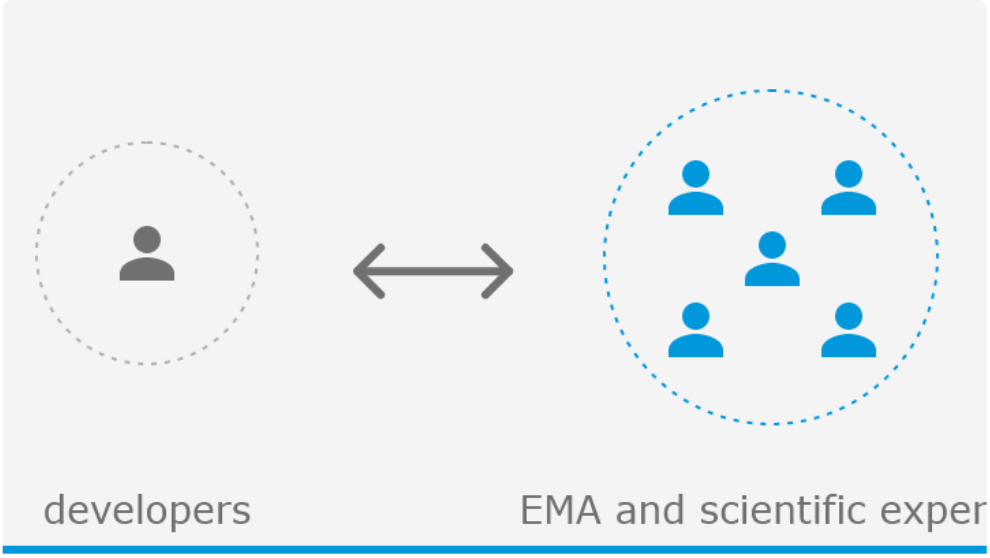


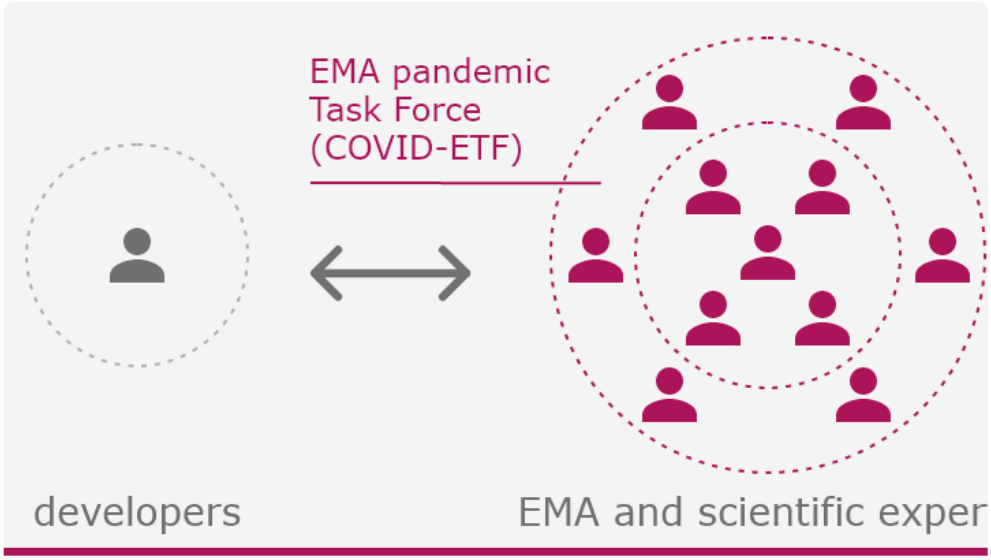
COVID-19 vaccines

Continuous dialogue

COVID-19 vaccine development is supported by early, continuous dialogue between developers and a dedicated group of regulatory experts.



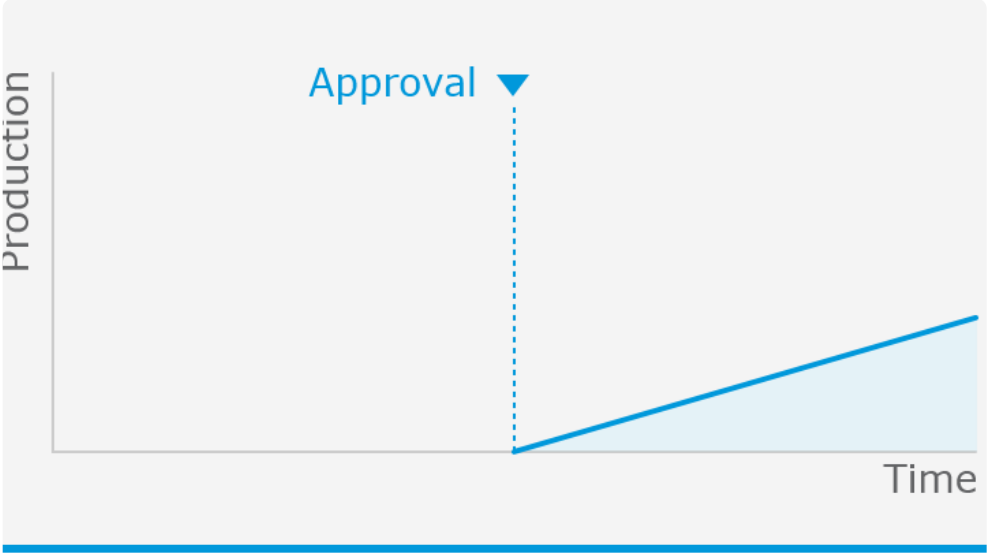
Standard vaccines



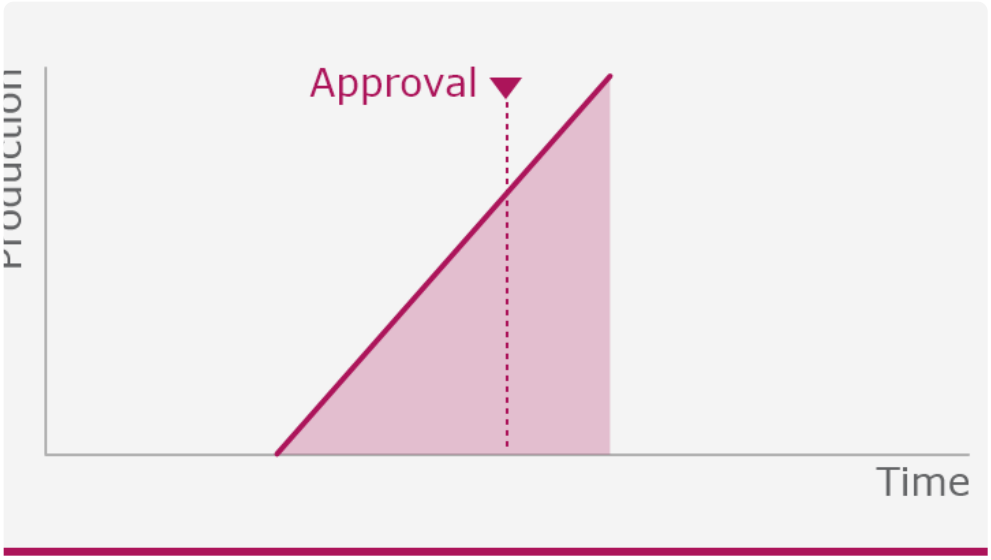
COVID-19 vaccines

Manufacturing

Companies are expanding manufacturing and production capacity to ensure efficient vaccine deployment.



Standard vaccines



COVID-19 vaccines

Did you know..?

EMA is not involved in providing **incentives** to developers of COVID-19 vaccines, other than enabling access to regulatory procedures, such as providing free scientific advice for vaccine development. EMA also has no role in negotiating potential **vaccine availability**, funding or deployment at EU or national level.

For more information on these topics, see:

- European Commission: Safe COVID-19 vaccines for Europeans
- Decisions on vaccines in use in different European countries: European Vaccination Information Portal

Scientific evaluation and approval

COVID-19 vaccines can only be approved and used if they comply with all the requirements of **quality**, **safety** and **efficacy** set out in the EU pharmaceutical legislation. For more information, see Authorisation of medicines.

In view of the pandemic, EMA and regulatory agencies in Europe are diverting **resources** to speed up processes and reduce **timelines** for the evaluation and authorisation of COVID-19 vaccines.

EMA public stakeholder meeting COVID 19 - EU's regulatory process for evaluation and approval

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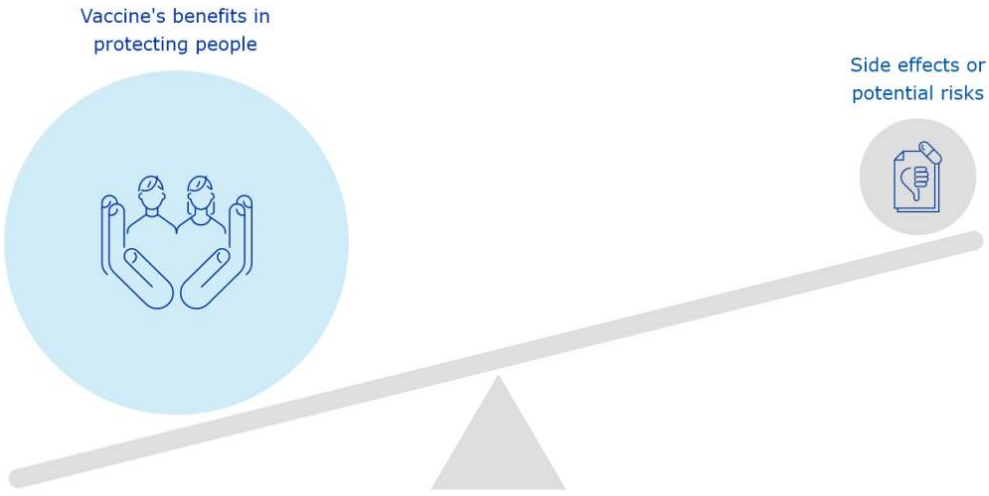
Robust regulatory framework and scientific expertise in the EU

The EU's pharmaceutical legislation ensures that vaccines are only approved after scientific evaluation has demonstrated that their overall benefits outweigh their risks.

A vaccine's benefits in protecting people against COVID-19 must be far greater than any **side effect** or potential risks.



EMA ensures that scientific **experts** evaluating medicines do not have any financial or other interests that could affect

their impartiality. For more information see Handling competing interests.

A high level of transparency, which opens EMA's scientific evaluation work to public scrutiny, safeguards the **independence** of EMA's scientific evaluations. For more information, see Transparency: exceptional measures for COVID-19 medicines.

Scientific evaluation and approval processes

To gain approval for a vaccine in the EU, the vaccine developer submits the results of all testing / investigations to the medicines regulatory authorities in Europe. This is part of a marketing authorisation application.

Figure 4: Evaluation and approval steps for COVID-19 vaccines

Most COVID-19 vaccines in the EU will be evaluated by EMA via the centralised procedure (which is mandatory for any vaccine using **biotechnology**).

EMA's expert scientific committees on human medicines (CHMP and PRAC) carry out EMA's evaluations. EMA has set up the multidisciplinary COVID-19 EMA pandemic Task Force (COVID-ETF) bringing together key experts from across the European medicines regulatory network to ensure a fast and coordinated response to the pandemic.

EMA also collaborates with international experts during the review of COVID-19 vaccines through the OPEN initiative, launched in December 2020. OPEN allows non-EU regulators from Australia, Canada, Japan, Switzerland, as well as WHO, to take part as observers in the scientific evaluation of EMA's ETF and CHMP, while maintaining their scientific and regulatory independence.

For more information see:

- The evaluation of medicines, step-by-step
- Authorisation of medicines
- From laboratory to patient: the journey of a centrally authorised medicine
- Committees, working parties and other groups
- EMA COVID-19 assessments 'OPEN' to non-EU regulators (04/02/2021)
- World Health Organization (WHO)

Did you know..?

A vaccine is introduced into national healthcare systems only after regulatory approval and thorough quality control. The details differ for each EU Member State but each batch released onto the EU market is always tested prior to release.

Stringent **testing** is done by the company holding the marketing authorisation and batches must meet the specifications approved by authorities.

For vaccines used in public health **immunisation programmes**, an official medicines control laboratory performs an additional independent control for each batch of vaccine. This independent control is referred to as Official Control Authority Batch Release (OCABR) and includes testing of agreed quality parameters and compliance check of the manufacturer's own test results.

For more information, see:

- European Directorate for the Quality of Medicines
- European Vaccination Information Portal

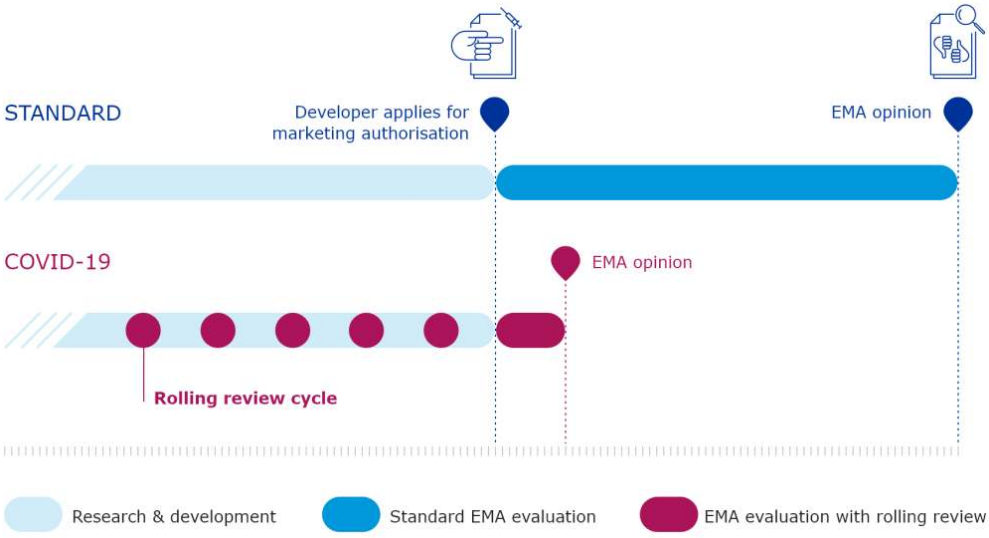
Accelerated evaluation

According to the EU pharmaceutical legislation, the standard timeline for the evaluation of a medicine is a maximum of 210 active days.

However, EMA treats marketing authorisation applications for COVID-19 products in an expedited manner. This allows the timeline for evaluation to be reduced to less than 150 working days.

For this scope, EMA can use its rolling review procedure for promising medicines for COVID-19. This allows EMA to begin assessing data as they become available during the development process, to expedite the subsequent formal marketing authorisation application assessment even further.

Figure 5: Standard evaluation process compared with rolling review of COVID-19 vaccines



When an evaluation is complete, EMA has the option of recommending a conditional marketing authorisation, a type of approval for medicines addressing unmet medical needs, and in particular those to be used in emergency situations in response to public health threats recognised by the WHO or the EU.

For more information, see Accelerated procedures for COVID-19 treatments and vaccines.

Did you know..?

A **conditional marketing authorisation** guarantees that the approved vaccine:

- meets rigorous EU standards for safety, efficacy and quality
- is manufactured and controlled in approved, certified facilities in line with high pharmaceutical standards that are compatible with large-scale commercialisation.

Conditional marketing authorisation is a tool that allows regulators to approve a medicine quickly and in a pragmatic manner when there is an urgent need.

A conditional marketing authorisation is different from an **emergency use authorisation**, which some countries use to permit the temporary use of an unauthorised medicine in an emergency situation. An emergency use authorisation is not a marketing authorisation.

EU legislation foresees that conditional marketing authorisation is used as the fast-track authorisation procedure during public health emergencies to speed up approval and save lives.

It is the most appropriate tool to grant access to a vaccine to all EU citizens at the same time and to underpin mass vaccination campaigns.

Monitoring vaccine effectiveness, safety and real-life use

The scientific evaluation needs to show that a vaccine's benefits in protecting people against a specific disease, like COVID-19, are far greater than any potential risk.

Like any medicine, vaccines have benefits and risks. Even highly effective vaccines are not one hundred per cent effective in preventing disease or one hundred per cent safe in all vaccinated people.

At the time of approval, the main body of **evidence** for vaccine safety and efficacy comes from large, controlled, randomised clinical trials. As part of such trials, selected volunteers are randomly given either the vaccine being tested or a placebo injection. They are then monitored under controlled conditions, in line with strict protocols.

After approval, many people will be vaccinated. Certain rare or very rare **side effects** may only emerge when millions of people are vaccinated. EU law requires that the safety of vaccines is monitored while they are in use in routine clinical practice.

Safety information on COVID-19 vaccines is available:

- Safety of COVID-19 vaccines

Standard monitoring

The EU has a comprehensive **safety monitoring** and **risk management** (pharmacovigilance) system, which ensures measures are in place for:

- providing advice to minimise risk;
- reporting suspected side effects;
- conducting studies after authorisation;
- detecting any potential side effects;
- conducting rigorous scientific assessments of all safety data;
- introducing any necessary mitigating actions early on.

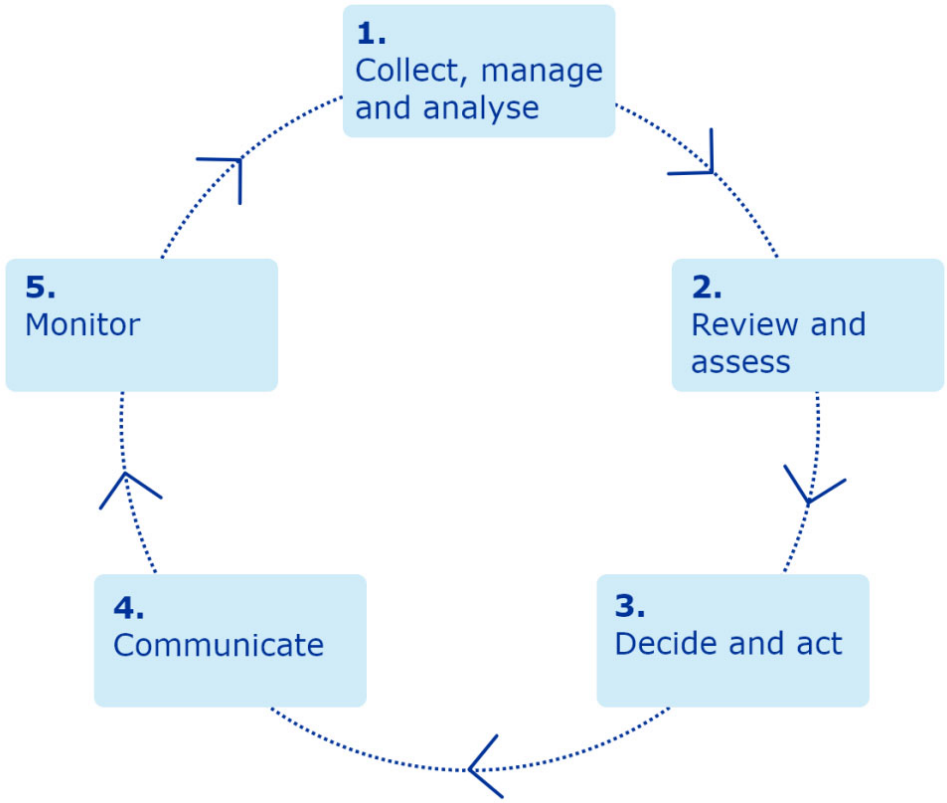
Competent authorities may carry out safety and efficacy studies after authorisation and can also require a marketing authorisation holder to carry out such studies as an obligation of the authorisation. Public health authorities responsible for vaccination programmes will also conduct other studies.

Studies collecting effectiveness data give additional information, for example, on **long-term protection,** on the need for and timing of **booster** doses, or on the effectiveness of a vaccine against new variants, to complement the 'efficacy' data obtained in clinical trials before the vaccine was authorised.

For more information, see:

- Pharmacovigilance: Overview.
- Monitoring vaccine safety and reporting side effects: European Vaccination Information Portal

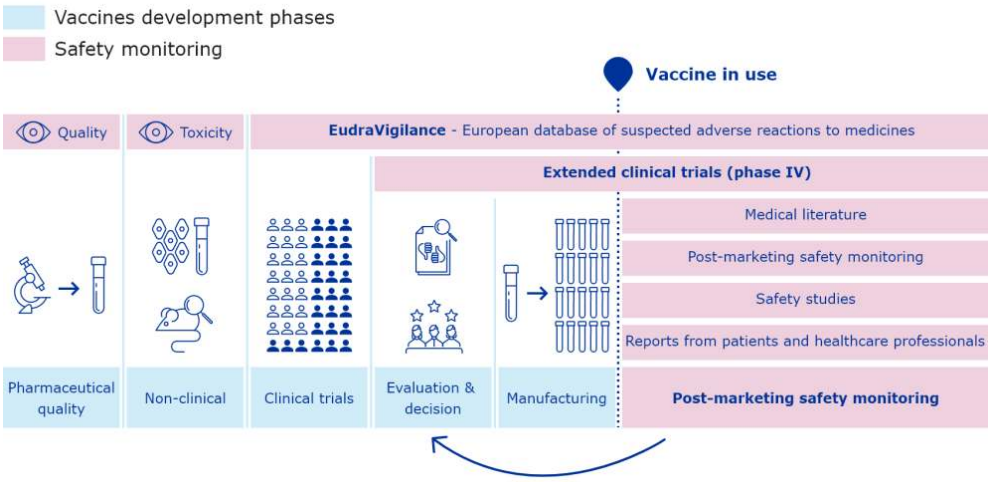
Figure 6: Pharmacovigilance cycle



Large scale monitoring activities in the pandemic context

Regulators and vaccine developers are also mobilising extra resources to **monitor safety** and manage risk during the **pandemic**. This is important because exceptionally large numbers of people receive COVID-19 vaccines once they are authorised; many more than the large numbers who have been receiving the vaccines in clinical trials. In addition, people vaccinated as part of mass vaccination campaigns are more diverse than those selected to take part in trials.

Figure 7: How vaccine safety is studied



The pharmacovigilance plan for COVID-19 vaccines sets out how EMA and the national competent authorities in the EU Member States identify and evaluate any new information that arises promptly, including any safety signals that are relevant for the benefit-risk balance of these vaccines:

- Pharmacovigilance plan of the EU Regulatory Network for COVID-19 vaccines

This plan also ensures that regulators can take any appropriate regulatory actions and communicate these to the public as quickly as possible.

The **monitoring** activities in the plan apply to all vaccines, but they take place on a larger scale during this pandemic:

- Collecting exposure data to COVID-19 vaccines
- Adopting specific safety signal detection and management measures
- Setting up a European infrastructure for monitoring COVID-19 treatments and vaccines
- Using real-world data from clinical practice
- Applying exceptional transparency measures

EMA's guidance on preparing risk management plans for COVID-19 vaccines helps marketing authorisation applicants develop risk management plans for COVID-19 vaccines:

- Risk management for COVID-19 vaccines

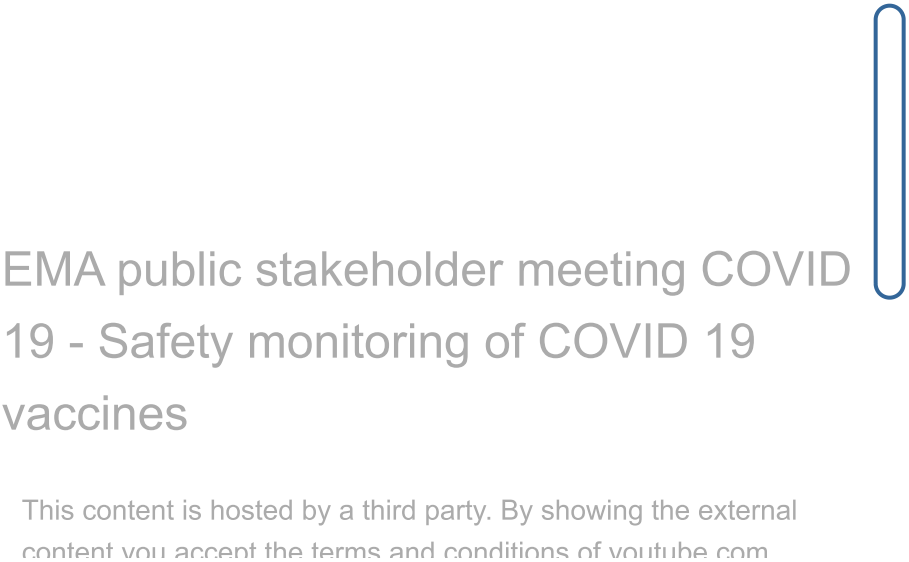
These risk management plans set out how the company will monitor and report on safety and how it will characterise

and manage risks following authorisation of a COVID-19 vaccine.

For a period of at least six months after authorisation, companies responsible for COVID-19 vaccines need to submit monthly safety summaries for COVID-19 vaccines, in addition to periodic safety update reports. They also need to put processes in place to manage a high volume of safety reports. They need to carry out further studies on COVID-19 vaccines that receive a conditional marketing authorisation.

Additional considerations in this guidance address traceability tools that can help record who has received which vaccine and from which batch.

EMA publishes the full body of the risk management plans for all authorised COVID-19 vaccines, in line with its exceptional transparency measures for COVID-19 medicines.



For more information, see:

- Treatments and vaccines for COVID-19: post-authorisation
- Transparency: exceptional measures for COVID-19 medicines
- Pharmacovigilance: Overview

Related content

- Public stakeholder meeting: development and authorisation of safe and effective COVID-19 vaccines in the EU (11/12/2020)
- Authorisation of medicines
- From laboratory to patient: the journey of a centrally authorised medicine
- The evaluation of medicines, step-by-step
- COVID-19 medicines
- COVID-19 vaccines: key facts
- Clinical trials in human medicines
- Pharmacovigilance: Overview

Related documents

EMA considerations on COVID-19 vaccine approval

Adopted
First published:
19/11/2020
Reference Number:
EMA/592928/2020

English (EN) (205.33 KB - PDF)
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External links

- European Commission: Safe COVID-19 vaccines for Europeans
- European Vaccination Information Portal

- European Council: COVID-19 vaccines: Why so fast?
- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): Report on the "ENCePP in the time of COVID" virtual ENCePP Plenary meeting

Publications

- The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines

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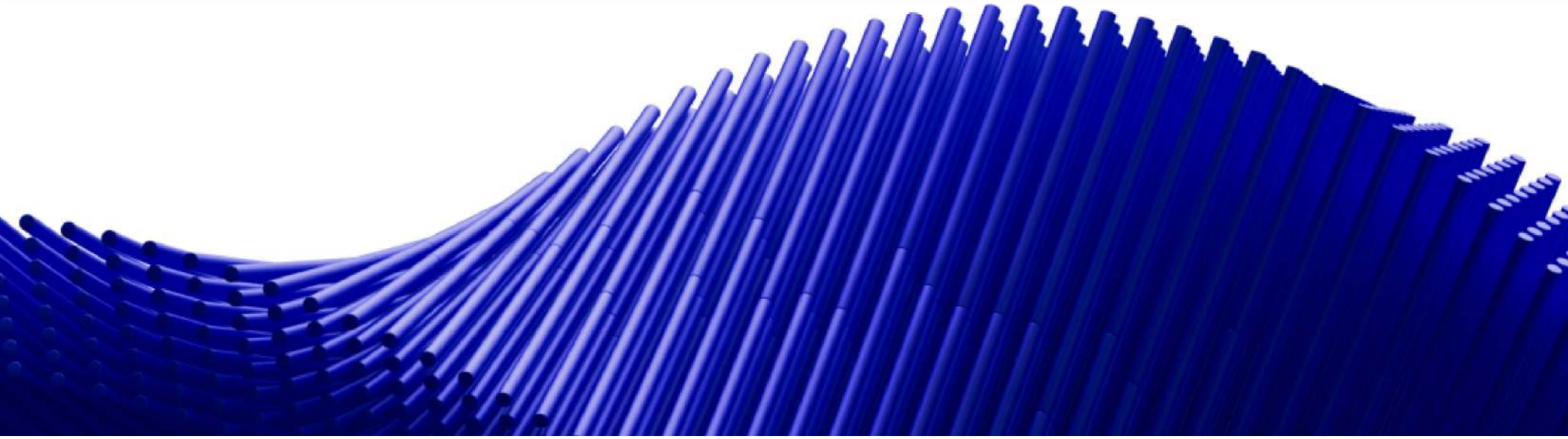

Pfizer Press release Covid-19 Vaccines

Pfizer Outlines Five-Point Plan to Battle COVID-19

Friday, March 13, 2020 - 03:25pm

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Dr. Albert Bourla, Chairman and CEO, made the following statement:

“In this troubling time, Pfizer is committed to doing all we can to respond to the COVID-19 pandemic. Many companies, including Pfizer, are working to develop antiviral therapies to help infected patients fight this emerging virus as well as new vaccines to prevent infection and halt the further spread of this disease. Pfizer is working to advance our own potential antiviral therapies and is engaged with BioNTech on a potential mRNA coronavirus vaccine. We are committed to work as one team across the industry to harness our scientific expertise, technical skills and manufacturing capabilities to combat this evolving crisis.”

Pfizer is making five promises that will help scientists more rapidly bring forward therapies and vaccines to protect humankind from this escalating pandemic and prepare the industry to better respond to future global health crises.

1. **Sharing tools and insights:** With very little known about this virus, many are working to develop cell-based assays, viral screening, serological assays, and translational models to test potential therapies and vaccines. Pfizer is committed to making the vital tools we develop available on an open source platform to the broader scientific community and to sharing the data and learnings gained with other companies in real time to rapidly advance therapies and vaccines to patients.

2. **Marshalling our people:** Human capital is our most valuable resource. Pfizer has created a SWAT team of our leading virologists, biologists, chemists, clinicians, epidemiologists, vaccine experts, pharmaceutical scientists and other key experts to focus solely on addressing this pandemic. This team is applying their passion, commitment and

existing therapies for activity against the virus causing COVID-19, but some lack the experience in late stage development and navigating the complex regulatory systems. Pfizer is committed to sharing our clinical development and regulatory expertise to support the most promising candidates these companies bring forward.

4. **Offering our manufacturing capabilities**: Once a therapy or vaccine is approved it will need to be rapidly scaled and deployed around the world to put an end to this pandemic. As one of the largest manufacturers of vaccines and therapeutics, Pfizer is committed to using any excess manufacturing capacity and to potentially shifting production to support others in rapidly getting these life-saving breakthroughs into the hands of patients as quickly as possible.

5. **Improving future rapid response:** Finally, to address future global health threats, Pfizer is reaching out to federal agencies including NIH, NIAID and CDC to build a cross-industry rapid response team of scientists, clinicians and technicians able to move into action immediately when future epidemics surface.

“In recent years, the biopharmaceutical industry has brought forward some of the most impactful medical breakthroughs known to society, from therapies for HIV and cancer that have extended millions of lives to novel gene therapies that are seeing cure-like outcomes for some the most devastating rare diseases,” said Albert Bourla. “Pfizer calls on all members of the innovation ecosystem – from large pharmaceutical companies to the smallest of biotech companies, from government agencies to academic institutions – to commit to work together in addressing this dire crisis. With our combined efforts we know that there is no health challenge that we cannot overcome.”

Disclosure Notice: The information contained in this release is as of March 13, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

uncertainties regarding the results of screening and the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable pre-clinical or clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications for any potential antiviral compounds may be filed or approved in any jurisdictions, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of any such products; our manufacturing capabilities; and competitive developments. A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10- K for the fiscal year ended December 31, 2019 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to

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Pfizer and BioNTech to Co-Develop Potential COVID-19 Vaccine

03/17/2020

Companies will jointly develop BioNTech's mRNA-based vaccine candidate BNT162 to prevent COVID-19 infection

Collaboration aims to accelerate global development of BNT162, leveraging expertise and resources of both companies

Builds on 2018 agreement to jointly develop an mRNA-based influenza vaccine

NEW YORK & MAINZ, Germany--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE, "Pfizer") and BioNTech SE (Nasdaq: BNTX, "BioNTech") today announced that the companies have agreed to a letter of intent regarding the co-development and distribution (excluding China) of a potential mRNA-based coronavirus vaccine aimed at preventing COVID-19 infection. The companies have executed a Material Transfer and Collaboration Agreement to enable the parties to immediately start working together.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20200316005943/en/

The collaboration aims to accelerate development of BioNTech's potential first-in-class COVID-19 mRNA vaccine program, BNT162, which is expected to enter clinical testing by the end of April 2020. The rapid advancement of this collaboration builds on the research and development collaboration into which Pfizer and BioNTech entered in 2018 to develop mRNA-based vaccines for prevention of influenza.

"We are proud that our ongoing, successful relationship with BioNTech gives our companies the resiliency to mobilize our collective resources

with extraordinary speed in the face of this worldwide challenge," said Mikael Dolsten, Chief Scientific Officer and President, Worldwide Research, Development & Medical, Pfizer. "We believe that by pairing Pfizer's development, regulatory and commercial capabilities with BioNTech's mRNA vaccine technology and expertise as one of the industry leaders, we are reinforcing our commitment to do everything we can to combat this escalating pandemic, as quickly as possible."

"This is a global pandemic, which requires a global effort. In joining forces with our partner Pfizer, we believe we can accelerate our effort to bring a COVID-19 vaccine to people around the world who need it," said Ugur Sahin, Co-Founder and CEO of BioNTech.

The companies expect to utilize multiple research and development sites from both companies, including in the United States and Germany, to house the activities identified by the collaboration agreement.

The companies will begin collaborating immediately. They will finalize details of the agreement regarding financial terms, and all activities related to development, manufacturing and potential commercialization over the next few weeks.

On March 13, 2020, Pfizer issued a five-point plan calling on the biopharmaceutical industry to join the company in committing to unprecedented collaboration to combat COVID-19.

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150

years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Pfizer Disclosure Notice:

The information contained in this release is as of March 17, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer's efforts to combat COVID-19, BioNTech's potential COVID-19 mRNA vaccine, BNT162, a letter of intent regarding the co-development and co-commercialization (excluding China) by Pfizer and BioNTech of BNT162 and a Material Transfer and Collaboration Agreement, including their potential benefits, and the expected timing of a Phase 1 trial, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, whether and when a definitive agreement will be reached for the co-development and co-commercialization by Pfizer and BioNTech of BNT162 ; uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from the clinical studies; whether and when any biologics license applications may be filed in any other jurisdictions for BNT162 or any other vaccine candidates under the collaboration; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if

approved, whether BNT162 will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of BNT162; uncertainties regarding the ability to obtain recommendations from vaccine technical committees and other public health authorities regarding BNT162 and uncertainties regarding the commercial impact of any such recommendations; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov *and* www.pfizer.com.

About BioNTech

Biopharmaceutical New Technologies (BioNTech) is a next generation immunotherapy company pioneering novel therapies for cancer and other serious diseases. The company exploits a wide array of computational discovery and therapeutic drug platforms for the rapid development of novel biopharmaceuticals. Its broad portfolio of oncology product candidates includes individualized and off-the-shelf mRNA-based therapies, innovative chimeric antigen receptor T cells, bi-specific checkpoint immuno-modulators, targeted cancer antibodies and small molecules. Based on its deep expertise in mRNA vaccine development and in-house manufacturing capabilities, BioNTech and its collaborators are developing multiple mRNA vaccine candidates for a range infectious diseases alongside its diverse oncology pipeline. BioNTech has established a broad set of relationships with multiple global pharmaceutical collaborators, including Eli Lilly and Company, Genmab, Sanofi, Bayer Animal Health, Genentech, a member of the Roche Group, Genevant, Fosun, and Pfizer.

For more information, please visit www.BioNTech.de.

Forward-looking statement

This press release contains "forward-looking statements" of BioNTech within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, the ability of BioNTech to develop and commercialize a vaccine for COVID-19, BioNTech's potential COVID-19 mRNA vaccine, BNT162, a letter of intent regarding the co-development and co-commercialization (excluding China) by Pfizer and BionNTech of BNT162 and a Material Transfer and Collaboration Agreement, including their potential benefits, and the expected timing of a Phase 1 trial of BNT162. Any forward-looking statements in this press release are based on BioNTech's current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: competition to create a vaccine for Covid-19 and potential difficulties. For a discussion of these and other risks and uncertainties, see the section entitled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in BioNTech's Registration Statement on Form F-1 filed with the SEC on September 9, 2019, as amended, which has been filed with the SEC and is available on the SEC's website at www.sec.gov. All information in this press release is as of the date of the release, and BioNTech undertakes no duty to update this information unless required by law.

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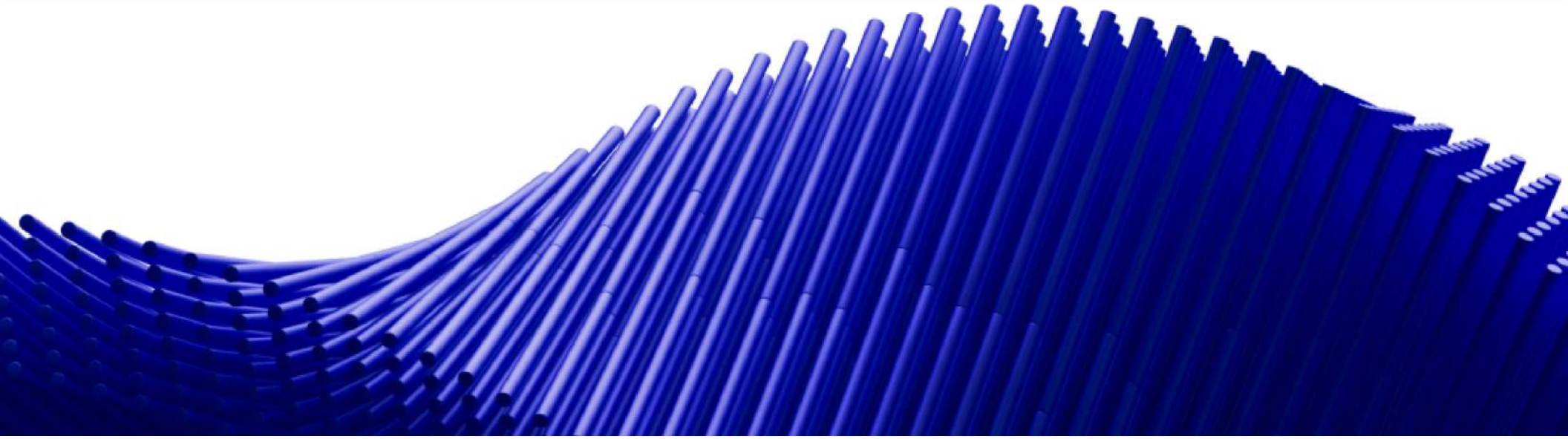

Pfizer Press release Covid-19 Partnerships Vaccines

Pfizer and BioNTech Announce Further Details on Collaboration to Accelerate Global COVID-19 Vaccine Development

Thursday, April 09, 2020 - 07:50am

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and approval by regulatory authorities, and then rapidly scale up capacity to produce hundreds of millions of doses in 2021.

- *BioNTech will contribute multiple mRNA vaccine candidates as part of its BNT162 COVID-19 vaccine program, which are expected to enter human testing in April 2020*
- *Pfizer will contribute its leading global vaccine clinical research and development, regulatory, manufacturing and distribution infrastructure and capabilities*
- *BioNTech will receive an upfront payment of $185 million, including an equity investment of approximately $113 million, and be eligible to receive future milestone payments of up to $563 million for a potential total consideration of $748 million*

MAINZ, Germany & NEW YORK--(BUSINESS WIRE)-- BioNTech SE (Nasdaq: BNTX, “BioNTech” or “the Company”), and Pfizer Inc. (NYSE: PFE) today disclosed additional details of their collaboration to advance candidates from BioNTech’s mRNA vaccine program, previously announced on March 17, 2020.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20200409005405/en/

BIONTECH

The collaboration aims to rapidly advance multiple COVID-19 vaccine candidates into human clinical testing based on BioNTech’s proprietary mRNA vaccine platforms, with the objective of ensuring rapid worldwide access to the vaccine,

States and Europe across multiple sites. BioNTech and Pfizer intend to initiate the first clinical trials as early as the end of April 2020, assuming regulatory clearance.

During the clinical development stage, BioNTech and its partners will provide clinical supply of the vaccine from its GMP-certified mRNA manufacturing facilities in Europe. BioNTech and Pfizer will work together to scale-up manufacturing capacity at risk to provide worldwide supply in response to the pandemic. BioNTech and Pfizer will also work jointly to commercialize the vaccine worldwide (excluding China, which is already covered by BioNTech's collaboration with Fosun Pharma) upon regulatory approval.

"Combatting the COVID-19 pandemic will require unprecedented collaboration across the innovation ecosystem, with companies coming together to unite capabilities like never before," said Mikael Dolsten, Chief Scientific Officer and President, Worldwide Research, Development & Medical, Pfizer. "I am proud of Pfizer's collaboration with BioNTech and have every confidence in our ability to harness the power of science – together – to bring forth a potential vaccine that the world needs as quickly as possible."

"We have already started working with Pfizer on our COVID-19 vaccine and are pleased to announce these further details of our ongoing collaboration, which reflects both companies' strong commitment to move quickly to bring a safe and efficacious vaccine to patients worldwide," says Co-Founder and CEO of BioNTech, Ugur Sahin, M.D.

Under the terms of the agreement, Pfizer will pay BioNTech $185 million in upfront payments, including a cash payment of $72 million and an equity investment of $113 million. BioNTech is eligible to receive future milestone payments of up to $563 million for a potential total consideration of $748 million. Pfizer and BioNTech will share

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Pfizer Disclosure Notice

The information contained in this release is as of April 9, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer's efforts to combat COVID-19, BioNTech's mRNA vaccine program, BNT162, a collaboration between BioNTech and Pfizer to develop a potential COVID-19 vaccine and manufacturing capacity, including their potential benefits, and the expected timing of clinical trials and potential supply, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties

clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from the clinical studies; whether and when any biologics license applications may be filed in any jurisdictions for any potential vaccine candidates under the collaboration; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether any such vaccine candidates will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of any such vaccine candidates, including development of products or therapies by other companies; manufacturing capabilities or capacity; uncertainties regarding the ability to obtain recommendations from vaccine technical committees and other public health authorities regarding any such vaccine candidates and uncertainties regarding the commercial impact of any such recommendations; and competitive developments.

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About BioNTech

Biopharmaceutical New Technologies (BioNTech) is a next generation immunotherapy company pioneering novel therapies for cancer, infectious diseases and rare diseases. The company exploits a wide array of computational

pipeline. Its broad portfolio of product candidates includes individualized and off-the-shelf mRNA-based therapies, innovative chimeric antigen receptor T cells, bi-specific checkpoint immuno-modulators, targeted cancer antibodies and small molecules. BioNTech has established a broad set of relationships with multiple global pharmaceutical collaborators, including Eli Lilly and Company, Genmab, Sanofi, Bayer Animal Health, Genentech, a member of the Roche Group, Genevant, Fosun Pharma, and Pfizer.

For more information, please visit www.BioNTech.de

BioNTech Forward-looking statements

This press release contains "forward-looking statements" of BioNTech within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, BioNTech's efforts to combat COVID-19, the ability of BioNTech and Pfizer to co-develop and co-commercialize a vaccine for COVID-19, the ability of BioNTech and Pfizer to develop manufacturing capacity, BioNTech's potential COVID-19 mRNA vaccine, BNT162, an agreement regarding the co-development and co-commercialization by Pfizer and BioNTech of BNT162, including its potential benefits and the expected timing of a Phase 1 trial of BNT162. Any forward-looking statements in this press release are based on BioNTech's current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: competition to create a vaccine for Covid-19 and potential difficulties. For a discussion of these and other risks and uncertainties, see the section entitled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in BioNTech's Annual Report on Form 20-F filed with the SEC on March 31, 2020 which has been filed with the SEC and is available on the SEC's website at www.sec.gov. All information in this press

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Read our full disclaimer (https://clinicaltrials.gov/about-site/disclaimer) for details.

UNKNOWN STATUS

A Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-2019 in Healthy and Immunocompromised Adults

ClinicalTrials.gov ID NCT04380701

Sponsor BioNTech SE

Information provided by BioNTech SE (Responsible Party)

Last Update Posted 2022-01-13

Study Details Tab

Study Overview

Brief Summary

This trial has two parts. Part A and Part B. Due to changes in the overall clinical development plan, Part B will no longer be conducted. The objectives originally described for Part B have been implemented in the ongoing development via a pivotal Phase I/II/III trial BNT162-02/C4591001 (ClinicalTrials.gov NCT: 04368728).

Part A is for dose ranging of four different vaccines (BNT162a1, BNT162b1, BNT162b2, and BNT162c2) which will be undertaken with dose escalation and de-escalation plus the evaluation of interim dose levels. It also includes dose ranging in older participants.

The vaccines BNT162a1, BNT162b1, BNT162b2, and BNT162c2 will be administered using a Prime/Boost (P/B) regimen. The vaccine BNT162c2 will also be administered using a Single dose (SD) regimen. Three additional cohorts aged from 18 to 85 years receiving BNT162b2 only.

Feedback

BNT162b2 has entered a Phase II/III evaluation of efficacy, with the intent to support an application for marketing authorization. The dosing regimen under investigation is two BNT162b2 doses given ~21 d apart.

Official Title

A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy and Immunocompromised Adults

Conditions

Infections, Respiratory | Virus Diseases | Infection Viral | Vaccine Adverse Reaction

Intervention / Treatment

- Biological: BNT162a1
- Biological: BNT162b1
- Biological: BNT162b2
- Biological: BNT162c2

Other Study ID Numbers

- BNT162-01
- 2020-001038-36 (EudraCT Number)
- U1111-1249-4220 (Other Identifier) (OTHER: WHO UTN)

Study Start (Actual)

2020-04-23

Primary Completion (Estimated)

2023-04

Study Completion (Estimated)

2023-04

Enrollment (Actual)

512

Study Type

Interventional

Phase

Phase 1
Phase 2

Resource links provided by the National Library of Medicine

MedlinePlus (https://medlineplus.gov/) related topics: Vaccines (https://medlineplus.gov/vaccines.html)

Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/gard) resources: Acute Graft Versus Host Disease (https://rarediseases.info.nih.gov/diseases/6544/acute-graft-versus-host-disease) Severe Acute Respiratory Syndrome (https://rarediseases.info.nih.gov/diseases/9237/sars)

Other U.S. FDA Resources (https://classic.clinicaltrials.gov/ct2/info/fdalinks)

Contacts and Locations

This section provides the contact details for those conducting the study, and information on where this study is being conducted.

Germany

Berlin, Germany
Contract Research Organization

Frankfurt am Main, Germany
Universitäts Klinikum

Heidelberg, Germany
Universitäts Klinikum

Kiel, Germany
Contract Research Organization

Mannheim, Germany
Contract Research Organization

Click to view interactive map

Participation Criteria

Researchers look for people who fit a certain description, called eligibility criteria. Some examples of these criteria are a person's general health condition or prior treatments.

For general information about clinical research, read Learn About Studies (https://clinicaltrials.gov/study-basics/learn-about-studies).

Eligibility Criteria

Description

Inclusion Criteria:

- Have given informed consent by signing the informed consent form (ICF) before initiation of any trial-specific procedures.
- They must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions (e.g., to practice social distancing and to follow good practices to reduce their chances of being infected or spreading COVID-19), and other requirements of the trial.
- They must be able to understand and follow trial-related instructions.
- For younger adult cohorts, volunteers must be aged 18 to 55 years, have a body mass index (BMI) over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. OR For older adult cohorts, volunteers must be aged 56 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0. OR For the immunocompromised adult cohort (Cohort 13), volunteers must be aged 18 to 85 years, have a BMI over 19 kg/m^2 and under 30 kg/m^2, and weigh at least 50 kg at Visit 0.
- They must be healthy, in the clinical judgment of the investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), vital signs (systolic/diastolic blood pressure, pulse rate, body temperature, respiratory rate), and clinical laboratory tests (blood chemistry, hematology, and urine chemistry) at Visit 0. Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. OR For the immunocompromised cohort (Cohort 13); volunteers who have previously received solid organ transplant, or peripheral blood stem cell transplantation ≥6 months after transplantation, or individuals with human immunodeficiency virus (HIV) infection with a CD4+ T-cell count of ≥200 x 10^6 /L at Visit 0. Individuals with lower T-cell counts will be excluded from the trial on the basis that this represents a significant medical complication. In the clinical judgment of the investigator, volunteers must be immunocompromised but otherwise healthy. After consultation with the Medical Monitor, this may include individuals receiving immunosuppressant therapy due to another confounding disease at least 2 weeks prior to enrollment and/or at least 6 weeks following immunization with BNT162b2, and/or individuals with immunosuppressive treatment of an autoimmune disease if the disease is stable.
- Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin urine test at Visit 0 and Visit 1. Women that are postmenopausal or permanently sterilized will be considered as not having reproductive potential.
- WOCBP must agree to practice a highly effective form of contraception during the trial, starting after Visit 0 and continuously until 60 days after receiving the last immunization. WOCBP must agree to require their male partners to use condoms during sexual contact (unless male partners are sterilized or infertile).

- WOCBP must confirm that they practice at least one highly effective form of contraception for the 14 days prior to Visit 0.
- WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting after Visit 0 and continuously until 60 days after receiving the last immunization.
- Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a highly effective form of contraception with their female partner of childbearing potential during the trial, starting after Visit 0 and continuously until 60 days after receiving the last immunization.
- Men must be willing to refrain from sperm donation, starting after Visit 0 and continuously until 60 days after receiving the last immunization.
- They must have confirmation of their health insurance coverage prior to Visit 0.
- They must agree to not be vaccinated during the trial, starting after Visit 0 and continuously until 28 days after receiving the last immunization.

Exclusion Criteria:

- Have had any acute illness, as determined by the investigator, with or without fever, within 72 hours prior to the first immunization. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
- Are breastfeeding on the day of Visit 0 or who plan to breastfeed during the trial, starting after Visit 0 and continuously until at least 90 days after receiving the last immunization.
- Have a known allergy, hypersensitivity, or intolerance to the planned investigational medicinal product (IMP) including any excipients of the IMP.
- Had any medical condition or any major surgery (e.g., requiring general anesthesia) within the past 5 years which, in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
- Have any surgery planned during the trial, starting after Visit 0 and continuously until at least 90 days after receiving the last immunization.
- Had any chronic use (more than 21 continuous days) of any systemic medications, including immunosuppressant's or other immune-modifying drugs (except for Cohort 13), within the 6 months prior to Visit 0 unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise subject safety. Note: Healthy volunteers with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.
- Had any vaccination within the 28 days prior to Visit 0.
- Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Visit 0.
- Had administration of another investigational medicinal product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Visit 0.

- Have a known history of active or ongoing hepatitis B or hepatitis C infection; or except for Cohort 13: HIV-1 or HIV-2 infection within the 30 days prior to Visit 0.
- Have a positive polymerase chain reaction (PCR)-based test for SARS-CoV-2 within the 30 days prior to Visit 1.
- Have a positive drugs of abuse (for amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, opiates, methadone, methamphetamines, phencyclidine, and tricyclic antidepressants) result at Visit 0 or Visit 1.
- Have a positive breath alcohol test at Visit 0 or Visit 1.
- Previously participated in an investigational trial involving lipid nanoparticles.
- Are subject to exclusion periods from other investigational trials or simultaneous participation in another clinical trial. When entering the follow-up phase, i.e., after completing the end of treatment (EoT) visit, subjects are allowed to participate in other clinical trials not investigating COVID-19 vaccines or treatments; subjects immunized with BNT162 vaccines in this clinical trial are allowed to participate in other clinical trials involving immunization with BNT162b2.
- Have any affiliation with the trial site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the trial site).
- Have a history (within the past 5 years) of substance abuse or known medical, psychological, or social conditions which, in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
- Have a history of hypersensitivity or serious reactions to previous vaccinations.
- Have a history of Guillain-Barré Syndrome within 6 weeks following a previous vaccination.
- Have a history of narcolepsy.
- Have history of alcohol abuse or drug addiction within 1 year before Visit 0.
- (Except for Cohort 13) Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Visit 0.
- Have any abnormality or permanent body art (e.g., tattoo) that, in the opinion of the investigator, would obstruct the ability to observe local reactions at the injection site.
- Have had any blood loss >450 mL, e.g., due to donation of blood or blood products or injury, within the 7 days prior to Visit 0 or plan to donate blood during the trial, starting after Visit 0 and continuously until at least 7 days after receiving the last immunization.
- Have symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
- Have had contact with persons diagnosed with COVID-19 or who tested positive for SARS-CoV-2 by any diagnostic test within the 30 days prior to Visit 1.
- Are soldiers, volunteers in detention, contract research organization (CRO) or sponsor staff or their family members.
- Regular receipt of inhaled/nebulized corticosteroids (except for Cohort 13).
- For older volunteers and for Cohort 13 only: Have a condition known to put them at high risk for severe COVID-19, including those with any of the following risk factors:
- Uncontrolled hypertension.

- Diabetes mellitus (HbA1c >8.5% ≥3 months, according to the medical history reported by the subject).
- Chronic obstructive pulmonary disease.
- Asthma.
- Chronic liver disease.
- Known Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2); Except for post-renal transplant patients who should have (estimated) GFR ≥40 mL/min/1.73 m^2.
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies.
- Sickle cell disease.
- Cancer (except for Cohort 13).
- Are immune compromised due to stem cell or organ-transplantation with significant medical complications such as acute or chronic graft rejection or graft versus host disease requiring intensive immunosuppressive treatment, transplant failure or infectious complications or other conditions that would be considered a contraindication for vaccination.
- Are immune compromised due to HIV infection with a CD4+ count of < 200 x 10^6 /L at screening or significant medical complications such as opportunistic infections, malignant complications (e.g., lymphoma, Kaposi sarcoma), other organ manifestations consistent with advanced AIDS or other conditions that would be considered a contraindication for vaccination.
- Resident in a long term facility.
- Current vaping or smoking (occasional smoking is acceptable).
- History of chronic smoking within the prior year.

Ages Eligible for Study

18 Years to 85 Years (Adult, Older Adult)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

Yes

Study Plan

This section provides details of the study plan, including how the study is designed and what the study is measuring.

How is the study designed?

What is the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 days after each immunization.		up to 7 days following each dose administration
Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7 days after each immunization.		up to 7 days following each dose administration

The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE):	For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 21 days after the prime immunization.	21 days following dose administration
The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE):	For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B): occurring up to 28 days after the boost immunization. For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 days after the immunization.	28 days following dose administration

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):	Functional antibody responses (titers) as compared to baseline at 7 and 21 days after primary immunization and at 7, 14, 21, 28, 63, and 162 days after the boost immunization.	up to 162 days following dose administration
For BNT162a1, BNT162b1, BNT162b2, and BNT162c2 (P/B):	Fold increase in functional antibody titers as compared to baseline at 7 and 21 days after primary immunization and at 7, 14, 21, 28, 63, and 162 days after the boost immunization.	up to 162 days following dose administration
For BNT162a1, BNT162b1,	Number of subjects with seroconversion defined as a minimum of 4-fold increase	up to 162 days following

BNT162b2, and BNT162c2 (P/B):	of functional antibody titers as compared to baseline at 7 and 21 days after primary immunization and at 7, 14, 21, 28, 63, and 162 days after the boost immunization.	dose administration
For BNT162c2 (SD):	Functional antibody responses (titers) as compared to baseline at 7, 21, 28, 42, 84, and 183 days after the primary immunization.	up to 183 days following dose administration
For BNT162c2 (SD):	Fold increase in functional antibody titers as compared to baseline at 7, 21, 28, 42, 84, and 183 days after the primary immunization.	up to 183 days following dose administration
For BNT162c2 (SD):	Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7, 21, 28, 42, 84, and 183 days after the primary immunization.	up to 183 days following dose administration
For BNT162b2 (P/B):	Functional antibody responses (titers) as compared to baseline at 7, 14, and 21 days after the primary immunization and at 7, 28, and 162 days after the boost immunization.	up to 162 days following dose administration
For BNT162b2 (P/B):	Fold increase in functional antibody titers as compared to baseline at 7, 14, and 21 days after primary immunization and at 7, 28, and 162 days after the boost immunization.	up to 162 days following dose administration

For BNT162b2 (P/B):	Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline at 7, 14, and 21 days after primary immunization and at 7, 28, and 162 days after the boost immunization.	up to 162 days following dose administration

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor

BioNTech SE

Collaborators

No information provided

Investigators

- Study Director: BioNTech Responsible Person, BioNTech SE

Publications

The person responsible for entering information about the study voluntarily provides these publications. These may be about anything related to the study.

General Publications

No publications available

*** Find Publications about Study Results and related Pubmed Publications in the "Results" section of the study record.**

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates

First Submitted
2020-05-06

First Submitted that Met QC Criteria
2020-05-07

First Posted
2020-05-08

Study Record Updates

Last Update Submitted that met QC Criteria
2022-01-12

Last Update Posted
2022-01-13

Last Verified
2022-01

More Information

Terms related to this study

Keywords Provided by BioNTech SE

SARS-CoV-2
Severe Acute Respiratory Syndrome (SARS)
Coronavirus Disease 2019
COVID-2019
Virus Diseases

Additional Relevant MeSH Terms

Disease Attributes
Pathologic Processes
Respiratory Tract Diseases
Infections
Communicable Diseases
Virus Diseases
RNA Virus Infections
Respiratory Tract Infections

Plan for Individual Participant Data (IPD)

Plan to Share Individual Participant Data (IPD)?

No

Drug and device information, study documents, and helpful links

Studies a U.S. FDA-Regulated Drug Product

No

Studies a U.S. FDA-Regulated Device Product

No

Product Manufactured in and Exported from the U.S.

No

Study Documents

No study documents available

Productie 14

The U.S. government does not review or approve the safety and science of all studies listed on this website.

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COMPLETED

Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

ClinicalTrials.gov ID NCT04368728

Sponsor BioNTech SE

Information provided by BioNTech SE (Responsible Party)

Last Update Posted 2023-02-28

Study Details Tab

Study Overview

Brief Summary

This is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part.

The study will evaluate the safety, tolerability, and immunogenicity of 3 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- As a booster;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55 or >55 years of age]).

The candidate selected for efficacy evaluation in Phase 2/3 is BNT162b2 at a dose of 30 µg.

Feedback

Participants who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

In order to describe the boostability of BNT162, and potential heterologous protection against emerging SARS-CoV-2 VOCs, an additional dose of BNT162b2 at 30 µg will be given to Phase 1 participants approximately 6 to 12 months after their second dose of BNT162b1 or BNT162b2. This will provide an early assessment of the safety of a third dose of BNT162, as well as its immunogenicity.

The assessment of boostability will be further expanded in a subset of Phase 3 participants at selected sites in the US who will receive a third dose of BNT162b2 at 30 µg or a third and potentially a fourth dose of prototype BNT162b2VOC at 30 µg (BNT162b2s01, based upon the South African variant and hereafter referred to as BNT162b2SA). A further subset of Phase 3 participants will receive a third, lower, dose of BNT162b2 at 5 or 10 µg.

To further describe potential homologous and heterologous protection against emerging SARS-CoV-2 VOCs, a new cohort of participants will be enrolled who are COVID-19 vaccine-naïve (ie, BNT162b2-naïve) and have not experienced COVID-19. They will receive BNT162b2SA given as a 2-dose series, separated by 21 days.

To reflect current and anticipated recommendations for COVID 19 vaccine boosters, participants in C4591001 who meet specified recommendations and have not already received one, will be offered a third dose of BNT162b2 after their second dose of BNT162.

Official Title

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Conditions

SARS-CoV-2 Infection COVID-19

Intervention / Treatment

- Biological: BNT162b1
- Biological: BNT162b2
- Other: Placebo
- Biological: BNT162b2SA

Other Study ID Numbers

- C4591001
- 2020-002641-42 (EudraCT Number)

Study Start (Actual)

2020-04-29

Primary Completion (Actual)

2023-02-10

Study Completion (Actual)

2023-02-10

Enrollment (Actual)

47079

Study Type

Interventional

Phase

Phase 2
Phase 3

Resource links provided by the National Library of Medicine

MedlinePlus (https://medlineplus.gov/) related topics: COVID-19 (Coronavirus Disease 2019) (https://medlineplus.gov/covid19coronavirusdisease2019.html) Vaccines (https://medlineplus.gov/vaccines.html)

Other U.S. FDA Resources (https://classic.clinicaltrials.gov/ct2/info/fdalinks)

Contacts and Locations

This section provides the contact details for those conducting the study, and information on where this study is being conducted.

United States

Alabama Locations

Athens, Alabama, United States, 35611
North Alabama Research Center, LLC

Click to view interactive map

Birmingham, Alabama, United States, 35216
Birmingham Clinical Research Unit

Huntsville, Alabama, United States, 35801
Medical Affiliated Research Center

Participation Criteria

Researchers look for people who fit a certain description, called eligibility criteria. Some examples of these criteria are a person's general health condition or prior treatments.

For general information about clinical research, read Learn About Studies (https://clinicaltrials.gov/study-basics/learn-about-studies).

Eligibility Criteria

Description

Inclusion Criteria:

• Male or female participants between the ages of 18 and 55 years, inclusive, 65 and 85 years, inclusive, or ≥12 years, inclusive, at randomization (dependent upon study phase). For the boostability and protection-against-VOCs subset: Existing participants enrolled to receive a third dose of BNT162b2 at 30 µg or BNT162b2SA; male or female participants between the ages of 18 and 55 years, inclusive, at rerandomization.

Newly enrolled participants enrolled to receive 2 doses of BNT162b2SA; male or female participants between the ages of 18 and 55 years, inclusive, at enrollment.

Existing participants enrolled to receive a third dose of BNT162b2 at 5 or 10 µg; male or female participants ≥18 years at rerandomization.

Note that participants <18 years of age cannot be enrolled in the EU.

- Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
- Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.
- Participants who, in the judgment of the investigator, are at risk for acquiring COVID-19.
- Boostability and protection-against-VOCs existing participant subset only: Participants who provided a serum sample at Visit 3, with Visit 3 occurring within the protocol-specified window.
- Capable of giving personal signed informed consent

Exclusion Criteria:

- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
- Phases 1 and 2 only: Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
- Receipt of medications intended to prevent COVID 19.
- Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID 19
- Phase 1 only: Individuals at high risk for severe COVID-19, including those with any of the following risk factors:
    - Hypertension
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Asthma

    - Current vaping or smoking
    - History of chronic smoking within the prior year
    - BMI >30 kg/m2
    - Anticipating the need for immunosuppressive treatment within the next 6 months
- Phase 1 only: Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Phase 1 only: Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study.
- Phase 1 only: Regular receipt of inhaled/nebulized corticosteroids.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry through and including 6 months after the last dose of study intervention, with the exception of non-Pfizer interventional studies for prevention of COVID 19, which are prohibited throughout study participation.
- Previous participation in other studies involving study intervention containing lipid nanoparticles.
- Phase 1 only: Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.
- Phase 1 only: Any screening hematology and/or blood chemistry laboratory value that meets the definition of a ≥ Grade 1 abnormality.
- Phase 1 only: Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.
- Phase 1 only: SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.
- Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Ages Eligible for Study

12 Years and older (Child, Adult, Older Adult)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

Yes

Study Plan

This section provides details of the study plan, including how the study is designed and what the study is measuring.

How is the study designed?

What is the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Percentage of participants in Phase 1 reporting local reactions	Pain at the injection site, redness, and swelling as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
Percentage of participants in Phase 1 reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
Percentage of participants in Phase 1 reporting adverse events	As elicited by investigational site staff	From dose 1 through 1 month after the last dose
Percentage of participants in Phase 1 reporting	As elicited by investigational site staff	From dose 1 through 6 months

serious adverse events		after the last dose
Percentage of Phase 1 participants with abnormal hematology and chemistry laboratory values	As measured at the central laboratory	1 day after dose 1
Percentage of Phase 1 participants with abnormal hematology and chemistry laboratory values	As measured at the central laboratory	7 days after dose 1
Percentage of Phase 1 participants with abnormal hematology and chemistry laboratory values	As measured at the central laboratory	7 days after dose 2
Percentage of Phase 1 participants with grading shifts in hematology and chemistry laboratory assessments	As measured at the central laboratory	Between baseline and 1 day after dose 1
Percentage of Phase 1 participants with grading shifts in	As measured at the central laboratory	Between baseline and 7 days

hematology and chemistry laboratory assessments		after dose 1
Percentage of Phase 1 participants with grading shifts in hematology and chemistry laboratory assessments	As measured at the central laboratory	Between before dose 2 and 7 days after dose 2
In the first 360 participants randomized into Phase 2/3, percentage of participants reporting local reactions	Pain at the injection site, redness, and swelling as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
In the first 360 participants randomized into Phase 2/3, percentage of participants reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
In the first 360 participants randomized into Phase 2/3, percentage of participants	As elicited by investigational site staff	From dose 1 through 1 month after the last dose

reporting adverse events		
In the first 360 participants randomized into Phase 2/3, percentage of participants reporting serious adverse events	As elicited by investigational site staff	From dose 1 through 6 months after the last dose
In a subset of at least 6000 participants randomized in Phase 2/3, percentage of participants reporting local reactions	Pain at the injection site, redness, and swelling as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
In a subset of at least 6000 participants randomized in Phase 2/3, percentage of participants reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
Percentage of participants in Phase 2/3 reporting adverse events	As elicited by investigational site staff	From dose 1 through 1 month after the last dose
Percentage of participants in	As elicited by investigational site staff	From dose 1 through 6

Phase 2/3 reporting serious adverse events		months after the last dose
Confirmed COVID-19 in Phase 2/3 participants without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed COVID-19 in Phase 2/3 participants with and without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years
Percentage of participants 12-15 years of age in Phase 3 reporting adverse events	As elicited by investigational site staff	From dose 1 through 1 month after the last dose
Percentage of participants 12-15 years of age in Phase 3 reporting adverse events	As elicited by investigational site staff	From dose 1 through 6 months after the last dose
In participants 12-15 years of age	Pain at the injection site, redness, and swelling as self-reported on	For 7 days after dose

randomized in Phase 3, percentage of participants reporting local reactions	electronic diaries.	1 and dose 2
In participants 12-15 years of age randomized in Phase 3, percentage of participants reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after dose 1 and dose 2
In participants who receive BNT162b2SA given as 1 or 2 doses, percentage of participants reporting adverse events	As elicited by investigational site staff	From dose 1 through 1 month after the last dose
In participants who receive BNT162b2SA given as 1 or 2 doses, percentage of participants reporting serious adverse events	As elicited by investigational site staff	From dose 1 through 5 or 6 months after the last dose
In participants, who receive BNT162b2SA given as 1 or 2 doses, percentage of participants	Pain at the injection site, redness, and swelling as self-reported on electronic diaries.	For 7 days after dose 1 (and dose 2)

reporting local reactions		
In participants who receive BNT162b2SA given as 1 or 2 doses, percentage of participants reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after dose 1 (and dose 2)
In participants who receive a third dose of BNT162b2 as part of the subset for evaluation of boostability and protection against emerging VOCs, percentage of participants reporting adverse events	As elicited by investigational site staff	From the third dose through 1 month after the third dose
In participants who receive a third dose of BNT162b2 as part of the subset for evaluation of boostability and protection against emerging VOCs, percentage of participants reporting serious adverse events	As elicited by investigational site staff	From the third dose through 6 months after the third dose

In participants who receive a third dose of BNT162b2 as part of the subset for evaluation of boostability and protection against emerging VOCs, percentage of participants reporting local reactions	Pain at the injection site, redness, and swelling as self-reported on electronic diaries.	For 7 days after the third dose
In participants who receive a third dose of BNT162b2 as part of the subset for evaluation of boostability and protection against emerging VOCs, percentage of participants reporting systemic events	Fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain as self-reported on electronic diaries.	For 7 days after the third dose
In participants who receive a third dose of BNT162b2 as a result of current or anticipated recommendations, percentage of participants reporting adverse events	As elicited by investigational site staff	From the third dose through 1 month after the third dose

In participants who receive a third dose of BNT162b2 as a result of current or anticipated recommendations, percentage of participants reporting serious adverse events	As elicited by investigational site staff	From the third dose through 6 months after the third dose
Noninferiority of the SARS-CoV-2 reference strain neutralizing titers after a third dose of BNT162b2 at 30 µg compared to after 2 doses of BNT162b2, in the same individuals	As measured at the central laboratory	1 month after the third dose
Noninferiority of the SARS-CoV-2 SA strain neutralizing titers after one dose of BNT162b2SA compared to the SARS-CoV-2 reference strain neutralizing titers after 2 doses of BNT162b2, in the same individuals	As measured at the central laboratory	1 month after the third dose
Noninferiority of the SARS-CoV-2	As measured at the central laboratory	1 month after the

SA strain neutralizing titers after 2 doses of BNT162b2SA compared to the SARS-CoV-2 reference strain neutralizing titers after 2 doses of BNT162b2		second dose

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
In Phase 1 participants, SARS-CoV-2 serum neutralizing antibody levels, expressed as GMTs	As measured at the central laboratory	Through 2 years after the final dose
In Phase 1 participants, GMFR in SARS-CoV-2 serum neutralizing titers from before vaccination to each subsequent time point	As measured at the central laboratory	Through 2 years after the final dose
Proportion of participants in Phase 1	As measured at the central laboratory	Through 2 years after the final dose

achieving a greater than or equal to 4-fold rise from before vaccination in SARS-CoV-2 serum neutralizing antibody levels		
In Phase 1 participants, SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels, expressed as GMCs	As measured at the central laboratory	Through 2 years after the final dose
Proportion of participants in Phase 1 achieving a greater than or equal to 4-fold rise from before vaccination in SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels	As measured at the central laboratory	Through 2 years after the final dose

In Phase 1 participants, GMFR in SARS-CoV-2 anti-S1 binding antibody levels and anti-RBD binding antibody levels from before vaccination to each subsequent time point	As measured at the central laboratory	Through 2 years after the final dose
In Phase 1 participants, GMR of the geometric mean of SARS-CoV-2 serum neutralizing titers to the geometric mean of SARS CoV 2 (anti-S1 and anti-RBD) binding antibody levels	As measured at the central laboratory	Through 2 years after the final dose
Confirmed COVID-19 in Phase 2/3 participants without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years

Confirmed COVID-19 in Phase 2/3 participants with and without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed severe COVID-19 in Phase 2/3 participants without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed severe COVID-19 in Phase 2/3 participants without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed severe COVID-19 in Phase 2/3 participants with and	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years

without evidence of infection before vaccination		
Confirmed severe COVID-19 in Phase 2/3 participants with and without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed COVID-19 (according to the CDC-defined symptoms) in Phase 2/3 participants without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed COVID-19 (according to the CDC-defined symptoms) in Phase 2/3 participants	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years

without evidence of infection before vaccination		
Confirmed COVID-19 (according to the CDC-defined symptoms) in Phase 2/3 participants with and without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 7 days after the second dose of study intervention to the end of the study, up to 2 years
Confirmed COVID-19 (according to the CDC-defined symptoms) in Phase 2/3 participants with and without evidence of infection before vaccination	Per 1000 person-years of follow-up	From 14 days after the second dose of study intervention to the end of the study, up to 2 years
GMR of SARS CoV 2 neutralizing titers in the 2	As measured at the central laboratory	1 month after the second dose

age groups (12-15 years of age to 16-25 years of age)		
Incidence of asymptomatic SARS CoV-2 infection based on N binding antibody seroconversion in participants with no serological or virological evidence of past SARS CoV-2 infection or confirmed COVID-19 prior to 1 month after receipt of the second dose	Per 1000 person-years of follow-up	Through 1 month after the second dose
Incidence of asymptomatic SARS CoV-2 infection based on central laboratory-confirmed NAAT in participants with no serological or virological	Per 1000 person-years of follow-up	Through 6 months after the second dose

evidence (up to the start of the asymptomatic surveillance period) of past SARS-CoV-2 infection		
Noninferiority of the SARS-CoV-2 SA strain neutralizing titers after a third dose of BNT162b2 at 30 µg compared to the SARS-CoV-2 reference strain neutralizing titers after 2 doses of BNT162b2, in the same individuals	As measured at the central laboratory	1 month after the third dose
Noninferiority of the SARS-CoV-2 reference strain neutralizing titers after one dose of BNT162b2SA compared to after 2 doses of BNT162b2,	As measured at the central laboratory	1 month after the first dose of BNT162b2SA

in the same individuals		
Comparison of the SARS-CoV-2 SA strain neutralizing titers after 1 dose of BNT162b2SA to after a third dose of BNT162b2 at 30 µg	As measured at the central laboratory	1 month after the first dose of BNT162b2SA/third dose of BNT162b2
Comparison of the SARS-CoV-2 SA strain neutralizing titers after 2 doses of BNT162b2SA to the SARS-CoV-2 reference strain neutralizing titers after 2 doses of BNT162b2, in the same individuals	As measured at the central laboratory	1 month after the second dose of BNT162b2SA
Comparison of the SARS-CoV-2 SA strain neutralizing titers after 2 doses of BNT162b2SA	As measured at the central laboratory	1 month after the second dose

to after 2 doses of BNT162b2		
Comparison of the SARS-CoV-2 reference strain neutralizing titers after 2 doses of BNT162b2SA to after 2 doses of BNT162b2	As measured at the central laboratory	1 month after the second dose

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor

BioNTech SE

Collaborators

- Pfizer

Investigators

- Study Director: Pfizer CT.gov Call Center, Pfizer

Publications

The person responsible for entering information about the study voluntarily provides these publications. These may be about anything related to the study.

General Publications

No publications available

*** Find Publications about Study Results and related Pubmed Publications in the "Results" section of the study record.**

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates

First Submitted
2020-04-27

First Submitted that Met QC Criteria
2020-04-29

First Posted
2020-04-30

Study Record Updates

Last Update Submitted that met QC Criteria
2023-02-27

Last Update Posted
2023-02-28

Last Verified
2023-02

More Information

Terms related to this study

Keywords Provided by BioNTech SE

COVID-19
Coronavirus

Vaccine
SARS-CoV-2
RNA Vaccine

Additional Relevant MeSH Terms

Pneumonia, Viral
Pneumonia
Respiratory Tract Infections
Infections
Virus Diseases
Coronavirus Infections
Coronaviridae Infections
Nidovirales Infections
RNA Virus Infections
Lung Diseases
Respiratory Tract Diseases
COVID-19

Plan for Individual Participant Data (IPD)

Plan to Share Individual Participant Data (IPD)?

No

Drug and device information, study documents, and helpful links

Studies a U.S. FDA-Regulated Drug Product

Yes

Studies a U.S. FDA-Regulated Device Product

No

Study Documents

No study documents available

Helpful Links Provided by BioNTech SE

To obtain contact information for a study center near you, click here.
(https://pmiform.com/clinical-trial-info-request?StudyID=C4591001)

Productie 15

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.2*[1,2]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] Correction dated 19 February 2021 to clarify ERA statement
[2] Correction dated 20 October 2023 to correct figures in the Effects Table and clarify the report accordingly

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BDR	blinded data review
BLQ	below the level of quantitation
BMI	body mass index
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention (United States)
CGE	Capillary gel electrophoresis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	case report form
CRM	Clinical Reference Material
CRO	contract research organization
CSR	clinical study report
CV	curriculum vitae
C&E	Cause and Effect Matrices
DCT	data collection tool
DLS	Dynamic Light Scattering
DMC	data monitoring committee
DOE	Design of experiments
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
e-diary	electronic diary
EU	European Union
FIH	first-in-human
FSFV	first subject first visit
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCS	human convalescent serum
HCV	hepatitis C virus
HCV	Ab hepatitis C virus antibody
HIV	human immunodeficiency virus
HPLC-CAD	High-Performance Liquid Chromatography - Charged Aerosol Detector
IA	interim analysis
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
IPT-C	In-process testing control
IPT-M	In-process testing monitoring
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IVT	in vitro transcription
IWR	interactive web response
LAL	Limulus Amebocyte Lysate
LC-UV/MS	Liquid Chromatography – Ultraviolet / Mass Spectometry
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid

NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NMT	Not more than
NOR	Normal Operating Range
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PAR	Proven Acceptable Range
(q)PCR	(quantitative) Polymerase Chain Reaction
PD	protocol deviation
Ph.Eur.	European Pharmacopoeia
PPQ	Process Performance Qualification
PRM	Primary Reference Material
Prevax	prevaccination
PT	preferred term
QA	quality assurance
QA	Quality Attribute
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RT-PCR	Real Time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SMQ	standardized MedDRA queries
SOC	system organ class
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

TME	targeted medical event
TSE	Transmissible Spongiform Encephalopathy
UFDF	Ultrafiltration/diafiltration
US	United States
Vax	vaccination
VE	vaccine efficacy
WBC	white blood cell count
WCB	Working Cell Bank
WHO	World Health Organization
WRM	Working Reference Material
YOA	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioNTech Manufacturing GmbH submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Comirnaty, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication:

"Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of Comirnaty vaccine should be in accordance with official guidance."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0480/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0480/2020 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

New active Substance status

The applicant requested the active substance Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike

(S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product[1]

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibly to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	06 November 2020

[1] These steps do not reflect the additional submissions made by the applicant during the active assessment phases.

The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020.	15 December 2020
– A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020.	6 November 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Comirnaty on	21 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

2.1.2. Epidemiology and risk factors

Every individual is at risk of infection as there is no pre-existing immunity to the SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts.

According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

2.1.4. Clinical presentation and diagnosis

The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and subsequent multi-organ failure and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

The US Centres for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrheal
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. For example, in Italy the CFR was 0.3% in adults <40 years of age but 12.8% in adults 70 to 79 years of age and 20.2% in patients ≥80 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.5. Management

The management of COVID-19 has developed during 2020, and now includes antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins, anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a prophylactic vaccine during the ongoing pandemic, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic at a population level, e.g. to maintain a functioning health care system, and to avoid the social and economic consequences of the stringent measures needed to diminish virus spread. There is currently no approved vaccine in EU for prevention of COVID-19.

About the product

BNT162b is a mRNA vaccine for prevention of COVID-19. The vaccine is made of a mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The sequence of the S protein was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu-1", which was available when the program was initiated: GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein).

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2. The RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (see section 2.2). The LNPs protect the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (IM) delivery.

The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein is identified as a target for neutralising antibodies against the virus and is therefore considered a relevant vaccine component.

The vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) in two 30 µg doses of the diluted vaccine solution given 21 days apart.

Intended indication: *'Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older'*.

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

According to the Applicant, there is a positive benefit-risk balance for Comirnaty in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2, in individuals 16 years of age and older. This is based on evidence from the pivotal study C4591001 (also referred to as BNT162-02), a Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding Study investigating the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in healthy individuals.

The Applicant stated that the available data to date indicate that its vaccine was 95 percent effective and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant intends to continue the ongoing pivotal Phase 3 study with participants as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. In case of availability of any COVID-19 vaccine, the sponsor will appeal to participants to remain in the ongoing study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COMIRNATY in individuals <16 years of age have not been established for this application. Four studies in paediatric subjects are planned as laid down in the paediatric investigation plan. A study in pregnant women is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of Comirnaty (Study C4591010) will be conducted in the EU using primary data collection that monitors a cohort of vaccinees and evaluates risk of AESIs. The Applicant will also conduct, non-interventional studies (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 in a real-world setting. These studies will allow to determine the effectiveness of vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

- Unmet medical needs will be addressed

According to the Applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, Efficacy of COMIRNATY to prevent COVID-19 was demonstrated at the final analysis. The observed VE in each subgroup as defined by age, including elderly ≥ 65 years old, sex, race/ethnicity, country, obese subjects, and subjects at risk due to comorbidities, was overall consistent with the effectiveness of BNT162b2 to protect vaccinees against the disease. The benefit of immediate availability of Comirnaty through conditional marketing authorisation is based on the fact that there is no approved vaccine or successful COVID-19 therapy available in the European Union. An effective vaccine can impact the pandemic at this critical time and a COVID-19 vaccination program implemented soon can likely prevent further pandemic waves and thus substantially reduce mortality due to disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for dispersion for injection containing 225 µg/ 0.45 mL (prior to dilution) of BNT162b2 (5'capped mRNA encoding full length SARS-CoV-2 Spike protein) as active substance (AS).

Other ingredients are: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-

Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injections.

The product is available in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Pack size: 195 vials.

The multidose (5 dose) vial is stored frozen and must be thawed prior to dilution. After thawing, the vaccine should be diluted and used immediately.

After dilution with 1.8 mL sodium chloride (0.9%) solution (not supplied), one dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

2.2.2. Active Substance

General Information

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The vaccine is based on the spike glycoprotein (S) of SARS-CoV-2. The sequence was chosen based on the sequence for the "Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1". The protein sequence contains two proline mutation, which ensures an antigenically optimal pre-fusion confirmation (P2 S). The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. The applicant will provide clarification on the mechanism of action for BNT162b2.

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for both the Andover and the BNT Mainz & Rentschler manufacturing sites were provided.

The manufacturing process of BNT162b2 active substance involves five major steps. The RNA is synthesised from linear DNA via an in vitro transcription (IVT) step. The IVT step is followed by a number of purification and filtration steps. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen.

Flow diagrams were provided, presenting the process steps, process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The ranges of hold times and process parameters and routine in-process controls are listed with corresponding acceptance criteria, for each step. It is noted that not all process parameters are listed, but that the lists include all critical and several non-critical process parameters. It is agreed that the key process parameters are described in the dossier. The applicant has agreed to upgrade these parameters to critical process parameters (CPPs) and to include acceptable ranges for these CPPs. Updated information has been submitted during the procedure which comprised modifications of the acceptable ranges of several process parameters and the addition of some controls. The strategy is found acceptable, and the Applicant will provide information on acceptable ranges for some parameters.

The active substance is stored between -15°C and -25°C. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined. Shipping validation of the intermediate has been agreed as recommendation.

The batch numbering system is sufficiently described.

Control of materials

An adequate overview of the raw materials and solutions used in the active substance manufacturing process is provided.

Representative certificates of analysis have been provided. The submitted information supports the appropriate quality of raw materials. It is recommended that the applicant should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials **(REC1)** and should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases **(REC2).** The description of synthesis of 5'cap and its related impurities were requested during the procedure. Appropriate information was given. The applicant should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021 **(REC3)**.

The BNT162b2 active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells.

The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance. Changes to the manufacturing process of the linear DNA template (e.g. change to plasmid host cell) may result in a different impurity profile in the active substance. Additional details on the manufacturing process and the control strategy for this starting material, initially only shortly described, have been provided and the dossier will be updated accordingly.

The cell banks involved in the plasmid manufacturing process are described. Master cell bank (MCB) and working cell bank (WCB) qualification tests are listed. Relevant specifications are set and data from the current MCB and WCB are provided. The plasmid MCBs and WCBs are enrolled in a cell bank stability program. The strategy is considered adequate, noting that the dossier will be updated as appropriate. A protocol for establishment of future WCBs is provided.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. The strategy for establishing the initial shelf-life is endorsed and data provided support the proposed shelf life. A list of the raw materials as well as other materials used in the manufacture of the

linear DNA template is provided. All materials used are animal origin free and sourced from approved suppliers.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are routinely quantified. The reference material is described. Implementation of any changes in the manufacture of the linear DNA template should be applied for in a variation application.

Control of critical steps and intermediates

Process parameters and tests that are used to control the process and active substance quality are provided. The list of CPPs was provided with corresponding updated acceptable ranges.

A summary of the quality attributes with the rationale for the criticality assignment is provided. The rationale for classification into CQA or QA is presented for each attribute and appears reasonable.

The in-process test methods are defined and described in the dossier.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7).** The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6)**.

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

finished product manufacturing sites were validated to maintain product temperature in the acceptable range for a defined duration.

A transport verification study is planned and results will be available in Q1/2021. The recommendation to provide shipping performance qualification data has been agreed **(REC6)**.

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation **(SO1)**.

Regarding the 5’ cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute ‘capped-intact RNA’ is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5’-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5’-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

According to the Applicant, the majority of fragments are expected to be comprised of truncated transcripts including the 5’ region but lacking the 3’ region and poly(A)tail. However, the results indicating a substantial proportion of shorter/truncated mRNA with both cap and poly(A)tail are not in agreement with this statement. Therefore, the Applicant was asked to discuss and justify the obtained results and explain the apparent discrepancy. Additional characterisation data using an orthogonal method with enriched samples for fragmented species was provided. Preliminary characterization data on isolated fragmented species suggests they predominantly include the 5’-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction. The characterisation data are requested to be completed with analysis of the main peak from ion pairing RP-HPLC and analysis of other samples from Process 1 and optimised Process 2 **(SO1).** The Applicant will continue to evaluate any potential overestimation of poly(A) tail and should characterise fragments for any future AS process changes **(SO1)**.

Furthermore, the poly(A)tail of the 3’ end was characterised by LC-UV/MS. While the results were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified. As expected, poly(A) tail heterogeneity was observed both for Process 1 and Process 2 batches. Thus, slight differences in the poly(A)tail pattern were observed when comparing Process 1

and Process 2 AS batches. The Applicant explains that the redistribution is probably due to the use of a linearised DNA plasmid template in Process 2 instead of a PCR-derived DNA template in Process 1. For both processes, the poly(A)tail is anticipated to be sufficiently long to guarantee stability of the RNA and function in translation. This explanation is considered reasonable by the CHMP.

The overall primary sequence of BNT162b2 active substance was demonstrated to be comparable by LC/MS/MS -oligonucleotide mapping. Circular dichroism (CD) spectroscopy confirmed that the higher-order structure of Process 1 and Process 2 AS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 active substance was determined. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, further clarification is requested and include correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **(SO1)**.

A second comparability study was presented to assess comparability across the Process 2 manufacturing facilities, batches each from the Andover and BioNTech sites were included in the study. In addition, Process 2 batches, planned for clinical supply and for emergency supply in the US market and representative batches from Process 1 were included in the comparison.

In conclusion, the Process 2 batches manufactured at the Andover and BioNTech sites were demonstrated to be comparable with respect to identity as monitored by agarose gels and 5'Cap structure characterised by LC-UV and subsequent MS analysis. Furthermore, the primary sequence and the secondary structure was demonstrated to be comparable for all Process 1 and Process 2 batches included in the study. Poly(A) tail length and distribution was investigated by RP-HPLC and MS analysis. All process 2 batches were found comparable, while the Process 1 batches showed a somewhat different poly(A) tail pattern.

The expressed protein size after in-vitro expression of BNT162b2 active substance was determined and the results demonstrate comparability between batches. However, the identity of the bands identified by WB are not sufficiently justified and further clarification is requested **(SO1)**.

Overall, the submitted data confirm consistent and comparable quality of Process 2 batches manufactured at the Andover and BioNTech sites.

Process characterisation studies using scale-down models of individual unit operations, were performed.

It should be noted that future changes to any of the process parameters, regardless of the classification of CPP or non-CPP, should be applied for as variation to the terms of the MA.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following additional manufacturing campaigns and additional small-scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. It is noted that after the adjustment of these volumes, the percentage of RNA integrity has increased to levels more consistent with Process 1 batches. Nevertheless, since the target volumes for ATP and CTP have been increased to avoid that these nucleotides are rate-limiting in order to increase the percentage of RNA integrity, the PAR ranges need to be adjusted and the dossier updated accordingly **(REC8)**.

The acceptable ranges for CPPs will be updated in the dossier.

A safety risk assessment for potential process-related impurities included in the active substance process relative to patient safety was performed. The sources of the impurities are sufficiently addressed.

The safety risk assessment strategy involves comparison of the theoretical worst-case concentration of impurities, assuming no removal, to calculated safety concern thresholds.

The worst-case levels of residual raw materials and reagents from the BNT162b2 active substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable.

Characterisation

Analytical characterisation was performed on BNT162b2 active substance manufactured at commercial scale. This is found acceptable.

The physico-chemical characterisation involved primary structure, 5' cap structure, poly(A)tail and higher order structure evaluation. Primary structure was confirmed by oligonucleotide mapping and the orthogonal method, RNA sequencing using Next Generation Sequencing (NGS) technology. The results confirm the RNA sequence. The 5'-cap and 3' poly A tail were confirmed by two separate LC-UV/MS-methods. It was demonstrated that the predominant form of the 5' terminus is the full-length nucleotide sequence with the 5'-Cap. The higher order structure of BNT162b2 mRNA active substance was characterised in solution using biophysical techniques.

Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes. It is recommended that the applicant should comprehensively describe the capability of a specific analytical method to detect lower amounts of product related impurity in the presence of the correct form in the active substance. **(REC9)**.

An uncertainty in the characterisation section is that no biological characterisation is presented. In response to questions during the procedure, the applicant has committed to update dossier with the strategy for potency determination and to address relevant functional assays including the in vitro expression (potency) results and results from the analysis of expressed protein size for active substance lot 20Y513C101. It is recommended that the applicant should discuss the results and the assay suitability for a certain method used for biological characterization of protein expression for the active substance **(REC10)**.

As described above, the expressed protein size results are currently not sufficiently confirmed and a specific obligation is laid down in the terms of the MA requiring their adequate characterisation **(SO1).**

Process-related and product-related impurities as well as potential contaminants are described. A number of batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches from both manufacturing sites.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the active substance batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the AS specification in terms of RNA integrity. However, the characterisation of BNT162b2 AS is currently not found to be complete in relation to a specific parameter. This is especially important considering that the current AS and finished product acceptance criteria allow for a proportion of fragmented species. The Applicant should provide additional data to further characterise the truncated and modified mRNA species present in the finished product. Relevant protein/peptide characterization data for predominant species should be provided **(SO1)**.

Residual DNA template is a process-related impurity derived from the linearised DNA template added to the in-vitro transcription reaction. Residual DNA template is measured as defined in the active substance specification. The levels are controlled by a specification limit which is considered suitably low.

The potential contaminants described in this section are endotoxin and bioburden. Acceptable results are shown for the Proteinase K pool, UF retentate pre recovery, UF-product pool and the active substance, for all batches investigated.

Specification

The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for active substance is considered acceptable for authorisation with respect to the attributes chosen for routine release testing. During the procedure the specification limits for a number of attributes were tightened in response to questions.

The length of the poly(A) tails in BNT162b2 active substance is important for RNA stability and translational efficiency and even though comparable results have been reported to date, the poly(A) tail length should be included to the active substance release testing **(SO2)**.

The rationale used to establish the acceptance criteria is described in detail and based on a limited data set representative of BNT162b2 active substance manufactured at the intended commercial scale and process. From the available data, mRNA integrity, dsRNA and Poly(A) tail acceptance criteria are considered in relation with batches used in clinical studies and with the demonstrated manufacturing capability and need to be re-assessed and revised as appropriate as further data becomes available **(SO2).**

Potency testing is not included in the control of active substance but instead is performed at the level of finished product release testing. Considering the nature of this product, the approach is endorsed by the CHMP.

Analytical methods

All analytical methods used for testing of the active substance are sufficiently described in the dossier. The following tests are performed in accordance with Ph Eur chapters; clarity (Ph Eur 2.2.1), colour (Ph Eur 2.2.2), pH (Ph Eur 2.2.3), bacterial endotoxins (Ph Eur 2.6.14) and bioburden (Ph Eur 2.6.12).

All non-compendial analytical methods are sufficiently described. These analytical methods were suitably validated against the parameters presented in ICH Q2(R1).

The technical procedure for the quantification of the poly(A) tail is considered, in general, sufficiently described but the suitability of this method for the intended purpose remains to be confirmed **(SO2)**.

Batch analysis

Batch results are presented for active substance batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply and stability.

In general, the results obtained using the commercial process (Process 2) demonstrate batch to batch consistency with a few exceptions.

Reference materials

The current reference standard is referred to as the Clinical Reference Material (CRM). A stability protocol is provided. The Applicant has agreed to provide additional information such as protocol on preparation and qualification on the future reference material, as requested **(REC12)**.

In future, a two-tiered system for future commercial reference material will be implemented. A primary reference material (PRM) and an initial working reference material (WRM) will be established for the active substance reference material.

Container closure

The information regarding container closure system is acceptable. Compliance with Ph. Eur. has been verified.

Stability

Based on the limited stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system. The stability program is designed to follow ICH guidelines. The test methods used are stability indicating. Data from the sites Andover, Mainz, Rentschler are included.

It is noted that the Applicant states that testing is currently in progress on the clinical batches and the dossier will be updated with data for these batches, as well as any new data available for the primary process validation batches. Thermal cycling studies have been initiated and a minimum of one process validation batch will be subjected to photostability studies at a future date.

Based on the stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The BNT162b2 finished product (FP) is supplied as a preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the finished product at pH 6.9 - 7.9 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution to a total volume of 2.25 mL. Each dose contains 30 µg of RNA in 0.3 mL.

The overfill in the vial is required to ensure that the full five doses can be removed from the multi-dose vial after dilution and correctly administered, taking account of potential loss of product during these dilution and administration steps. The justification for the overfill is sufficiently discussed and considered to be acceptable. The applicant development data and finished product testing confirm that 5 doses can be consistently extracted from the vial and delivered after dilution.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The full list of excipients is listed above in section 2.2.1; ALC-0315 and ALC-0159 (functional lipids), DSPC and cholesterol (structural lipids), potassium chloride, potassium dihydrogen phosphate, sodium

chloride and disodium phosphate dihydrate (buffer components), sucrose (cryoprotectant) and water for injections.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply with Ph. Eur. The functional lipid excipients ALC-0315 and ALC-0159, are classified as novel excipients. Both structural lipids DSPC and cholesterol are used in several already approved finished products. A justification was provided for why DSPC is not considered to be a novel excipient. DSPC is used as part of the LNP for the EU approved finished product Onpattro which is administered intravenously in a much higher dose than the intramuscular dose for this product. Additionally; DOPC, a structurally related lipid, is present in finished products approved in the EU for intramuscular administration. It was therefore concluded that the level of information provided for DSPC, is in line with the requirements for a known excipient are sufficient and appropriately justified.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Formulation development

The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles. Furthermore, the accumulated batch-data to date show consistent manufacture of lipid nanoparticles both with respect to size and polydispersity.

Lipid-related impurities have been identified in the finished product and have been characterized. An investigation has been initiated and is ongoing to assess and review potential root causes. The outcome of the investigation shall be provided (SO2).

Visual particulate matter has occasionally been observed in finished product batches. Characterization data have been presented and the control strategy has been discussed. The data demonstrates that the particles are comprised of components of the finished product formulation. A 100% visual inspection is performed during manufacturing and the automatic inspection system is updated to improve the inspection. Routine release or routine stability data indicate that the propensity of particles to form following storage is low. If particles are observed in the diluted vaccine the vial should be discarded.

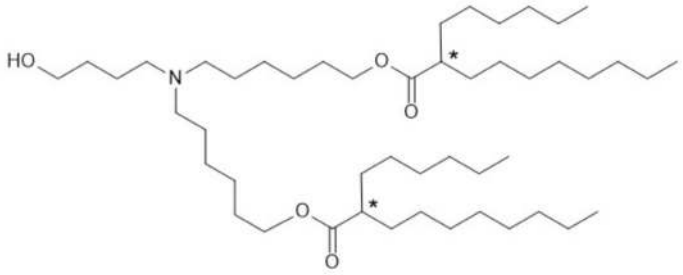
Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

Figure 1 ALC-0315 structure



Asterisks (*) indicate chiral centers.

A brief description of the chemical synthesis is provided. The suppliers are defined in the dossier. A similar manufacturing process is used for ALC-0315 in clinical and commercial finished product batches.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. (**SO4**)

The proposed specification is considered acceptable based on the available data. However, additional information regarding specifications that should be provided **(SO4)**.

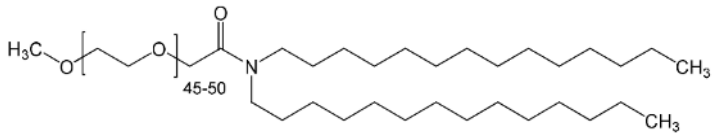
Stability data from one supplier indicate that ALC-0315 is stable when stored at the recommended storage conditions. Additionally, the excipient is stable at room temperature suitable for use in further manufacturing steps. Stability data from one supplier is considered representative for lipid from another supplier.

Lipid related impurities have been observed in some recently manufactured finished product batches, correlated with ALC-0315 lipid batches. The quality of ALC-0315 excipient is considered acceptable based on the available data on condition that specific impurities in the finished product will be further evaluated **(SO2)**.

ALC-0159 (PEGylated lipid)

The ALC-0159 novel excipient is a PEGylated lipid, 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

Figure 2 ALC-0159 structure



A brief description of the chemical synthesis is provided.

The suppliers are defined in the dossier. The same supplier was used during development for clinical phase 1, 2 and 3 studies. The same synthetic route was used for ALC-0159 throughout development of the finished product.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant is requested to provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **(SO5)**

The proposed specification is considered acceptable based on available data. However, in order to improve impurity control strategy and to ensure batch to batch consistency of the finished product, there are additional information regarding specifications that should be provided **(SO5)**.

Stability data indicate that ALC-0159 is stable when stored at the recommended storage conditions.

Manufacturing process development

The development history of the finished product is sufficiently described. The process has been transferred to commercial facilities for manufacture of later clinical materials, emergency supply and commercial supply. A table on finished product lot genealogy and usage has been provided.

The applicant states that comparability is demonstrated in a stepwise approach through a combination of release testing and extended characterization methods. It is agreed that comparability was sufficiently demonstrated with only small differences noted.

During the present regulatory procedure, release testing results of a number of recently manufactured GMP-batches was presented. The release data for the GMP-batches are compared to the clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification and that comparability has been sufficiently demonstrated subject to the specific obligations further described, for the attributes tested and given the pandemic situation. In addition, the comparison will be further extended with additional characterization testing on future batches of finished product. The applicant has confirmed that testing will be performed according to the agreed finished product comparability testing protocol and the results will be submitted in the frame of a specific obligation (**SO3**).

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented and is agreed. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program at the commercial facility has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data (**SO3**).

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies using scale-down models of individual unit operations, were performed.

Overall control strategy was presented but some parameters and ranges may be updated after PPQ and additional characterization studies completed. As for assessment of overall control strategy, a complete set of data and information is needed, this document will be assessed when finalised. A time-plan for the provision of the final data set has been agreed with the applicant **(SO3)**.

The analytical testing strategy of finished product has changed throughout the development and these changes have been described. Bridging studies have been performed for analytical tests that have been changed or replaced (subvisible particles, identity of encoded RNA sequence and RNA integrity). This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The primary packaging is composed of glass vial and rubber stopper and are compliant with the compendial requirements of Ph. Eur.

Controlled extraction studies have been performed on the bromobutyl rubber stopper. The applicant will provide the updated results from the leachables study for assessment. (**REC13**)

Microbiological attributes

Container closure integrity testing has been performed to demonstrate that the 2 mL container closure presentation is integral.

In order to improve the control strategy, the MAH should provide validation results of alternative sterility test i.e. rapid sterility test for assessment before implementation (**REC14**).

Compatibility

The studies described have been performed to assess physicochemical stability of the FP after dilution with 0.9% sodium chloride solution in the original glass vial as well with commonly used commercially available administration components and using worst-case conditions for dosage and administration in the clinical setting. The thawed hold time (in-use period) of undiluted finished product has been defined as 5 days at 2-8 °C and 2 hours at up to 30 °C.

Results presented support physicochemical stability of FP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures (2-30°C) following an in-use thawed hold time of up to 5 days at 2-8 °C and 2 hours at 30 °C.

Compatibility with dosing components (syringes and needles) has been established for up to 6 hours. Furthermore, a microbiological in-use hold time study has been performed by a challenge test including five compendial micro-organisms. No significant growth (>0.5log10 from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted FP in 0.9% sodium chloride solution. Therefore, based on the results from the microbiological in-use hold time study, the proposed in-use period for up to 6 hours at ambient temperatures is agreed, as reflected in the product information. Furthermore, it is also stated by the applicant that the in-use period is in alignment with the WHO policy on the use of opened multi-dose vaccine vials (WHO Policy Statement: Multi-dose vial policy (MDVP) – handling of multi-dose vaccine vials after opening, rev 2014).

The compatibility of finished product is acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

The finished product is batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium or BioNTech Manufacturing GmbH, Mainz, Germany. The GMP status of the manufacturing and testing sites of the finished product have been confirmed.

The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Dossier should be updated to provide more details on increase batch size including range number of AS bag and batches used, configuration of filters filter surfaces used and process controls (**REC14**). The absence of a test for residuals is considered acceptable.

Shipping validation

This section gives a summary of the qualification of the shipping process for transport of BNT162b2 finished product by passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60 °C from the finished product manufacturing and packaging site to dosing sites in the EU.

Short periods of time outside of the intended routine shipping condition of -90 to -60 °C during transport and at distribution sites have been defined.

The shipping temperature range of -90 to -60 °C is based on available stability data.

One thaw and refreeze cycle is allowed during transportation. Time during transportation out of the intended storage and shipping temperature range (-90 to -60 °C) without thaw is allowed for specified times and conditions for multiple transfers and redistribution during shipping with subsequent refreezing to -90 to -60 °C between transfers. The temperature excursion allowances are supported by data.

The selected shipping methods include shipping containers designed to maintain product temperature through a combination of insulation and dry ice. The applicant has prior experience with these passive thermal conveyances and has demonstrated that they maintain the -90 to -60 °C temperature range during product shipments, including minor shipping delays and short exposures to extreme temperatures occasionally observed during shipping and handling.

All shipments are continuously monitored using temperature data loggers.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal conveyance, supported by operational qualification and performance qualification testing. A summary of the shipping qualification strategy has been provided.

For the passive thermal conveyance, the qualification is focused on the ability of the passive system to maintain the required temperatures with specified phase change materials or dry ice when exposed to ambient temperature profiles for worst-case season. These studies are carried out in laboratory chambers to simulate the summer as worst-case ambient profiles.

A simulated distribution study demonstrated finished product and package integrity after exposure to simulated distribution hazard conditions, following the durations outlined in the worst-case extended transport lanes.

Results of thermal qualification have met specified acceptance criteria and support shipments of BNT162b2 finished product using the passive thermal conveyance shipping containers either directly or

via qualified distribution centres. Passive thermal conveyance performance qualification and the simulated shipping study finished product impact testing have been performed to complete shipping qualification assessing both thermal and mechanical aspects of shipping.

Process parameters for storage and shipping are found acceptable.

Media fills

Media fills have been performed for the filling line to validate the aseptic filling process and were run in accordance to guidelines. Results have been provided from three consecutive simulation studies and gave satisfactory results without any contaminated units. Results for the media fill cover the maximum process time for the manufacturing of finished product and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process. For the filling line, the maximum time will be established upon completion of media fill qualification studies. This is found acceptable.

Verification of in-process test methods

Data on verification of in-process test methods was pending at the time of the present regulatory procedure and should be provided during Q2 2021 (**REC15**).

Hold times

Hold times have been established. It is noted that any change of this section needs to be submitted to the Agency via a variation application.

Process validation plan

A FP process validation plan has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

It is described in the dossier that commercial scale PPQ-batches will be manufactured during Dec 2020 to Jan 2021 and the applicant has provided a process validation plan. In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation data, by March 2021. (**SO3**)

Filter validation

Acceptable information has been provided during the procedure for filter validation on the filters used for sterile filtration, describing the material, pore size and surface area. All study results met the predetermined acceptance criteria and the studies for microbial retention, membrane compatibility, extractable substances and integrity test determination have shown that the filters are appropriate for sterile filtration of the finished product. In addition, the applicant has clarified that the filter used for bioburden reduction is identical to the filters used for sterile filtration.

The MAH should provide the results for assessment from the filter validation as soon as they are available (**REC23**).

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved finished product within EU. Additional information is provided separately in Section A.3 of the dossier.

DSPC is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is sufficiently controlled according to the Ph. Eur. monograph with additional tests for residual solvents and microbial contamination.

The other excipients (sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection) are controlled according to respective Ph. Eur. monograph.

The processing aids ethanol and citrate buffer are controlled according to Ph. Eur. standards and for HEPES and EDTA, reference is made to the active substance.

Product specification

The release and stability testing specifications for BNT162b2 finished product include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications document for finished product in section 3.2.P.5.1 of the dossier includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmolality, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at FP release, all other analytical procedures are conducted at release and stability studies for finished product. It is stated by the applicant that the acceptance criteria used for stability during shelf-life will be the same as the acceptance criteria used for lot release.

Several questions in relation to the acceptance criteria in the FP specifications were raised during the procedure (i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity). The acceptance criteria were tightened.

For potency, RNA integrity, RNA encapsulation, lipid content and polydispersity index, the acceptance criteria will be re-assessed during Q2 2021 in order to ensure a consistent product quality by providing additional information to enhance the control strategy. This is found acceptable subject to a specific obligation. (**SO2**)

The vial contains an overfill in order to ensure that the full required volume (5 doses) can be delivered following dilution and administration in line with the product information. The finished product specification includes a test to confirm the extractable volume from the vial provides 5 doses. During the procedure the applicant proposed to update the product information and instructions for use to indicate that up to 6 doses can be delivered from the vial. This proposed change to the product information was not considered acceptable as no supporting data were provided to demonstrate that 6 doses can be consistently extracted. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses (**REC21**).

A risk evaluation regarding the risk of N-nitrosamines impurities was provided concluding that there is no risk of the presence of nitrosamines in the finished product taking into account the active

substance, the finished product formulation and primary packaging. The risk assessment is considered acceptable.

It is recommended that a risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D **(REC17)**.

A question was raised during the procedure since no information and discussion was provided in the dossier on lipid-related impurities originating from the degradation of the LNP. It is argued by the applicant that with respect to potential lipid-related impurities originating from the degradation of LNPs, no degradation of the LNP FP has been observed in the stability studies at the recommended storage temperature (-70 to -90 °C) for the LNP as shown by specifications for size and polydispersity, RNA encapsulation, RNA and lipid content and RNA integrity quality attributes. This is acknowledged. In addition, further evaluation of lipid-related impurities in the finished product should be performed and the results submitted and discussed in the frame of a specific obligation (**SO2**).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The dossier includes release testing results of four recently manufactured GMP-batches. These finished product GMP batches were manufactured at the commercial FP manufacturing site. The release data for these GMP-batches are compared to min-max ranges of the small-scale clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification. Therefore, it can be concluded that comparability has been sufficiently demonstrated for the attributes tested given the pandemic situation and considering that further data is to be provided in the frame of a specific obligation. In addition, the comparison will be further extended with additional characterization testing on future PPQ-batches of finished product. The applicant has confirmed that testing will be performed according to the finished product comparability testing protocol. and the results will be provided in the frame of specific obligation **(SO3)**.

Reference materials

The finished product reference materials is the same as for active substance.

Stability of the product

A shelf-life of 6 months for the finished product is proposed when stored at the recommended storage condition of -90°C to -60°C.

The applicant has provided stability results up to 6 months at -80 to -60°C of one clinical batch and up to 6 months of a non-clinical batch of finished product. Two weeks data are also provided for two emergency supply under recommended storage conditions. In addition, there are newly initiated stability studies on the recently manufactured GMP-batches as well as plans to initiate stability studies on the future PPQ-batches.

Stability data have also been provided at accelerated (-40°C to +5°C) and stressed (+25°C to +30°C) storage conditions.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological products: Stability testing of biotechnological/biological products) and the same or representative container-

closure system are used in these stability studies as will be used for commercial batches. The test methods used are stability indicating.

Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality at the recommended storage condition (-90 to -60°C).

The applicant has provided updated reports from the ongoing stability studies and the presented data are considered sufficient and in support of the shelf-life claim since comparability has been sufficiently demonstrated between commercial scale GMP batches and the small-scale clinical batches.

In addition, the initial in-use period for the thawed, undiluted vial is 5 days at 2-8°C followed by storage at up to 30°C for not more than 2 hours. This is found acceptable.

Chemical and physical in-use stability has also been demonstrated for 6 hours at 2ºC to 30ºC after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection.

It is described that the future PPQ-lots will be enrolled in the stability program and the stability protocol has been defined in the dossier. This is acceptable; however, the applicant should commit to provide the 6 months stability data for the PPQ-batches for assessment as soon as they are available. (**REC20**). Notwithstanding requests for further stability updates, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

It has been clarified by the applicant that results on photostability testing studies will be provided for assessment (**REC19**).

It is recommended that the applicant should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70°C to -20°C. In addition, the applicant should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8°C as well as the possibilities to extend the claims for transport conditions at 2-8°C **(REC22)**.

A shelf-life of 6 months for the finished product at -90 to -60°C is accepted.

Adventitious agents

Adventitious agents' safety evaluation has been provided for the AS manufacturing sites and for the finished product manufacturing site.

Reagents used in active substance manufacturing and in the establishment of the MCB and WCB are the only materials of animal origin used in the manufacture of BNT162b2. The applicant has identified contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents as the main theoretical risk associated with these ingredients and it is deemed of minimal risk.

Additional clarifications were requested and provided for a number of other materials.

Sufficient details on the aseptic validation filling and media fills have been provided. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process. Therefore, no additional concerns are raised.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the absence of validation data on finished product manufactured at the commercial site. These issues were classified as Major Objections (MOs).

After further information was obtained from the sites and inspectors, questions regarding the manufacturing were addressed and manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing and testing sites.

Some of the proposed sites for batch control testing are currently located in the USA. The following time-limited derogation has been introduced as a condition to the MA:

'*In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application'.*

Additional data have been submitted by the applicant during the procedure in response to the other MOs and other questions raised.

Having considered the emergency situation and the quality documentation provided, the CHMP imposed some specific obligations (SOs) with clearly defined due dates (refer to Conclusions for details). In addition, the CHMP adopted some Recommendations (RECs) to be addressed by the Applicant.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

Overall, the information provided is satisfactory. However, certain information is still pending due to the very short time frame of product development and will either be updated in the dossier imminently or further addressed in specific obligations and other post-approval measures.

Information on the manufacturing process and process controls for the manufacturing sites Andover and BNT Mainz & Rentschler have been provided and are considered satisfactory.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: increased process scale, DNA template changed from a PCR template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UFDF steps. Based on the differences observed between batches manufactured by active substance Process 1 and 2 for the CQA mRNA integrity and lack of characterisation data, a MO was raised regarding comparability, characterisation and clinical qualification of the one proposed acceptance criteria. Biological characterisation of the active substance was limited, and additional data and discussion were requested to address functionality. Additional characterisation data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay **(SO1).**

Truncated RNA species are regarded as product-related impurities and can be expected due to the principle of the in-vitro transcription reaction (i.e. directional polymerase activity) and (theoretical) hydrolysis during manufacturing. Analysis of RNase treated samples showed that all species detected

by the capillary gel electrophoresis (CGE)-based method are composed of RNA. Manufacturing consistency with respect to fragmented species has been sufficiently demonstrated.

There were some differences in truncated RNA species level, however further analyses revealed a comparable overall fragmentation profile among Process 1 and Process 2 active substance batches. Additionally, oligonucleotide mapping data demonstrated no significant differences observed between Process 1 and Process 2 active substance batches.

The company does not expect truncated transcripts formulated in the finished product to pose a safety or efficacy concern, as in their view no protein expression is expected from truncated transcripts. Further, clinical trials with process 1 material have not revealed major safety concerns to date. Truncated BNT162b2 RNA species lacking either the 5′ cap or the poly(A) tail are expected to be rapidly targeted for degradation in the cytoplasm or would show a decrease or loss of translation efficiency. Preliminary characterization data on isolated fragment species suggest that fragment species predominantly include the 5′-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction.

However, as the overall characterisation of the truncated species is still limited, additional analysis of truncated species, additional translated protein characterisation, additional characterisation of lipid-related impurities and potential lipid-RNA species should be provided to support that they are not impacting clinical performance in terms of safety and/or efficacy. The current specification allows for a certain level of truncated mRNA species to be present however data from recent batches have shown levels of truncated species below that level. No related safety issues have been identified in the clinical studies thus far in subjects who received vaccine containing up to a certain level of truncated species. Therefore, the current specification is considered acceptable subject to the submission of additional data in the frame of a specific obligation (**SO1**).

Based on available data, the proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing. However, the length of the poly(A) tails in BNT162b2 active substance is critical for RNA stability and translational efficiency and therefore should be introduced in active substance release testing in the frame of a specific obligation (**SO2**). Moreover, the active substance specification acceptance limits should be re-assessed and revised as appropriate, as further data become available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

It is noted that the Applicant states that testing is currently in progress on the clinical batches and data for these batches, as well as any new data available for the primary process validation batches, will be provided. Based on the limited stability data presented, a shelf-life is approved for the active substance.

Finished product

The finished product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described including studies that were performed with available active substance, representative of the mRNA platform and included in the finished product.

The development of the manufacturing process is extensively described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication and bulk finished product formulation followed by fill and finish, and the process has been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for the attributes tested and will be subject to a specific obligation.

Limited data on the finished product batches manufactured at the commercial facility (entire manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, active substance from process 2) were presented. A process validation plan for PPQ lots has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program, also comprising the commercial facility at Puurs, Belgium, has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(SO3).**

The specifications for finished product include a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised, i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity. Whilst FP specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

Two novel excipients are included in the LNP. Complete information is not provided for both the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. In order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch to batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with specific obligations **(SO4, SO5).**

Lipid-related impurities have been observed in some recently manufactured finished product batches. For the batches with lipid-related impurities the existing quality control parameters including RNA integrity remain unchanged.

Considering the above and the emergency situation, the characterisation of the active substance and finished product is considered acceptable, and the proposed specifications for RNA Integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. These data are requested to be provided as specific obligations to the applied conditional marketing authorisation **(SO1, SO2)**.

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine from Process 1. The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities. The suitability of the analytical methods used for control of potency and poly(A) tail have not been fully demonstrated.

Data demonstrate the presence of significant amounts of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are poorly characterised, and the limited data provided for protein expression do not fully address the uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein.

The control strategy for active substance and finished product is important to guarantee acceptable quality and ensure batch to batch consistency of the finished product. Regarding the proposed control strategy, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Truncated and modified RNA are present as impurities. Considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell there is a possibility that aberrant proteins will be expressed with possibilities for unwanted immunological events. The risk of this occurring is considered low based on the following observations and considerations:
    - Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
    - The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA.
    - The level of any individual aberrant mRNA species would in any way be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The amount of the protein would be expected to be too low to elicit an immune response. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the aberrant protein would be non-significant.
- Lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to the specific obligations abovementioned.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While the characterisation data still

need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In addition, and in accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

In the context of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs):

- SO1: In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. **Due date: July 2021. Interim reports: March 2021.**
- SO2: In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. **Due date: July 2021. Interim reports: March 2021.**
- SO3: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data. **Due date: March 2021.**
- SO4: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **Due date: July 2021, Interim reports: January 2021, April 2021.**
- SO5: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **Due date: July 2021, Interim reports: January 2021, April 2021.**

As regards SO1, the following data are requested in order to complete the information on the active substance and finished product characterisation.

a) Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into

truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. **Due date: July 2021. Interim reports: March 2021, and on a monthly basis.**

b) The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail. **Due date: July 2021. Interim report: March 2021**

c) Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **Due date: July 2021. Interim report: March 2021**

As regards SO2, the following data are requested to be provided in order to ensure a comprehensive control strategy, including active substance and finished product specifications:

a) The active substance and finished product specifications acceptance limits, should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. **Due date: July 2021, Interim reports March 2021, and on a monthly basis.**

b) Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set. **Due date: July 2021, Interim reports: March 2021**

c) The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes. **Due date: July 2021, Interim reports: March 2021**

d) Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability. **Due date: July 2021, Interim reports: March 2021.**

e) Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. **Due date: July 2021, Interim reports: March 2021**

f) Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021. **Due date: July**

2021, Interim reports (LMS content in commercial FP batches, investigation results): March 2021, and on a monthly basis.

As regards SO3, the following data are requested to be provided in order to ensure batch to batch consistency and to complete the information on process validation of the finished product manufacturing process.

a) Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities. **Due date: March 2021.**

b) The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment. **Due date: March 2021.**

As regards SO4, the data are requested to be provided regarding the synthetic process and control strategy for the excipient ALC-0315 in order to improve the impurity control strategy, assure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product.

a) A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed **by July 2021. Interim report: January 2021**

c) Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. **Due date: July 2021, Interim report: January 2021**

d) Information and justification on critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate. **Due date: July 2021**

g) The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product. **Due date: July 2021**

h) Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided. **Due date: July 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

As regards SO5, the following data is requested to be provided regarding the synthetic process and control strategy for ALC-0159 in order to improve impurity control strategy, assure comprehensive control and batch-to-batch consistency throughout the lifecycle of the active product.

a) A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG. **Due date: July 2021, Interim report: January 2021**

c) Information and justification of critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

d) The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product. **Due date: July 2021, Interim report: April 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate. **Due date: July 2021**

g) Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis. **Due date: January 2021**

h) Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided. **Due date: July 2021, Interim report: April 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

2.2.6. Recommendations for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1. The MAH should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials.
2. The MAH should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases.
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.
4. The MAH should reassess the specification for the linear DNA template purity and impurities. The Applicant has already agreed to supply these by Q2 2021.
5. The MAH should perform and document a gap analysis to identify any supplemental qualification needed to align the methods used for the DNA template control with ICH requirements. The gaps identified should be addressed either prior to transferring the methods to relevant sites or during the transfer activities.
6. The MAH should provide active substance process validation data regarding the finalised

indirect filter qualification assessment and the shipping validation between sites.

7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step.
8. The MAH should tighten the low limits of the proven acceptable ranges for the target volumes for ATP and CTP, to the levels needed to ensure a sufficiently high mRNA integrity in the active substance manufacturing process.
9. The MAH should comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance.
10. The MAH should discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterization of protein expression for the active substance.
11. The MAH should provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in BNT162b2 active substance.
12. In order to improve the control strategy, the MAH should provide the protocol on preparation and qualification of future primary and working reference standards for the active substance.

Finished Product

13. The updated results from the finished product leachables studies should be provided for assessment.
14. In order to ensure batch to batch consistency of the finished product the MAH should expand the description of the manufacturing process with more details. (1) When the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated. (2) The MAH should confirm the configuration of filters used in finished product manufacture. (3) The surface area of the sterile filter should be adapted to the batch size, unless otherwise justified; (4) process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes
15. Data on verification of in-process test methods should be provided for assessment during Q1 2021.
16. In order to improve the control strategy, the MAH should provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation.
17. A risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). A summary of this risk assessment should be submitted. The risk assessment should cover all relevant elements and sources in accordance with the guideline. The summary must enable a quantitative comparison of observed or predicted levels with the PDE’s given in the guideline. It should contain what is necessary to evaluate the appropriateness and completeness of the risk assessment, including any assumptions, calculations etc. made. The control strategy for elemental impurities should be justified based on the risk assessment.
18. The MAH should provide the protocol on preparation and qualification of future primary and working reference materials for finished product testing.
19. In order to provide further information regarding the stability of finished product, Results from photostability testing and temperature cycling studies of the finished product should be provided for assessment in Q1 2021.
20. The applicant should provide the 6 months stability data for the finished product process performance qualification batches for assessment as soon as they are available.
21. This applicant proposed change to the product information to indicate that up to 6 doses can

be delivered from the vial was not considered acceptable as no supporting data was provided. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses.

22. The MAH should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70 °C to -20 °C. In addition, the MAH should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8 °C as well as the possibilities to extend the claims for transport conditions at 2-8 °C.
23. The MAH should provide the results for assessment from the filter validation as soon as they are available.

2.3. Non-clinical aspects

GLP inspections

The pivotal toxicological studies are stated to be GLP compliant by the Applicant. There were some issues identified during the assessment with repeat-dose toxicity study #38166 regarding the documentation which have led to a study audit GLP inspection conducted by the local German GLP Compliance Monitoring Authority at the facility where the study was performed, in November 2020. All the answers to the issues were acknowledged by the CHMP. The Applicant gave also comments on these issues. In light of all the elements provided, the issues identified were considered resolved.

With regard to repeat-dose toxicity study #20GR142 the only major concern identified was resolved with the answers from the Applicant that were considered satisfactory by the CHMP.

2.3.1. Pharmacology

The pharmacology dossier is based on initial studies of the functionality of the BNT162b2 (V9) RNA-based product and the encoded SARS-CoV-2 P2 S protein as well as on supporting studies of SARS-CoV-2 P2 S protein structure. This is followed by characterisation of the humoral and cellular immune response in mouse and nonhuman primate upon immunization with BNT162b2 (V9) and ends up with a SARS-CoV-2 challenge study of BNT162b2 (V9) immunized nonhuman primates.

No secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies have been conducted with BNT162b2 due to the nature of the RNA-based vaccine product, which is according to applicable guidelines (WHO guideline on nonclinical evaluation of vaccines, WHO Technical Report Series, No. 927, 2005).

Mechanism of action

SARS-CoV-2 infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, of which the angiotensin converting enzyme 2 (ACE2) may constitute a major part, as recently suggested. In addition to the initial attachment to a host cell, the S protein is also responsible for viral envelope fusion with the host cell membrane resulting in genome release. Due to its indispensable role, the S protein is a major target of virus neutralizing antibodies and has become a key antigen for vaccine development. By immunisation with the modified RNA (modRNA) product BNT162b2, encoding for the S protein, the intention is to trigger a strong and relatively long-lasting production of high affinity virus neutralizing antibodies, which can act through blocking the S-protein and it's receptor-binding domain (RBD) interaction with host cell receptors but also by opsonisation mediated virus clearance. In addition, the immunisation with BNT162b2 is also intended to elicit a concomitant T cell response of the Th1 type, supporting the B cells responsible for the production of S-specific antibodies and cytotoxic T cells that kill virus infected cells.

The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation before engaging with a target cell. BNT162b2 encodes a P2 mutant (P2 S) variant of S where two consecutive proline mutations have been introduced in order to lock the RBD in the prefusion conformation. In addition, BNT162b2 is nucleoside-modified by a substitution of 1-methyl-pseudouridine for uridine and thus its inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors (TLRs) 7 and 8, is dampened, but not abrogated. Furthermore, the structural elements of the vector backbones of the BNT162b2 are optimised for prolonged and strong translation of the antigen-encoding RNA.

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al, 2019; Patel et al, 2019); ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface. The composition of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity.

Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Primary pharmacodynamic studies

Primary pharmacodynamic studies in vitro

To confirm the functionality of the BNT162b2 (V9) RNA-based product, protein expression, transfection frequency from BNT162b2 and cell surface expression of the SARS-CoV-2 P2 S protein antigen was assessed. BNT162b2 (V9) transfection of HEK293T cells indicated SARS-CoV-2 P2 S was correctly expressed on the cell surface, as indicated by flow cytometry staining of non-permeabilized cells with an anti-S1 monoclonal antibody. In addition, the cellular localisation of expressed S1 protein was investigated. The S protein co-localized with an ER marker, as detected by immunofluorescence experiments in HEK293T cells expressing BNT162b2-RNA, suggesting the S protein is processed within the ER.

In a set of supportive studies, it was investigated whether BNT162b2 RNA encodes for an amino acid sequence that authentically express the ACE2 binding site (RBD). Recombinant P2 S was expressed from DNA encoding for the same amino acid sequence as BNT162b2 RNA encodes for. Flow cytometry staining with spike protein (S) binding agents, as human ACE2 and monoclonal antibodies known to bind to authentic S-protein all indicated an authentically presented P2 S protein and ACE2 binding site. Low nanomolar affinity of P2 S binding to ACE2 PD and B38 mAb was demonstrated with the use of biolayer Interferometry.

To further structurally characterize the P2 spike protein, a cryo-electron microscopy (cryoEM) investigation of purified P2 S, expressed from DNA, was conducted. The cryoEM revealed, according to

the Applicant, a particle population closely resembling the prefusion conformation of SARS-CoV-2 spike protein. By fitting a previously published atomic model on to a processed and refined cryoEM dataset, a rebuilt model was obtained showing good agreement with reported structures of prefusion full-length wild type S and its ectodomain with P2 mutations. In the prefusion state the RBD undergo hinge-like conformational movements and can either be in an "up" position (open for receptor binding) or in a "down" position (closed for receptor binding). Three-dimensional classification of the dataset showed a class of particles that was in the conformation one RBD 'up' and two RBD 'down". This partly open conformation represented 20.4% of the trimeric molecules. The remainder were in the all RBD 'down' conformation. Although potent neutralizing epitopes have been described when the RBD is in the "heads down" closed conformation, the "heads up" receptor accessible conformation exposes a potentially greater breadth of neutralizing antibody targets. It is concluded that antibodies to both the up and down conformations will potentially be formed upon immunisation with the P2 S encoding BNT162b2.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates. The choice and relevance of the mouse for pharmacological animal model studies was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Non-human primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. The selection of rats as the toxicology test species is consistent with the World Health Organization (WHO) guidance documents on nonclinical evaluation of vaccines (WHO, 2005). The documents recommend conducting vaccine toxicity studies in a species which mounts an immune response to the vaccine. The Wistar Han (WH) rat developed an antigen-specific immune response following BNT162b2 vaccination.

Balb/c, females were immunized IM on day 0 with 0.2, 1 or 5 µg RNA/animal of BNT162b2 (V9), or with buffer alone (n=8). Blood samples were collected on Days 7, 14, 21 and 28 after immunization. The IgG antibody response to SARS-CoV-2- RBD or S1 was analysed by ELISA. Immunization with BNT162b2 induced IgGs that bound to S1 and RBD, as detected by ELISA, and on day 28 after immunization showed a binding affinity of KD 12 nM or 0.99 nM (geometric mean) respectively, as detected by surface plasmon resonance.

To further characterise the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virus type neutralization assay (pVNT) was used as a surrogate of virus neutralization since studies with authentic SARS-CoV-2 requires a BSL3 containment. The pVNT was based on a recombinant replication-deficient vesicular stomatitis virus (VSV) vector that had been pseudotyped with SARS-CoV-2 S protein according to published protocols. A dose-dependent increases in SARS-CoV-2-S VSV pseudovirus neutralizing antibodies were observed in sera from BNT162b2-immunized mice. On day 14, the difference of the group treated with 5 µg RNA compared to the buffer control was statistically significant ($p = 0.0010$). On days 21 and 28, the differences of the groups treated with 1 µg and 5 µg BNT162b2 compared to the buffer control were statistically significant. The relevance of the pseudovirus assay for authentic SARS-CoV-2 was not discussed. For technical reasons, it was not possible to determine a ratio of neutralizing to non-neutralizing antibodies.

Immunisation of mice with BNT162b2 also induced IFN-γ secreting cells of both the CD4+ and CD8+ T-cell subsets. This was shown by ELISPOT after *ex vivo* re-stimulation of splenocytes with an S-protein overlapping peptide pool Day 28 after immunization. Cytokine profiling was also carried out by Multiplex analysis of cytokine release from the Day 28 Splenocytes. High levels of the Th1 cytokines IFNγ and IL-2 but minute amounts of the Th2 cytokines IL-4, IL-5 and IL-13 were detected after re-stimulation with S but not RBD overlapping peptide mix. The much higher immune cellular responses

elicited against the S1 protein compared to the RBD domain could be explained by the presence of significantly more T cell epitopes in the larger full-length S peptide mix (in addition, S1 covers the RBD domain). It should be emphasized that cellular immune reactivity is much more important against S1 than against the RBD domain, where neutralizing antibodies are more important to the latter. In addition, an elevated secretion of TNFα, GM-CSF, IL-1β, IL-12p70 and IL-18 was recorded after re-stimulation. In order to characterize the immunophenotype of B-and T-cells appearing in lymph nodes from mice immunized with BNT162b2 (V9), B- and T-cell subsets in draining lymph node cells were quantified by flow cytometry 12 days after immunization. Higher numbers of B cells were observed in the samples from mice that received BNT162b2 compared to controls. That included plasma cells, class switched IgG1- and IgG2a-positive B cells, and germinal centre B cells. T-cell counts were elevated, particularly numbers of T follicular helper (Tfh) cells, including subsets with ICOS upregulation, which play an essential role in the formation of germinal centres (Hutloff 2015).

In the nonhuman primate (rhesus macaques) studies, BNT162b2 (V9) was shown to be immunogenic after intramuscular administration. The serum concentrations of both S1-binding and the SARS-CoV-2 neutralizing antibody titres were at least an order of magnitude higher after BNT162b2 immunization of rhesus macaques than for the panel of SARS-CoV-2 convalescent human sera. In this study, total antibody response is measured using a luminex assay and results expressed on U/ml and for the neutralization assay results are expressed in VNT 50.

Antigen specific S-reactive T-cell response after BNT162b2 immunization of the macaques was measured by ELISPOT and ICS. While S-specific T cells were low to undetectable in naïve animals, strong IFNγ but minimal IL-4 ELISpot responses were detected after the second 30 or 100 µg dose of the BNT162b2. Intra cellular staining (ICS) confirmed that BNT162b2 immunization elicited strong S-specific IFNγ producing T cell responses, including a higher frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-alpha but a lower frequency of CD4+ cells that produce IL-4. An S-specific IFNγ producing CD8+ T cell response was also recorded.

A challenge study in rhesus macaques was conducted as nonclinical proof of concept (PoC). Rhesus macaques share a 100% homology with the human ACE2 sequence that interacts with the RBD of the S protein. BNT162b2 (V9) immunized macaques were challenged with SARS-CoV-2 intra nasally and intratracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21, in order to align with the clinical vaccination regimen. Some other COVID-19 vaccine candidates have different prime-boost intervals, such as 4 weeks for both ChAdOx1 (Graham et al., 2020) and mRNA-1273 (Corbett et al., 2020). At the time of challenge, SARS-CoV-2 neutralising titres ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralising titres were undetectable in animals from the control-immunized and sentinel groups. The presence of SARS-CoV-2 RNA was monitored by nasal and oropharyngeal (OP) swabs and bronchoalveolar lavage (BAL). Viral RNA was detected in BAL fluid from 2 of the 3 control-immunized macaques on Day 3 after challenge and from 1 of 3, on Day 6. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2 (V9)-immunized and SARS-CoV-2 challenged macaques. The difference in viral RNA detection in BAL fluid between BNT162b2-immunized and control-immunized rhesus macaques after challenge is statistically significant (p=0.0014). From control-immunized macaques, viral RNA was detected in nasal swabs obtained on Days 1, 3, and 6 after SARS-CoV-2 challenge; from BNT162b2 (V9)-immunized macaques, viral RNA was detected only in nasal swabs obtained on Day 1 after challenge and not in swabs obtained on Day 3 or subsequently. The pattern of viral RNA detection from OP swabs was similar to that for nasal swabs. No signs of viral RNA detected vaccine-elicited disease enhancement were observed. The viral RNA levels between control-immunized and BNT162b2-immunized animals after challenge were compared by a non-parametric analysis (Friedman's test), and the p-values are 0.0014 for BAL fluid, 0.2622 for nasal swabs, and 0.0007 for OP swabs.

Despite the presence of viral RNA in BAL fluid from challenged control animals, none of the challenged animals, immunized or control, showed clinical signs of illness (weight change, body temperature change, blood oxygen saturation and heart rate). The Applicant concluded, the absence of clinical signs in any of the challenged animals, immunised or control, despite the presence of viral RNA in BAL fluid from challenged control animals, indicates that the 2-4 year old male rhesus monkey challenge model appears to be an infection model, but not a clinical disease model. However, a further investigation by lung radiograph and computerized tomography (CT) was conducted. Radiographic evidence of pulmonary abnormality was observed in challenged controls but not in unchallenged sentinels nor in challenged BNT162b2-immunized animals except for a CT-score signal in 1 of 6 pre infection and 2 out of six at Day 10/EOP in BNT162b immunised animals. The CT score signal was at the same level as the control at Day 10/EOP. No radiographic evidence of vaccine-elicited enhanced disease was observed.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2, which is acceptable to the CHMP.

Safety pharmacology studies

No safety pharmacology studies were conducted with BNT162b2. The Applicant refers to that they are not considered necessary according to the WHO guideline (WHO, 2005). In addition, no findings on vital organ functions have been recorded in the repeat dose toxicology studies. Thus, the absence of safety pharmacology studies is endorsed by the CHMP.

Pharmacodynamic drug interactions studies

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is agreeable to the CHMP.

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial t½ of 1.62 and 1.72 h, respectively. 24 hours post-dosing, less than 1% of the maximum plasma concentrations remained. A slower clearance rate was observed after 24 hours with ALC-0315 and ALC-0159 terminal elimination t½ of 139 and 72.7 h, respectively.

Following plasma clearance, the liver appears to be to major organ to which ALC-0315 and ALC-0159 distribute. The applicant has estimated the percent of dose distributed to the liver to be ~60% for ALC-0315 and ~20% for ALC-0159. The observed liver distribution is consistent with the observations from the biodistribution study and the repeat-dose toxicology, both using IM administration.

For ALC-0315 (aminolipid), the maximum detected concentration in the liver (294 µg/g liver) was reached 3 hours after IV injection. ALC-0315 was eliminated slowly from the liver and after 2-weeks the concentration of ALC-0315 was still ~25% of the maximum concentration indicating that ALC-0315 would be eliminated from rat liver in approximately 6-weeks. For ALC-0159 (PEG-lipid), the maximum detected concentration in the liver (15.2 µg/g liver) was reached 30 minutes following IV injection. ALC-0159, was eliminated from the liver faster than ALC-0315 and after 2-weeks the concentration of ALC-0159 was only ~0,04% of the maximum detected concentration. The applicant was asked to discuss the long half-life of ALC-0315 and its effect, discussion on the comparison with patisiran, as well as the impact on the boosts and post treatment contraception duration. The applicant considered that there were no non-clinical safety issues based on the repeat dose toxicity studies at doses (on a mg/kg basis) much greater than administered to humans; this was acceptable to the CHMP.

Both patisaran lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives. According to the applicant, it is difficult to further contextualize the pharmacokinetic data and therefore to understand the safety of these molecules, beyond consideration of dose. There is a large dose differential between the human BNT162b2 dose and the dose used in the toxicity studies (300-1000x) which provides an acceptable safety margin.

Moreover, according to the Applicant given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. Finally, the applicant is of the opinion that these results support no requirements for contraception. The CHMP found this position agreeable.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159.

Biodistribution of a LNP-formulated luciferase surrogate reporter:

To determine the biodistribution of the LNP-formulated modRNA, the applicant did study distribution of the modRNA in two different non-GLP studies, in mice and rats, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2 (mouse study) or the biodistribution of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation (rat study).

The mouse study used three female BALB-c mice per group and luciferase protein expression was determined by *in vivo* bioluminescence readouts using an *In Vivo* Imaging System (IVIS) following injection of the luciferase substrate luciferine. The readouts were performed at 6h, 24h, 48h, 72h, 6d and 9d post IM injection (intended clinical route) in the right and left hind leg with each 1 µg (total of 2µg) of LNP-formulated luciferase RNA.

In vivo luciferase expression was detected at different timepoints at the injection sites and in the liver region indicating drainage to the liver. As expected with an mRNA product, the luciferase expression was transient and decreased over time. Luciferase signals at the injection sites, most likely reflecting distribution to the lymph nodes draining the injection sites, peaked 6h post injection with signals of

approximately 10 000 times of buffer control animals. The signal decreased slowly during the first 72 hours and after 6 and 9 days the signals were further weakened to approximately levels of 18 and 7 times the signals obtained from animals injected with buffer control.

The signals from the liver region peaked 6h post injection and decreased to background levels 48h after injection. The liver expression is also supportive of the data from the rat PK study and the findings in the rat repeat-dose toxicological study showing reversible liver vacuolation and increased γGGT levels.

The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.

Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Immunogenicity of a LNP formulated luciferase modRNA:

Activation of the innate immune system following IM injection of a LNP-formulated luciferase reporter RNA into mice was assessed in a Luminex-based multiplex assay were serum samples (day -1 (pre), 6 h and day 9) were tested for levels of the following chemokines and cytokines: MCP-1, MIP-1β, TNF-α, IFN-α, IFN- γ, IL-2, Il-6, IL-10, IL1-β, IP-10. The applicant tested 3 different LNPs, all formulated together with luciferase RNA. The results suggest that the LNP formulation used in BNT162b2 (LNP8) slightly increased levels of MCP-1, IL-6, and IP-10 at 6h post immunisation. All chemokine/cytokine levels dropped to background levels at day 9.

In addition to innate immune activation, LNP formulated luciferase modRNA was able to induce IFN-γ T-cell responses (when challenged with MHC I-specific luciferase peptide pools) measured in splenocytes isolated from the mice at day 9.The LNP formulated luciferase modRNA did not induce the formation of luciferase-specific IgGs as measured by ELISA.

In an additional hPBMC study (R-20-0357), overall, low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. IP-10, MIP-1b, MCP-1 were seen to be increased among donors, because of transfection of antigen presenting cells after infection.

Metabolism of the two novel LNP-excipients ALC-0315 and ALC-0159:

Metabolism studies were conducted to evaluate the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid). No metabolic studies were performed with the modRNA or the other two lipids of the LNP. Overall, it seems as both ALC-0159 and ALC-0315 are metabolised by hydrolytic

metabolism of the amide or ester functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

The metabolism of the novel excipients, ALC-0159 and ALC-0315, were examined *in vitro* using blood, liver S9 fractions and hepatocytes, all from mouse, rat, monkey and human. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver from a rat pharmacokinetics study where a luciferase-encoding modRNA formulated in an LNP was used.

Metabolism of ALC-0315 appears to occur via two sequential ester hydrolysis reactions, first yielding the monoester metabolite followed by the doubly de-esterified metabolite. The monoester metabolite was observed *in vitro* in rat blood, monkey S9 fraction, and *in vivo* in rat plasma and rat liver. The doubly de-esterified metabolite was observed *in vitro* in mouse and rat blood; monkey liver S9 fraction; and *in vivo* in rat plasma, urine, faeces and liver. Subsequent metabolism of the doubly de-esterified metabolite resulted in a glucuronide metabolite which was observed in urine only from the rat pharmacokinetics study. Additionally, 6-hexyldecanoic acid, the acid product of both hydrolysis reactions of ALC-0315, was identified *in vitro* in mouse and rat blood; mouse, rat, monkey and human hepatocytes; mouse, rat and human liver S9 fractions; and *in vivo* in rat plasma.

ALC-0315 was stable over 120 min (>93% remaining) in liver microsomes and S9 fractions and over 240 min (>93% remaining) in hepatocytes in all species and test systems.

The primary route of metabolism for ALC-0159 appears to involve amide bond hydrolysis yielding *N*,*N*-ditetradecylamine. This metabolite was identified in mouse and rat blood as well as hepatocytes and liver S9 from mouse, rat, monkey and human.

ALC-0159 was stable over 120 min (>82% remaining) in liver microsomes and S9 fractions and over 240 min (>87% remaining) in hepatocytes in all species and test systems.

Excretion of the two novel LNP-excipients ALC-0315 and ALC-0159:

Excretion of the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) was studied in the rat PK study. No excretion studies were performed with the modRNA or the other two lipids of the LNP which is considered acceptable by the CHMP.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Since almost no unchanged ALC-3015 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.3.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies and one DART fertility-EFD rat study. The test substance in the repeat-dose toxicity studies is BNT162b2 (100 µg of variant 8 in one study (study 38166) and 30 µg of the clinically relevant variant 9 in the second study (study 20GR142)), which consists of a modified RNA in a lipid nanoparticle (LNP) formulation. The differences between the variants are due to codon optimization. The LNP contains four excipients whereof two are considered novel (ALC-0315 and ALC-0159).

Repeat dose toxicity

The two general/repeat-dose toxicity studies involved IM exposure of Han Wistar rats to BNT162b2 for a total of 17 days (three weekly administrations) followed by three weeks of recovery. Overall, the

study designs only included a single experimental group each with a variant of BNT162b2 (V8 or V9 variant), with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. No test substance-linked mortality or clinical signs were observed (except a slight increase [<1C] in body temperature). No ophthalmological and auditory effects were found. The animal model of choice, the rat, has not been assessed in the pharmacological dossier but a limited absorption/distribution study has been conducted in pharmacokinetics dossier. Immunogenicity was assessed in the toxicology studies.

Body weight and food intake: Exposure generated a slight reduction of absolute BW statistically significant at D9 (-6.8% to -11.3%; BNT162b2 V8) alternatively a weak body weight increase reduction [BNT162b2 v9]. No changes in food intake were observed.

Gross pathology and organ weights: At 100ug BNT162b2 V8 and 30ug BNT162b2 V9, the tissue at the injection site was thickened/enlarged with oedema and erythema at the end of exposure in a reversible manner. The spleen was enlarged (reversible) with up to 60% for both vaccine variants and doses. There was also an enlargement of the draining and inguinal lymph nodes at 100ug (BNT162b2 V8). Overall, there were signs of a significant immune response which is likely linked to the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8) but not at 30ug (BNT162b2 V9).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis inflammation and epidermis hyperplasia). Also, there was inflammation of the perineural tissue of the sciatic nerve and surrounding bone in most rats at d17. The bone marrow demonstrated increased cellularity and the lymph nodes showed plasmacytosis, inflammation and increased cellularity. The spleen demonstrated increased haematopoiesis in half the animals at d17. The liver showed hepatocellular periportal vacuolation at d17 (fully reversed during recovery) which may be related to hepatic clearance of ALC0315. Histopathology assessment of 30ug BNT162b2 V9 generated similar results as 100ug BNT162b2 V8 although not on as extensive level (possibly due to a lesser dose). Minimal to moderate inflammation and oedema was observed at the injection site (usually resolved after ~3d). There was minimal to moderate increased plasma cell cellularity in the lymph nodes and germinal center cellularity plus hematopoietic cell cellularity in the spleen at d17 (reversible at end of recovery). There was minimal increase cellularity in the bone marrow. Reversible vacuolisation in the liver was also observed.

The Applicant explained that peri-portal liver vacuolization was observed in both pivotal studies but are not related to any microscopic evidence of liver/biliary injury in animals (cellular hypertrophy, inflammation) nor any clinical data from Phase 1 study. Vacuoles are considered by the Applicant to be a result of ALC-0315 accumulation in liver and not PEG.

A novel finding at 30ug was minimal extra-capsular inflammation in the joints at d17.

Moreover, increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells does not provide additional information. The CHMP found this agreeable.

Immunogenicity: Treatment of rats with 100 ug BNT162b2 V8 generated SARS-CoV-2 neutralizing titers (based on a vesicular stomatitis virus (VSV)-based pseudovirus neutralization assay) and IgG antibodies against the S1 fragment and the RBD (based on ELISA) in serum samples. Treatment of

rats with 30 ug BNT162b2 V9 generated SARS-CoV-2 neutralizing antibodies (not a pseudovirus neutralization assay).

Haematology: At 30ug BNT162b2 V9 and 100ug BNT162b2 V8, there was a moderate to strong reduction of reticulocytes (48-74%, not specified for V9) coupled to lowered red cell mass parameters (RBC, HGB, and HCT). There was a moderate to strong increase (>100%) in large unclassified cells [LUC], neutrophils, eosinophils, basophils and fibrinogen that may be related to the inflammatory/immune response. The changes were reversible. No effects on coagulation were observed for V8 whereas a slight increase in fibrinogen was observed with V8 and V9.

Clinical pathology: A very strong but reversible increase (>100%) in pro-inflammatory acute phase proteins in the blood (A1AGP, A2M) was seen with both 30ug BNT162b2 V9 and 100ug BNT162b2 V8. Also, indicative of pro-inflammation, a slight to moderate reduced albumin/globulin ratio was seen for both variants. V8 (100ug) exposure generated increased levels of γGT (>200%) and increased γGT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate increases in AST and ALP levels (+20-100%), possible indicative of liver effects but no changes in γGT levels. There were no changes in cytokine levels (IFNγ, TNFalpha, Il-1b, Il6, Il-10) after 100ug V8 exposure (not measured for V9). For 100ug V8, there were no changes measured in urine whereas there was a slight-moderate reduction in pH for 30ug V9.

Genotoxicity

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

Reproduction Toxicity

In the DART study, the test substances used were BNT162b1, BNT162b2 and BNT162b3, which were given to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). The test substances were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 doses. A subgroup was terminated at GD21 and another (litter) group was terminated at PND21. SARS-CoV-2 neutralizing antibody titers were found in the majority of females just prior to mating (M-14), in most females and foetuses at the end of gestation (GD21), and in most offspring at the end of lactation (PND21). There was transient reduced body weight gain and food consumption after each dose. No effects on the estrous cycle or fertility index were observed. There was an increase (~2x) of pre-implantation loss (9.77%, compared to control 4.09%) although this was within historical control data range (5.1%-11.5%). Among foetuses (from a total of n=21 dams/litters), there was a very low incidence of gastroschisis, mouth/jaw malformations, right sided aortic arch, and cervical vertebrae abnormalities, although these findings were within historical control data. Regarding skeletal findings, the exposed group had comparable to control group levels of presacral vertebral arches supernumerary lumbar ribs, supernumerary lumbar short ribs, caudal vertebrae number < 5). There were no signs of adverse effects on the postnatal

pups (terminated at PND21). It is noted that there is currently no available data on the placental transfer of BNT162b2. This information is reflected in section 5.3 of the SmPC.

Local Tolerance

No dedicated local tolerance studies have been conducted; however the assessment of local tolerance was performed in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly slight to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The data for 30ug BNT162b2 V9 exposure indicated less severe but similar effects.

2.3.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The proposed medicinal product is composed of a modRNA formulated with functional and structural lipids forming lipid nano particles (LNPs), the latter having the purpose to protect the modRNA from degradation and enable transfection of the modRNA into host cells after IM injection. The composition of the LNPs is likely to affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity (see also toxicology below).

The general immune activating mode of action of LNP-formulated RNA vaccines have been described in the literature. The administration of LNP-formulated RNA results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Whether other cells than professional APCs may transiently express the vaccine derived spike protein and therefore from a theoretical point of view, as compared to SARS-CoV-2 infected cells, also could potentially be targets for previously primed spike protein reactive cytotoxic T cells, if present, is not known. However, no overt signs of such adverse pharmacological responses have been recorded in the repeat dose toxicity study or in the clinical trials. In the clinical trial, a second dose was administered to patients who had been immunologically primed by the first dose. Moreover, in the clinical trials it appeared around 270 patients that was shown to have been seropositive for SARS-COV-2 before vaccination. In these cases, the expression of the spike protein on host cells occurred in the presence of a primed immune response to the spike protein but no overt adverse pharmacological response has been observed. The low amount of vaccine product in a single dose may limit the distribution of modRNA/LNP mainly to the injection site and to migrating APCs. Due to the transient expression of the modRNA, no persistent expression is expected.

Regarding the structural and biophysical characterization of the modRNA, a schematic description shows that 5 different sequences are included in the BNT162b2, of which two being coding sequences.

Concerning the protein expression obtained from the V8 and V9 variants, specific immune responses (total IgG binding Ab + neutralizing Ab) were obtained at significant levels against the Spike S protein in animals with both variants (in mice and rats), indicating the efficiency of the *in vivo* expression of Spike S protein. An additional study was provided (R-20-0360) further demonstrating *in vitro* protein expression. Transfection efficiency, expression rate and cellular viability were analysed in HEK293T cells, upon transfection with different constructs (saRNA, uRNA, modRNA V8 and V9). HEK293T cells were efficiently transfected by both modRNA V8 and modRNA V9 with higher transfection rate for V9, but quite similar the expression rate by V8 and V9.

Although some of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided, it was investigated in supportive studies based on P2S expressed from DNA and not the product modRNA. While it is not considered to be of critical importance for the assessment in this procedure, it still provides a scientific understanding supporting the nonclinical key studies of humoral and cellular immune response, including SARS-CoV-2 neutralizing antibodies, as well as SARS-CoV-2 challenge nonclinical PoC.

In-vivo pharmacodynamics: The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates and was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Nonhuman primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. This is accepted but a more in-depth discussion on the suitability of these pharmacological animal models have not been provided (e.g. susceptibility for SARS-CoV-2 infection and similarity to COVID 19 disease; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains). Only single immunisation was conducted in mice, as compared to the clinical 2-dose regimen, which was adequate since only characterization of the immune response, but no challenge study was carried out in mice. Also, no or limited attention to the induction of long-term memory responses nor immunogenicity and protection in aged animals has been paid. That being said, the induction of virus neutralizing antibodies in both mice (VSV-SARS-CoV-2 S) and primates (SARS-CoV-2) indicated that BNT162b2 immunization has the potential to induce neutralizing antibodies also in humans. Thus, vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity.

In mice, the immune response was assessed by single immunization only. Taking the phenotyping of B and T cells in aggregate, the data indicates a concurrent induction of SARS-CoV-2 S-specific neutralizing antibody titers and a Th1-driven T-cell response by immunization with BNT162b2 (this was also seen in nonhuman primates).

Concerning the nonhuman primate (rhesus macaques) studies, the applicant considers the human convalescent serum panel as an assessable benchmark to judge the quality of the immune response to the vaccine; this is accepted by the CHMP.

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFNγ producing T cell responses, including a high frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-α but a low frequency of CD4+ cells that produce IL-4, indicates a Th1-biased response occurred after the BNT162b2 (V9) immunization. This reasoning appears acceptable to the CHMP. The role of such a Th1 biased response was put in the context of antigen-specific T-cell responses playing an important role in generation of antigen-specific antibody response as well as in elimination of infected cells to mediate protection against disease.

When immunised macaques were challenged with SARS-CoV-2, a clear and statistically significant effect was observed on reduced presence of viral RNA in bronchoalveolar lavage (BAL) and oropharyngeal (OP) swabs. A clear effect was also recorded by blinded X ray scoring of the lungs. A

protective effect is also evident in the CT score Day 3 after challenge, however at Day 10/EOP, there was a CT signal in 2 out of six BNT162b immunized monkeys at the same level as observed in the control group. That signal is of unclear significance since also in 1 out of 6 pre infection BNT162b immunized animals a similar CT-score signal was observed. During this time period the SARS-CoV-2 neutralizing GMT in the BNT162b2-immunised rhesus macaques continued to decrease but remained above the GMT of a human convalescent serum panel.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing antibodies and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters, provide support for the vaccination approach. Due to species differences in the immune system between animal model species and humans, the conclusion whether this candidate vaccine will be sufficiently effective in humans needs to be established in clinical studies.

Pharmacokinetic

Pharmacokinetic (regarding the two novel LNP excipients): The two novel lipid excipients play different roles in the formulation and have different pharmacokinetics. It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0315.

ALC-0159 is comprised of a polyethylene glycol (PEG) headgroup (~2000 M.Wt.) attached to hydrophobic carbon chains (ie, the lipid anchor). ALC-0159 is present in BNT162 at a low mol% (<2 mol%), and therefore dose, relative to the other lipids. PEGylated lipid can exchange out of the LNP after administration, thus allowing the desired binding of endogenous proteins (eg, Apolipoprotein E) and removing the steric barrier that would otherwise restrict interactions of the LNP with target cells and proteins.

ALC-0315 is an ionizable aminolipid in BNT162b2 and is the most important lipid component for efficient self-assembly and encapsulation of the mRNA within the LNP, and for providing successful delivery of mRNA into target cells.

The PEG-lipid (ALC-0159) is designed to largely exchange out of the LNP after administration and before uptake into target cells, whereas the aminolipid (ALC-0315) is critical to the efficient intracellular delivery of the mRNA through endosomal uptake and release and must remain with the LNP.

ALC-0159 is much more hydrophilic, in large part due to the presence of the PEG molecule which is known to be a strongly hydrophilic molecule (Ma et al, 1990). Due to the more hydrophilic and essential neutral nature of this molecule, ALC-0159 has a much lower affinity for tissues and relative to ALC-0315 there will be freer compound available for redistribution from tissue to plasma; thus, elimination will be more rapid.

The Applicant pointed out that during the course of the 2-week pharmacokinetic study, liver concentrations of ALC-0315 fell 4-fold from their maximum value indicating that 75% of the material delivered to the liver was eliminated over this two-week period.

ALC-0315 has no known biology. In the absence of this 'biological relevance' the applicant used an estimation of >95% elimination of ALC-0315 to represent the essential elimination from the body. The elimination half-life of ALC-0315 in the liver following IV administration in the rat is approximately 6-8 days. These data indicate that 95% elimination of ALC-0315 will occur approx. 30-40 days following final administration in the rat.

Based on the understanding of the process involved in the terminal half-life, redistribution from tissues into which the lipid nanoparticle is delivered, a similar half-life and time to 95% elimination in human is expected (Mahmood et al, 2010). Examination of the scaling of the comparable lipids (PEG2000-C-DMG, DLin-MC3-DMA) in patisiran indicates that the half-life of these lipids appears to scale with a value approaching the typically used exponent for half-life (0.25). If this is the case for ALC-0315 we may

expect a half-life approximating 20-30 days in human for ALC-0315 and 4-5 months for 95% elimination of the lipid (Mahmood et al, 2010).

Both lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives.

Given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. This is noted by the CHMP.

Biodistribution: Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain.

In line with this, results from the newly transmitted study 185350, indicate a broader biodistribution pattern with low and measurable radioactivity in the ovaries and testes. Given the current absence of toxicity in the DART data, the absence of toxicological findings in gonads in the repeat-dose studies and that the radioactivity in the gonads were low (below 0,1% of total dose), the current data does not indicate it to be a safety concern. The relative high dose used in the rats (500x margin to human dose based on weight) also supports a low risk from distribution to the gonads in humans.

RNA stability and kinetics are not expected to be the same for all RNAs and are influenced by the nucleosides of the RNA and although expression of the full-length spike (S) protein is expected to follow similar kinetics of that of the luciferase with a transient expression fading over time, it cannot be excluded that differences in stability/persistence of the signal could differ between the luciferase protein and the spike (S) protein.

In an additional hPBMC study (R-20-0357), low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. The Applicant underlines that no specific general trend in cytokine secretion can be observed, given variability among donors and based on the low numbers of donors in the experiment.

Toxicology

Although no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate), the rat was used as a toxicological animal model in the repeat-dose toxicity studies. The positive neutralization assay results in the repeat-dose toxicity studies demonstrate that V8 and V9 generate an immune response in this species (i.e. SARS-CoV-2 antibodies), partially supporting the use of the rat as an animal model. Other SARS-CoV-2 immune responses in rat remain unclear. The immune responses, especially at the injection sites (e.g. oedema, erythema), seem to increase with each injection in the studies (n=3). There was a marked increase in acute phase proteins, fibrinogen and reduced albumin-globulin ratio (but no increase in cytokines with V8, unclear for V9). There was also a general increase in immune cells (LUC, neutrophils, eosinophils, basophils) and a decrease in red blood cell parameters (reticulocytes, RGB, HGB, HCT). The spleen was enlarged at both 30ug V9 and 100ug V9 and the draining and inguinal lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30ug (V9).

Systemic complement activation (which sometimes may be induced by liposomal drugs and biologicals and potentially result in hypersensitivity reactions) was not investigated as no signs indicative of such clinical manifestations were detected. An absence of dose-response designs in the studies increases the difficulty to interpret the effects. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. Increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the

inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The Applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells would not provide additional information. The CHMP agreed with this position.

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

As the pharmacokinetic distribution studies in rat demonstrated that a relatively large proportion - second to the levels at the injection site - of the total dose distributes to the liver (up to 18%, and far more than levels seen in spleen [<1.1%], adrenal glands [<0.1%] and ovaries [<0.1%]). While there was no severe pathogenesis in liver, there were some reversible functional hepatic and/or biliary effects with V8 and V9 (enlarged liver, vacuolation, strongly increased γGT levels at >200% and activity, minor-moderate increase in levels of AST and ALP) which may be linked to the LNP. The γGT changes were not observed with 30ug V9, which may be due to variant differences and/or, more likely, a lower dose. The applicant is of the view that the vacuoles are a result of primarily ALC-0315 accumulation in liver. It can be noted that ALC-0159 needs to be lost from the surface of the LNP to facilitate efficient uptake into target cells. At the same time, ALC-0315 is present in the LNP at a high mol% (50 mol%) relative to the other lipids in the BNT162 vaccine, suggesting that this lipid is more likely to be present within the cells (and possibly in the vacuoles).

The assessment of the data available as regards to the DART study shows that there is no clear adverse signs on fertility and early embryogenesis effects. There were no effects on the oestrous cycle in dams but there was an ~2x increase in pre-implantation loss (~9.77% vs 4.1% in controls) but these effects are within historical control data (5.1% to 11.5%) so these findings do not raise any specific concern. It can be noted that the choice of rat as an DART animal model is supported by means of the repeat-dose toxicity rat studies which demonstrates an immune response to the vaccine candidates [V8 and V9] and the publication of Bowman et al (2013; PUBMED ID [PMID] 24391099) that reports that foetal-maternal IgG ratios are relatively low during organogenesis but that these ratios approach 1 by the end of gestation in both rat and human.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed other concerns raised to be granted MA from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

Some rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher exposure in rats due to body weight differences) developed some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) which is consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible. These findings are described in SmPC section 5.3.

As per guidance, no genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential. This is acceptable to the CHMP.

Finally, the combined fertility and developmental toxicity study showed that SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, gestation, or embryo-foetal or offspring development up to weaning. The CHMP noted that no data are available on vaccine placental transfer or excretion in milk.

2.4. Clinical aspects

2.4.1. Introduction

Pfizer and BioNTech have developed a vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application. Multiple vaccine candidates are being evaluated in this study. For each vaccine candidate, participants received escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pivotal study for registration. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

GCP

The Applicant claimed that the Clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic, EMA gathered additional information as indicated below from EU and non-EU regulatory authorities, and shared them with the CHMP to be considered in the assessment:

- a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;
- Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);
- A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 162-02).

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

- Tabular overview of clinical studies

Table 1 Overview of the Clinical Development

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

Table 2 Overview of the pivotal phase 3 study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
C4591001	131 United States 9 Turkey 6 Germany 4 South Africa 2 Brazil 1 Argentina.	randomized, multinational, placebo-controlled, observer-blind,	2 doses of 30 µg given 21 days apart	Primary: To evaluate the efficacy of BNT162b2 against confirmed severe COVID-19 occurring from 7 and 14 days after the 2nd dose in participants with and without evidence of infection before vaccination	Healthy volunteers at risk of COVID-19	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

For vaccines, pharmacodynamics relates to investigation of immunogenicity. The available data were generated from the phase 1/2 study BNT162-01 conducted in Germany, and from the phase 1 and 2 parts of the phase 1/2/3 study C4591001, conducted in the USA (later phases were multinational). Both studies were designed to choose the optimal vaccine candidate and an appropriate dose and schedule for further studies. Among the four prophylactic SARS-CoV-2 RNA vaccines initially tested the following two candidates were selected for further development:

BNT162b1: RNA-lipid nanoparticle (LNP) vaccine containing nucleoside-modified messenger ribonucleic acid (modRNA) that encodes the RBD (receptor-binding domain)

BNT162b2: RNA-LNP vaccine containing modRNA that encodes SARS-CoV-2 full-length, P2 mutant (see section 2.2.2), prefusion spike glycoprotein (P2 S).

Key features of the two studies are summarised in the below table.

Study id	BNT162-01	C4591001
Title	A multi-site, Phase 1/2, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using	A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine

	different dosing regimens in healthy adults	Candidates Against COVID-19 in Healthy Individuals
Design	This is an open-label, multi-site, Phase 1/2, 2-part, dose-escalation study. Part A of the study includes the first in human dose and dose ranging groups in healthy adults (aged 18 to 85yrs).	This is a Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s); and Phase 2/3 as an expanded cohort and efficacy part.
Immunogenicity objectives	To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titre	To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses
Study population	Healthy adults aged 18 to 55yrs BNT162b1: N=84 (12/group) BNT162b2: N=60 (12/group) Healthy adults aged 56-85 yrs BNT162b1: N=36 (12/group) BNT162b2: N=36 (12/group)	Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive Phase 1 comprised 15 participants (randomization ratio of 4:1 so that 12 received active vaccine and 3 received placebo) per group; 13 vaccine groups were studied, corresponding to a total of 195 participants (the 100 µg dose was only used in the younger adult cohort)
IMP and dose level	BNT162b1: 1µg, 3µg, 10µg, 20µg, 30µg, 50µg, and 60µg. BNT162b2: 1µg, 3µg, 10µg, 20µg, 30µg	BNT162b1: 10 µg, 20 µg, 30µg, 100 µg BNT162b2: 10µg, 20µg, 30µg Placebo: normal saline
Dosing frequency	Two injections ~21d apart	Two injections ~21d apart
Immunogenicity endpoints	Virus neutralization test (VNT). Antibody binding assay, CMI assays, e.g. ELISpot and intracellular cytokine staining (ICS).	SARS-CoV-2 neutralization assay S1-binding IgG level assay RBD-binding IgG level assay N- binding antibody assay

Endpoints and Assays used to evaluate immunogenicity

In Study BNT162-01, immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine neutralizing titres and the fold rise in SARS-CoV-2 serum neutralizing titres. Immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1 (Day 8); and at Day 22 (before Dose 2) and 7 days, 14 days, and 21 days after Dose 2. Only qualified assays were used. In addition, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from

whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immuno-spot (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS). Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFNγ and IL-2 and those associated with Th2 responses such as IL-4, to analyse the induction of balanced versus Th1-dominant or Th2-dominant immune responses.

In Study C4591001, immunogenicity was evaluated in Phase 1 and Phase 2 using a SARS-CoV-2 serum neutralization assay to determine titres and a SARS-CoV-2 RBD- or S1-binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were assessed also. Only qualified assays were used. In Phase 1, immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1; and at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarized for each dose level and age group. In Phase 2, immunogenicity was assessed at Day 1 (before Dose 1) and 1 month after Dose 2. Data were summarized for each age strata group and by evidence of prior SARS-CoV-2 infection at baseline per NAAT (PCR) or N-binding IgG assay. To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

These are the immunogenicity assays that were used in clinical trials:

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 S1-binding IgG in Human Serum

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 RBD-binding IgG in Human Serum

Roche Elecsys SARS-CoV-2 N Binding Antibody Assay

mNeonGreen SARS-CoV-2 Microneutralization Assay

ELISpot Assay

Intracellular Cytokine Staining (ICS) for BNT162b1 and BNT162b2

The SARS-CoV-2 Wuhan-Hu-1 isolate spike glycoprotein (GenBank accession # QHD43416.1) is the reference sequence for the recombinant S1 and RBD proteins used in the Luminex assays. The SARS-CoV-2 neutralisation assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020).

Study BNT162-01

Immunogenicity - functional antibody responses (secondary objectives)

Functional antibody titre data are available up until Day 43 for younger adults (18 to 55 yrs) dosed with 1, 10, 30, 50, and 60 µg BNT162b1 on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group). Data are available for the 10 and 30 µg up until Day 50 for younger adults dosed with 1, 10, 20, and 30 µg BNT162b2 on Days 1 and 22 (dose level 1 µg, n=9; dose levels 10, 20, and 30 µg, n=12).

Virus neutralizing antibody GMTs for participants aged 18 to 55 years after dosing with BNT162b1, are shown in Figure 3. On Day 22, at 21 d after the first dose, virus neutralizing antibody GMTs had increased in a dose-dependent manner for all dose groups. At 7 d after the second dose (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 µg dose group,

which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titres.

On Day 43 (21 d after the second dose of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs at least 14 d after confirmed diagnosis and at a time when the individuals were asymptomatic.

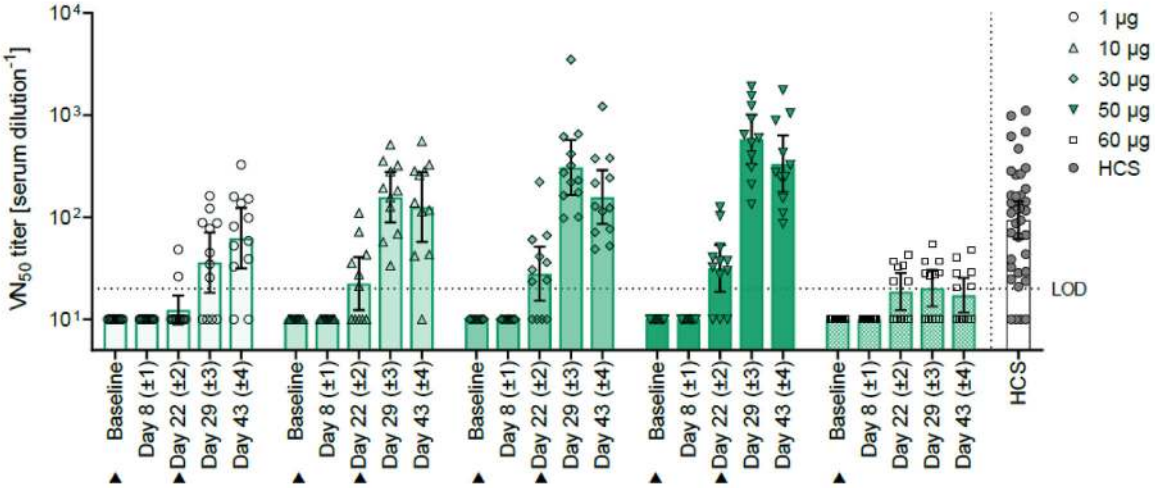


Figure 3: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN50) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 years) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum

For virus neutralizing antibody GMTs for participants aged 18 to 55 yrs after dosing with BNT162b2, see Figure 4. Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger participants (aged 18 to 55 yrs) immunized with ≥3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult in the 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

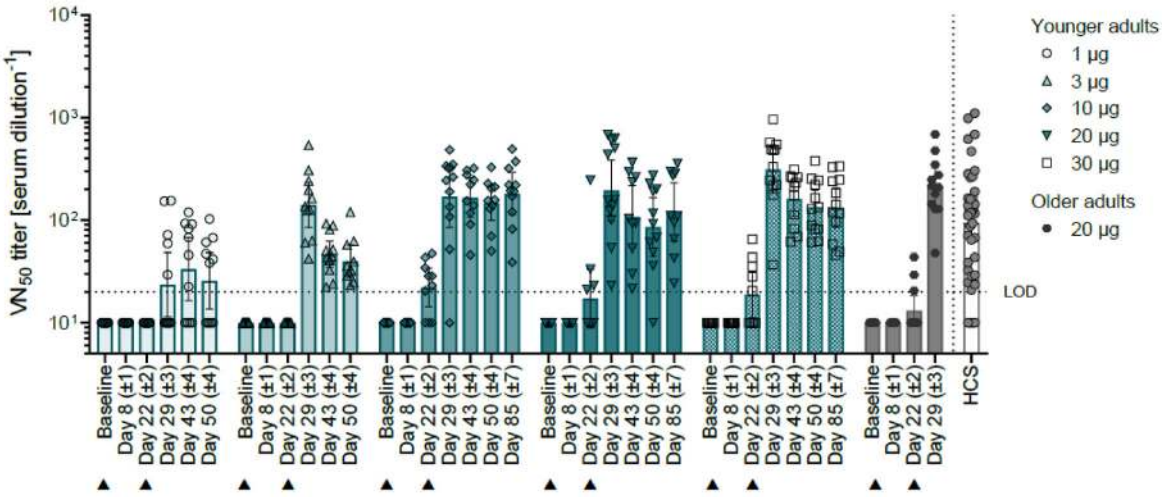
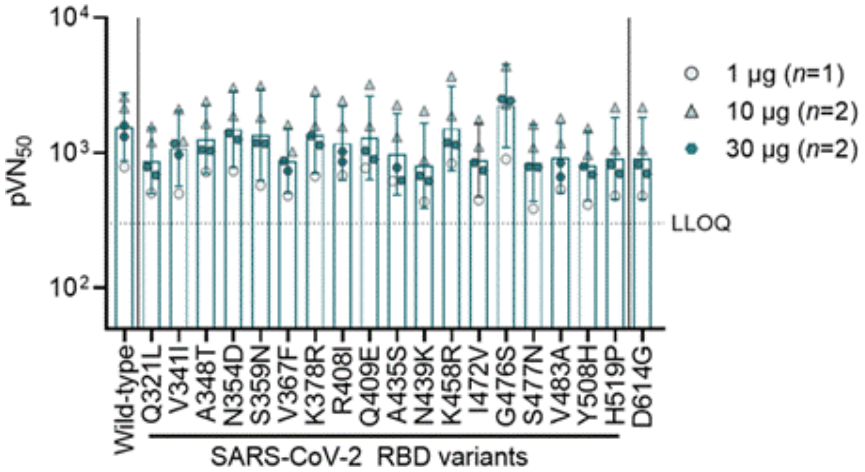


Figure 4: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titres (VN50) – IMM
VN50 titres with 95% confidence intervals are shown for younger adults (aged 18 to 55 years) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD.
IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum.

Neutralisation of different spike protein mutants

Different pseudoviruses including RBD sequence variants have been tested in a pseudovirus neutralization assay with sera from BNT162b1-and BNT162b2-immunized participants in the BNT162-01 study. Efficient neutralization of spike protein mutants was observed with sera from BNT162b1- and BNT162b2-immunized participants demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies.



BNT162b2-induced virus neutralization titers with pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel with 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G. LLOQ = Lower level of quantification (at 300). Data shown as group (total n=5) GMT with 95% CI.

Cell mediated immunity (CMI)

CMI were measured in terms of IFNγ- producing CD4+ and CD8+ T cells by ELISpot. Both vaccine candidates elicited clear responses (baseline vs post-dose 2). Further characterisation was determined using intracellular cytokine staining for Th1 cytokines (IFNγ, IL-2) and Th2 cytokines (IL-4). Both vaccine candidates stimulated predominantly Th1 responses, both in CD4 and CD8 T cells.

Study C4591001

Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations. Phase 1 and Phase 2 data were reported as the following, for SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-binding and RBD-binding IgG concentrations:

- geometric mean titers/concentrations (GMTs/GMCs)
- geometric mean-fold rise (GMFR)
- geometric mean ratio (GMR) (for Phase 1 only)
- proportions of participants with ≥4-fold rise (for Phase 1 only)
- antibody titers/levels at defined thresholds (for Phase 2 only)

For immunogenicity results of SARS-CoV-2 serum neutralizing titers and S1- or RBD-binding IgG concentrations, GMTs or GMCs were computed with associated 95% CIs.

The GMFR was calculated by exponentiating the mean of the difference of logarithm transformed assay results: (later time point) – (earlier time point) with two-sided CIs. The GMR was calculated as the mean of the difference of logarithm transformed assay results: (SARS-CoV-2 serum neutralizing titers) – (SARS-CoV-2 anti-S binding antibody) for each participant, then exponentiating the mean, with two-sided CIs.

Results

The study set out to evaluate 2 SARS-CoV-2 RNA vaccine candidates, as a 2-dose (separated by 21 days) schedule, at different dose levels (BNT162b1: 10, 20, 30, and 100 µg, BNT162b2: 10, 20, and 30 µg) and in different age groups (18 55 y; 65-85 y), to select a vaccine and dose level for further testing in Phase 2/3. Cut-off date: 24-Aug-2020 (1 month post-dose 2 = D52).

Immunogenicity results are available for both adult age groups up to 1 month post-Dose 2 for the BNT162b1 and BNT162b2 vaccine candidates at the 10-µg, 20-µg, and 30-µg dose levels, and up to 7 weeks after Dose 1 of BNT162b1 at the 100-µg dose level (younger age group only).

Results for the 7 days after Dose 1 time point are only analysed and presented in the younger age group (18 to 55 years of age) for 10 µg and 30 µg BNT162b1.

Immunogenicity results SARS-CoV-2 Neutralizing Titres

BNT162b1

In the younger age group, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b1 (Figure 5).

Generally similar trends were observed in the older age group, with higher GMTs observed in the 20-µg and 30-µg dose groups of BNT162b1 compared to the 10-µg dose group (Figure 6). In the older age

group, the SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.

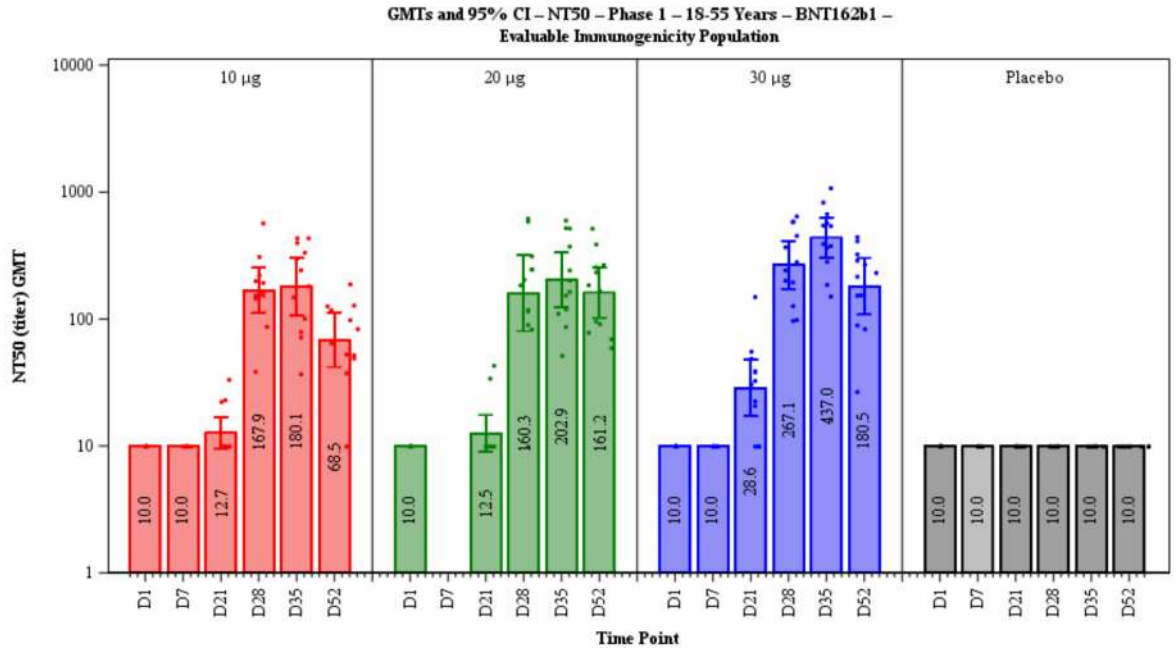


Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

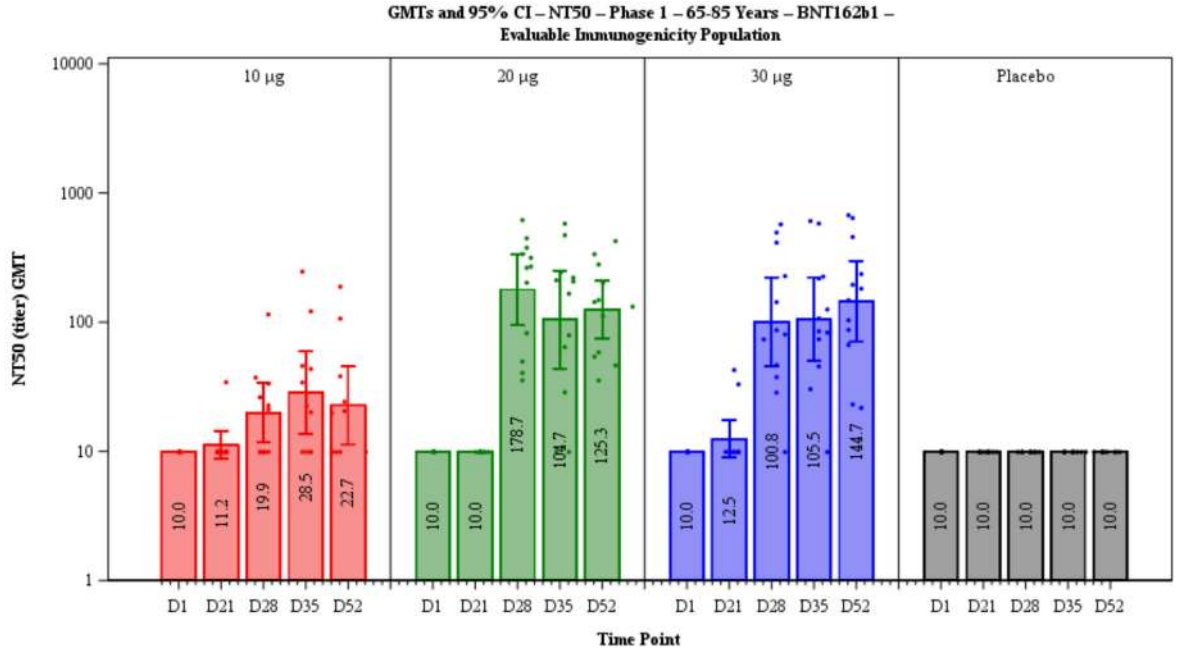
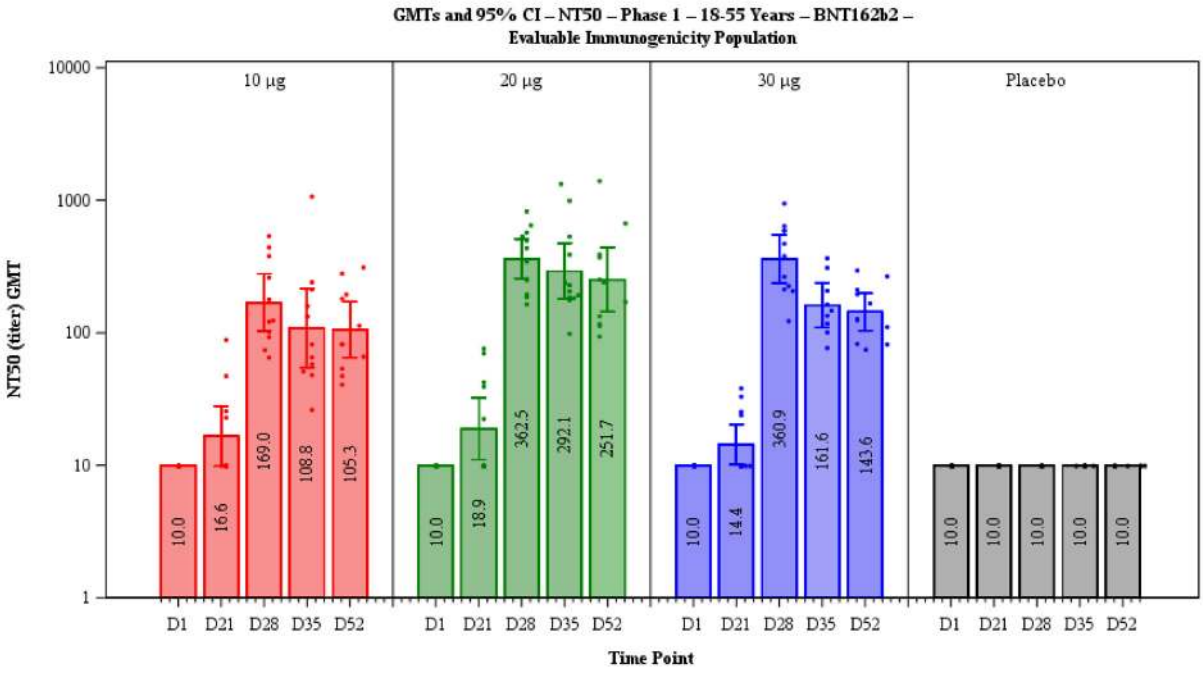


Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart– 65-85 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

BNT162b2

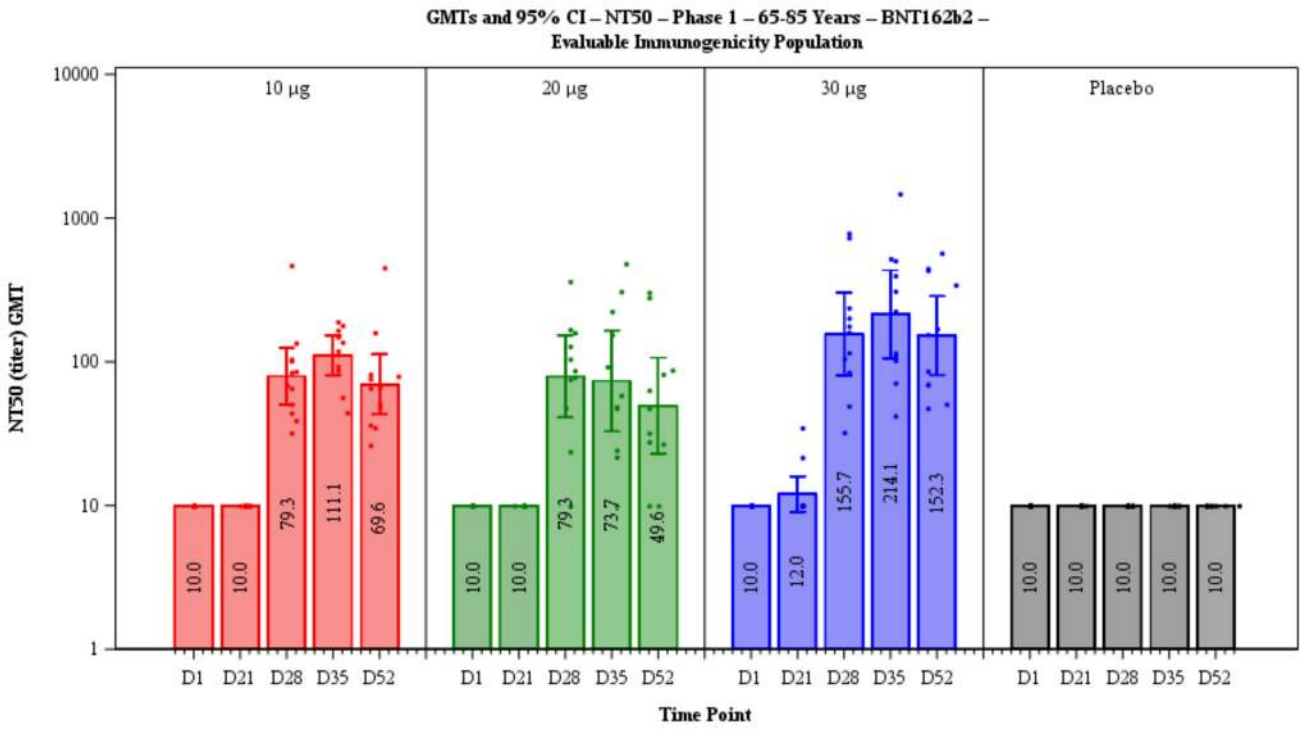
In the younger age group, SARS-CoV-2 50% neutralizing GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2 (Figure 7).

Similar trends were generally observed in the older age group, with higher GMTs observed in the 30-µg dose groups compared to the 20-µg and 10-µg dose groups (Figure 8). In the older age group, SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: ./nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

Figure 8. Geometric Mean Titres and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

2.4.4. Discussion on clinical pharmacology

The choice and dose of vaccine candidate was based on the results of two clinical phase I studies. Immune responses and safety of the two candidates were studied in both studies. The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first dose. Thus, in the absence of a serological correlate of protection, these data supported that two doses would be needed in adults. The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10ug and 30ug. The neutralising antibody responses between the two vaccine candidates are considered similar although no formal comparison was made. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001. In both studies subjects 55 years of age and older were included as well as younger adults. The responses in elderly were lower compared to younger adults, but the difference is likely of no clinical relevance, also considering the delayed peak.

For BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable to the kinetics of neutralizing antibodies, with lower IgG concentrations in older age group than in younger age group.

Further evaluation of antibody persistence is ongoing. Neutralizing antibody titres will be followed until the end of 162 days post-dose 2 for study BNT162-01 and up to 2-years for study C459001. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation).

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will be also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralization of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunized study BNT162-01 participants, demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies. This may be important to consider when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

Further characterisation of immune responses was included in study BNT162-001. Cellular immune responses were demonstrated in terms of IFNγ-producing CD4 and CD8 T cells. In addition, a clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 µg dose cohort vaccinated with BNT162b1, RBD-specific IL-2 producing CD4+ and CD8+ T cells were reduced in older adults.

2.4.5. Conclusions on clinical pharmacology

The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 µg. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation), including data on persistence of immune responses.

2.5. Clinical efficacy

2.5.1. Dose response study

See section 2.4.3.

2.5.2. Main study

Title of study

Study C4951001: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Methods

Study Participants

Main Inclusion criteria:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3) at randomization.
- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks

before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.

- Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent

Exclusion criteria:

- Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation
- Previous participation in other studies involving study intervention containing lipid nanoparticles.

Treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 µg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Available safety, efficacy and immunogenicity data pertain to vaccine made according with the manufacturing process employed for clinical trial batches.

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (commercial process) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. Data are expected in February 2021. See the Quality section regarding comparability of clinical lots and commercial lots.

Objectives

The outcomes of the primary efficacy objectives were included in the Clinical Study Report submitted in this application. Results of the secondary objectives are expected during 2021.

Primary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination

Primary safety objectives

- To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)
- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3

Secondary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

Secondary immunogenicity objectives

- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (data not included in this report)

Exploratory objectives

- To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination
- To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study
- To describe the serological responses to the BNT vaccine candidate in cases of:
  - Confirmed COVID-19
  - Confirmed severe COVID-19
  - SARS-CoV-2 infection without confirmed COVID-19
- To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease
- To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

Outcomes/endpoints

Immunogenicity

See pharmacodynamics section for description of immunological methods used in phase 1 and 2 of this study. The same methods are used also in phase 3, but results are not yet available.

Primary Efficacy Endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Secondary Efficacy Endpoints

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2.

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

COVID-19 Case Definitions

Participants who developed any potential COVID-19 symptoms were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (within 3 days of symptom onset and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a self-swab was used), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis. Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was only acceptable if it met protocol specified criteria and if a central laboratory result was not available.

Two definitions of SARS-CoV-2 related cases, and SARS-CoV-2 related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

Confirmed COVID-19 (defined for FDA guidance): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhoea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2<300mm Hg);

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

In addition, evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen. A serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

In addition, prior infection with SARS-CoV-2 was assessed also at Dose 2 (NAAT) and is being evaluated for up to 24 months. The purpose is to assess persistence of efficacy, explore efficacy against asymptomatic SARS-CoV-2 infections, and ensure safety in both seronegative and seropositive participants.

Sample size

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

Randomisation and Blinding (masking)

Allocation of participants to vaccine groups were performed through the use of an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants ≥12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

Exceptions to blinding for e.g. DMC activities were described and found acceptable.

Efficacy Analysis Methods

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (i.e., Pr[VE >30%|data] >99.5% at an interim analysis or >98.6% at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating vaccine efficacy at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated. VE is defined as 100% × (1 – IRR), where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (i.e., posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2.

The interim analysis was performed for the first primary efficacy endpoint only. Other efficacy data analysed for the interim analysis were summarized with descriptive summary statistics, including COVID-19 case counts in the BNT162b2 and placebo groups on the basis of:

- evidence of prior SARS-CoV-2 infection at baseline per NAAT or N-antigen binding assay
- subgroup status (i.e., age, sex, race, ethnicity baseline SARS-CoV-2 status)
- COVID-19 cases meeting protocol criteria as severe after the first and second doses.

Overwhelming efficacy success criteria were met at the first interim analysis, so further formal interim analyses would not be conducted. The final analysis of all protocol specified primary and secondary efficacy endpoints was pre-specified in the protocol to be conducted after accrual of the final number of COVID-19 cases (at least 164 cases). Subgroup analyses of VE were performed for the primary endpoints and secondary endpoint of severe COVID-19 cases. Additional post hoc analyses of subgroups defined by comorbidity risk assessment were performed. Secondary efficacy was analysed in the same manner as primary efficacy (Section 2.5.4.1.2.2), using the cases definitions for severe COVID-19 and CDC criteria for COVID-19

Statistical methods

The estimands to evaluate the efficacy objectives were based on evaluable populations for efficacy. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE was also analysed by all-available efficacy population.

The evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1),and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. This was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy populations, including all randomized participants who completed 1 and 2 vaccination doses respectively, were also performed.

The two primary endpoints were tested hierarchically. Key secondary efficacy endpoints were evaluated sequentially in a prespecified order after the primary endpoints were met. Missing data were not imputed for the primary or secondary analyses. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with MNAR assumption.

VE was estimated as follows: 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose.

A Bayesian approach was used for the primary and secondary endpoints. A beta prior, beta (0.700102, 1), was used for θ = (1-VE)/(2-VE). The prior was centred at θ = 0.4118 (VE=30%). The 95% interval for θ is (0.005, 0.964) and the corresponding prior 95% interval for VE is (-26.2, 0.995). The Bayesian approach was not used for the point estimate for VE. At final analysis, efficacy was to be declared if the posterior probability of VE greater than or equal to 30% ("p") > 98.60%.

During Phase 2/3, 4 interim analyses (IAs) were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. The final analysis was to be performed when 164 cases were observed. However, only one interim analysis was performed, at 94 cases. The final analysis was performed with 170 cases. At the time of the IAs, futility and VE with respect to the first primary endpoint were planned to be assessed. The IA that was performed was successful, as was the final analysis, and results were consistent with the IA.

The success threshold for each interim analysis was to be calibrated to protect overall type I error at 2.5%. The risk of falsely concluding the VE to be above 30% (the type I error rate) with the proposed Bayesian model and over the interim analyses and final analysis under assumption of 30% vaccine efficacy is 0.021 (one sided). Hence the type I error rate for the primary endpoint is controlled. Although only one interim analysis was performed, the overall Type I error (overall probability of success when true VE=30%) was controlled at 0.025 with the originally proposed success/futility boundaries.

Although Bayesian analysis are not usually accepted as confirmatory evidence in pivotal trials, the magnitude of the effect in this study, makes this concern redundant. Hence, the conclusions of the inference are considered robust.

Results

Disposition of All Randomised Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	Placebo (N[a]=18892) n[b] (%)	Total (N[a]=37796) n[b] (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post–Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)

Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	4 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	48 (0.3)	81 (0.4)	129 (0.3)
Withdrawal by subject	45 (0.2)	9 (0.0)	54 (0.1)
Adverse event	20 (0.1)	12 (0.1)	32 (0.1)
Pregnancy	4 (0.0)	4 (0.0)	8 (0.0)
Physician decision	2 (0.0)	1 (0.0)	3 (0.0)
Lost to follow-up	0	2 (0.0)	2 (0.0)
Medication error without associated adverse event	0	1 (0.0)	1 (0.0)
Other	2 (0.0)	1 (0.0)	3 (0.0)
Withdrawn from the study	180 (1.0)	259 (1.4)	439 (1.2)
Withdrawn after Dose 1 and before Dose 2	132 (0.7)	164 (0.9)	296 (0.8)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	44 (0.2)	84 (0.4)	128 (0.3)
Withdrawn after 1-month post–Dose 2 visit	4 (0.0)	11 (0.1)	15 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to follow-up	80 (0.4)	86 (0.5)	166 (0.4)
Adverse event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	3 (0.0)	5 (0.0)
Physician decision	1 (0.0)	2 (0.0)	3 (0.0)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	3 (0.0)	6 (0.0)

Note : 1 subject was randomised but did not sign informed consent and is not included in any analysis population
Note: because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30µg) and one dose of placebo
Note: HIV-positive subjects are included in this summary but not included in the analysis of the overall study objectives.
a. N=number of randomised subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations
b. n=number of subjects with the specific characteristics

Recruitment

This study is ongoing, and participants are continuing to be enrolled and evaluated in Phase 3.

Subject First Visit: 29 April 2020

Data Cut-off dates:

- 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
- 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
- 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)

As a result, 44,822 subjects have been enrolled and 43,386 subjects have been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

Conduct of the study

This study has gone through extensive changes or amendments. The amendments of the phase 1 of the study are deemed acceptable for a dose-finding design. Protocol amendments concerning the phase 3 of the study are overall adequately motivated and acceptable, since they are not expected to affect the conclusions on efficacy. Main Amendments have allowed to include adolescents from 12 to 15 years in the study and added corresponding objectives. Furthermore, secondary efficacy endpoints to include COVID-19 cases that occurred from 14 days after the second dose were added. The SAP was amended twice in line with protocol amendments.

Baseline data

Overall, demographic characteristics were well balanced between study groups.

Demographics (population for the primary efficacy endpoint)[a]

	Comirnaty (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
75 through 85 years	799 (4.4)	807 (4.4)
>85 years	5 (0.0)	5 (0.0)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.

c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥ 30 kg/m^2)
   - Diabetes (Type 1, Type 2 or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Baseline comorbidities - safety population 38,000 subjects- at final analysis:

Table 3. Baseline Charlson Comorbidities ~ 3800 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Charlson Comorbidity Index Category	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any Malignancy	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascular Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congestive Heart Failure	88 (0.5)	83 (0.4)	171 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	99 (0.5)	113 (0.6)	212 (0.6)
Diabetes Without Chronic Complication	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hemiplegia or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Leukemia	12 (0.1)	10 (0.1)	22 (0.1)
Lymphoma	22 (0.1)	32 (0.2)	54 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulcer Disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal Disease	123 (0.7)	133 (0.7)	256 (0.7)
Rheumatic Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:21) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_p3_saf

The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease

not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Numbers analysed

The disposition of the efficacy populations is described in the Table below. There was an imbalance between the two study groups on the number of subjects excluded from the evaluable efficacy population. The two reasons responsible for this imbalance were "Dosing/administration error, subject did not receive correct dose of vaccine" (n=105 in vaccines and n=3 in placebo) and "IP administered that was deemed not suitable for use by Almac" (n=144 in vaccines and n=0 in placebo). There may be several explanations for this imbalance as listed below:

- As the placebo was a fixed volume of saline, with no dilution required, the likelihood of a dosing error in the placebo group was lower compared to vaccine, which did required dilution.
- An isolated dosing/administrative error event in one clinical centre affecting a higher number of participants receiving BNT162b2 (n=52 participants) has contributed to this imbalance.
- Almac was responsible for determining suitability for use of investigational product that was subject to a temperature excursion. Due to the differences in the required storage conditions (ambient for the placebo versus ultracold for the BNT162b2), temperature excursions were not an issue for the placebo but were for BNT162b2.

The protocol design was such that, if a participant experienced any of the specified trigger symptoms that could indicate COVID-19, a potential COVID-19 illness visit should occur, including obtaining a swab for the central laboratory.

Table 4 Efficacy Populations

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			

Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

Outcomes and estimation

Primary Efficacy Endpoints – Final Analysis

The result for the first primary efficacy analysis is shown in Table 5. VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group.

Table 5 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2 (Table 6). VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with and 9 and 172 cases in the BNT162b2 and placebo group, respectively.

Table 6 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

However the seropositive subjects were not many: among 38,000 subjects there were 407 individuals seropositive in the vaccine group and 436 in the placebo group in the age strata 16-55 YOA, and 150 individual seropositive in the vaccine group and 152 in the placebo group in the >55 YOA age strata.

All Confirmed Cases of COVID-19 After Dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on onset of protection.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 7, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group (Table 7). Notably, in the BNT162b2 group, most cases occurred before Dose 2.

Figure 9 displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group. From table 7 and figure 9 it is evident that the first dose offers partial protection, while few cases occur after the second dose.

Table 7 Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

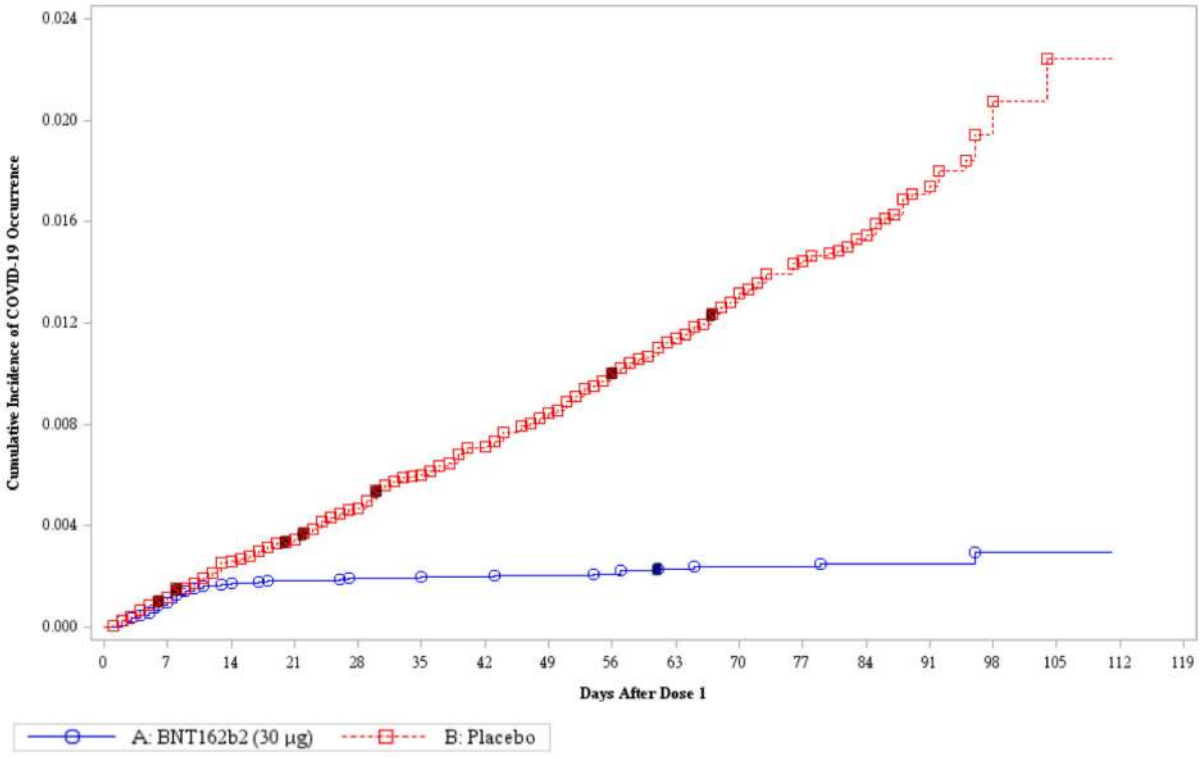


Figure 9. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Immunogenicity results

The immunogenicity part of study C4591001 are presented in this section and aimed to confirm the conclusions on safety and immunogenicity from phase 1. These are the only immunogenicity results from a larger study population available at this stage, and further results from phase 3 are expected post approval. In addition, any data generated in attempts to establish a serological correlate of protection are expected to be reported when available.

The results of the immunogenicity analyses here reported are generated from the Dose 2 evaluable immunogenicity population; baseline positive participants (by N-binding antibody or positive NAAT at Visit 1) were not excluded from these analyses.

SARS-CoV-2 Neutralizing Titres and S1-Binding IgG Concentrations GMTs/GMCs

At 1 month after Dose 2 (Day 52) of BNT162b2, there were substantial increases in SARS-CoV-2 50% neutralizing GMTs (Figure 10) and S1-binding IgG concentrations (GMCs) (Figure 11). GMTs/GMCs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Similar trends were observed for the SARS-CoV-2 90% neutralizing GMTs (data not shown in this report).

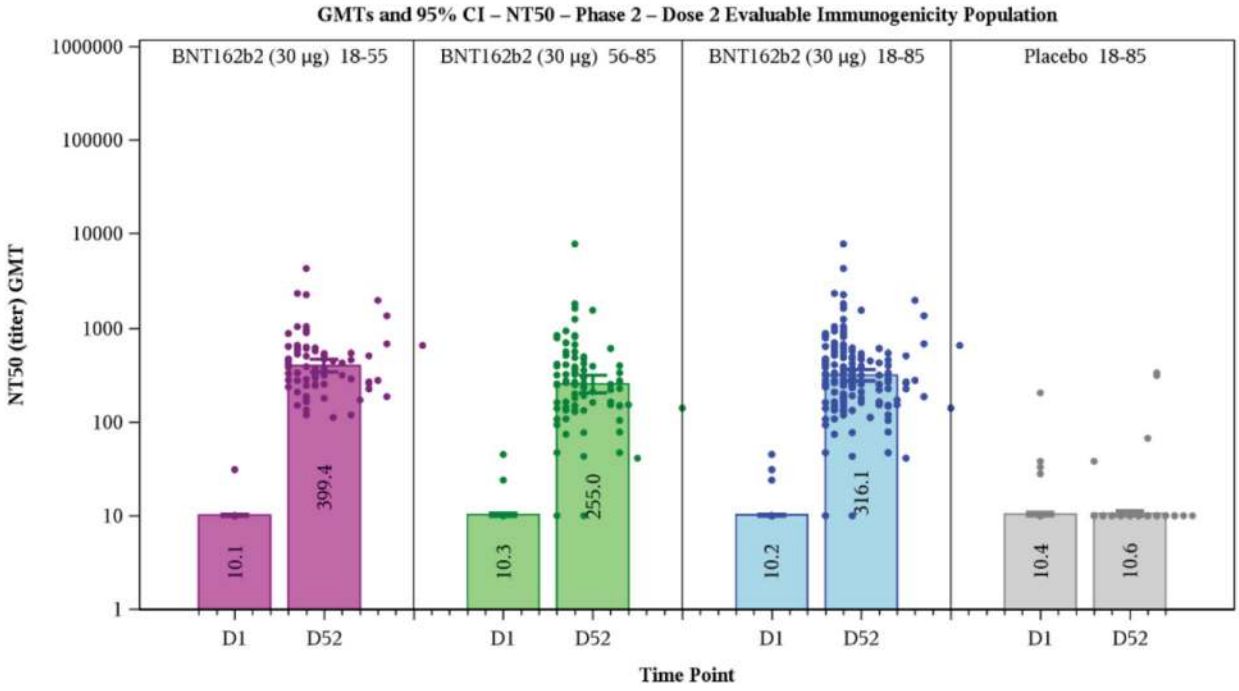


Figure 10. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – NT50 – Phase 2 – Dose 2 Evaluable Immunogenicity Population

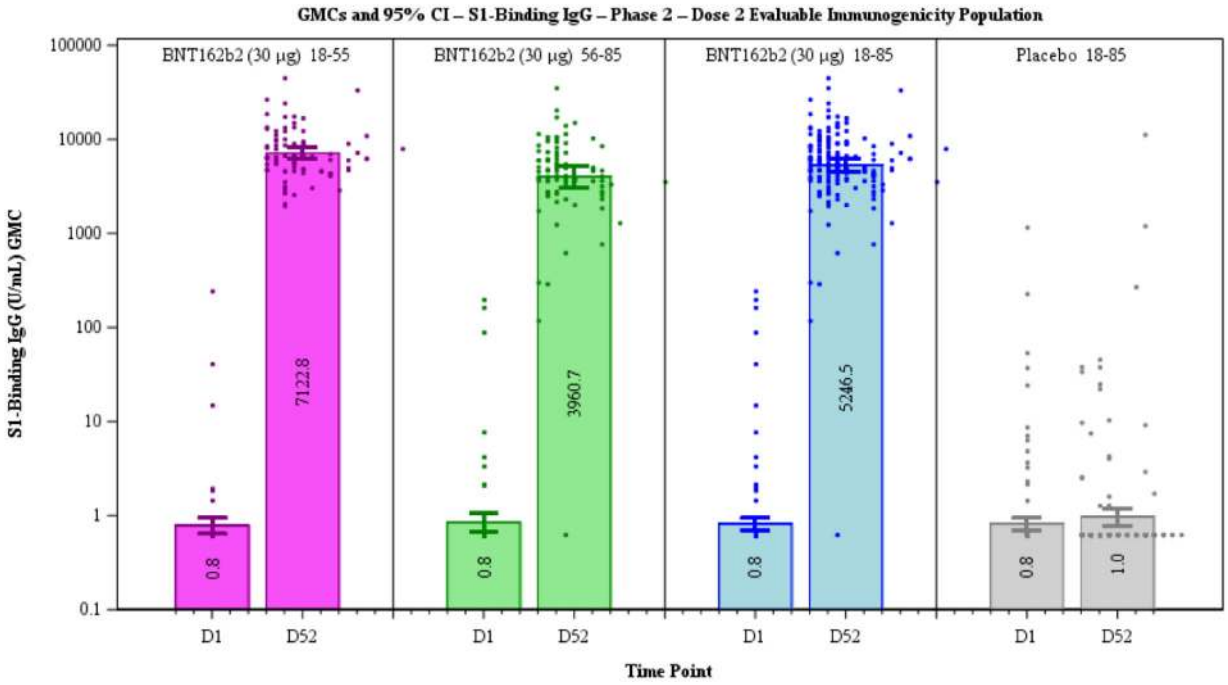


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay – Phase 2 Dose 2 Evaluable Immunogenicity Population

A few participants in the Dose 2 evaluable immunogenicity population had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants. In general, at 1 month after Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status (n=3) were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163).

Ancillary analyses

Vaccine Efficacy by Subgroup

For both primary endpoints, VE was also evaluated for subgroups of participants by age, sex race/ethnicity, and country, without evidence of prior infection (Table 8). Results for additional age groups are shown in Table 9.

Post hoc analyses of efficacy by risk status were performed. For these analyses, at-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥30 kg/m2) (table 11). Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

These subgroup analyses are considered of importance. There is no evidence of significantly reduced efficacy in older age groups, i.e. >90% vaccine efficacy even in over 75-year-old subjects, although not statistically significant as there were only few cases in this age stratum. There were no cases in the 16-17-year-old age stratum, but efficacy is not anticipated to be lower in younger age groups compared to the overall study population. Additionally, it is reassuring that other factors, e.g. ethnicity/race, gender did not impact efficacy. Efficacy was not demonstrated in subjects who were

seropositive at baseline, but the subgroup was very small and results are considered inconclusive rather than negative at this stage.

Table 8 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 9 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint Subgroup	**n1[b]**	**Surveillance Time[c] (n2[d])**	**n1[b]**	**Surveillance Time[c] (n2[d])**	**VE (%)**	**(95% CI[e])**
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; VE= vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.

i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

Table 10 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

Vaccine efficacy by different age subgroup is shown below in line with the information included in the SmPC.

Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection and participants with or without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine Na=18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo Na=18,325 Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Vaccine efficacy for Severe COVID-19 cases, Final analysis

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 12). The posterior probability for the true vaccine efficacy greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Consequently, statistical testing of subsequent secondary endpoints (i.e., the additional secondary endpoints related to severe disease with pre-specified control of overall type 1 error) ended. However, descriptive summaries for the additional endpoints were provided.

Table 12 Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial C4591001

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer- Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals		
Study identifier	C4591001	
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled	
	Follow-up for efficacy Follow-up for safety	Until nov 14, 2020 At least 1 month, median 2 months
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy	
Treatments groups	Active arm	BNT162b2 (30 µg), 2 doses, 21 days apart, randomized 22 000

	Control arm		Saline placebo, 2 doses, 21 days apart, randomized 22 000
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2
	Second Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.
	Secondary Endpoint	VE-14d-no-no/yes-SARS-Cov-2	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
	Secondary Endpoint	VE-7d/14d-no-no/yes-SARS-Cov-2-Severe	Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
Database lock	November 14, 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Per protocol, Evaluable Efficacy population		
Effect estimate per comparison VE=100x (1- IRR) IRR= caseN/groupN Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time., Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.	Primary endpoint	VE-7d-no-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=8/18198 Cases in Placebo arm N= 162/18325
		Vaccine Efficacy VE %	95.0
		95% Credible Interval	90.3, 97.6
		Pr (VE >30% |data)	>0.9999
	Co-Primary	VE-7d-no/yes-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=9/18559 Cases in Placebo arm N= 169/18708
		Vaccine Efficacy VE %	94.6
		95% Credible Interval	89.9, 97.3

		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no- SARS-CoV-2	Cases in Active arm N=8/18175 Cases in Placebo arm N= 139/18261
		Vaccine Efficacy VE %	94.2
		95% Credible Interval	88.7, 97.2
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no/yes-SARS-CoV-2	Cases in Active arm N=8/19965 Cases in Placebo arm N= 144/20171
		Vaccine Efficacy VE %	94.4
		95% Credible Interval	89.1, 97.3
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-7d-no-SARS-CoV-2-Severe	Cases in Active arm N=1/18198 Cases in Placebo arm N= 3/18325
		Vaccine Efficacy VE %	66.4
		95% Credible Interval	-124.8, 96.3
		Pr (VE >30% |data)	0.7429
Notes	Subgroup analyses support the overall results, e.g. elderly and patients with risk factors appear to be protected as well.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the selected vaccine BNT162b2 was investigated in one pivotal trial, BNT162-02 study. This is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. Safety and immunogenicity data generated during the phase 1 portion of this study supported the selection of BNT162b2 at 30 µg, as a prime/boost regimen (separated by 21 days) as the vaccine candidate to proceed into Phase 2/3.

Phase 2/3 was designed to evaluate the efficacy of BNT162b2, and to provide additional safety and immunogenicity data in a larger population. The study design for the pivotal phase 3 study is overall acceptable and in line with applicable guidelines. In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for

up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. It is an observer-blind study, which is considered acceptable as placebo and vaccine differed in appearance. Randomisation and blinding were considered acceptable.

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (46%, e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Immunocompromised subjects and pregnant or breastfeeding women were excluded from the study. Subjects with known stable infection with HIV, HBV, HCV could be enrolled. Further, individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the immunogenicity of the vaccine.

The study mainly recruited in the USA, but other sites worldwide were also included.

The primary endpoint (laboratory confirmed symptomatic COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 7 days after receipt of the second dose, and then in all participants regardless of serostatus) is considered relevant for the purpose of establishing vaccine efficacy.

SARS-CoV-2 genomic RNA has been detected in nasal swab samples using Cepheid Xpert Xpress SARS-CoV-2 PCR assay on the GeneXpert Molecular Diagnostic System. This method detects 2 structural genes of SARS-CoV-2: E and N2. A validation of this method was performed, and in addition the test was issued a EUA by FDA. In order to assess the analytical detection limit, live virus and commercial control (AccuPlexTM SARS-CoV-2) were used. Clinical sensitivity and specificity were evaluated in comparison with results obtained using another FDA authorised real-time RT-PCR method with positive or negative clinical specimens and pre-pandemic samples. Results showed that Cepheid Xpert Xpress PCR assay is a sensitive and specific method for the detection of SARS-CoV-2 RNA in nasal swabs. The positive rate of self-swab is similar to site-swab, 3.7% and 4.7% positive from self-swab and site-swab respectively in the BNT162b2 group.

The third main secondary endpoint evaluated vaccine efficacy against severe cases of the disease (defined as confirmed COVID-19 with the presence of at least one of pre-defined severity criteria), to determine whether the vaccine decreased the incidence of confirmed severe COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection, 7 to 14 days after the second dose. Prevention of severe disease is an important endpoint, but the relative rarity of severe cases would require either a very large study population and/or a very long study duration to be certain to achieve sufficient statistical power. Therefore, it is acceptable as a secondary endpoint.

The immunogenicity secondary and exploratory endpoints are considered acceptable.

This is an event-driven study. This case-driven approach is deemed appropriate as the rate of accumulation of cases was not certain which could allow a rapid assessment of efficacy in case of a high attack rate. With assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. The randomisation procedure is considered appropriate to control confounding factors.

The statistical methods are overall acceptable. The Bayesian approach used is not expected to affect the decisions from the hypothesis testing procedure. For consistency and ease of interpretation, the Clopper Pearson confidence intervals will be included in the SmPC rather than the Bayesian credible intervals. Of the four pre-planned interim analyses only one was performed, and the final analysis was also submitted. These analyses give highly consistent results with VE far from the null hypothesis limit

of 30%. Confidence intervals were not adjusted for multiplicity, which is considered acceptable in this context.

While it could be argued that alpha could be allocated according to a group sequential design, since no failed interim analysis has been performed, the alpha allocated to the interim analysis may be recycled to the final analysis. Hence the final analysis could have been performed at full alpha level and the coverage probability of the "naïve" confidence interval is therefor considered correct.

The interim and final analyses are conducted in an evaluable efficacy population of participants who receive the two doses within the predefined window and excluding subjects with other major protocol deviation, in order to obtain a best-case estimate of vaccine efficacy. However, this approach could result in bias due to exclusion of subjects. For this reason, sensitivity analyses assessing VE based on all laboratory-confirmed cases with symptom onset at any time after the first dose (dose 1 all-available efficacy population) and 7 days after the second dose (dose 2 all-available efficacy population) have been performed without excluding participants with major protocol deviations.

Overall, the study report including the final analysis is considered adequate. This is not the final report for the study, as the study is expected to continue for a total of 24 months.

Baseline data

At the cut-off date of 14 November 2020, the disposition of the 38,000 participants were similar in the BNT162b2 and placebo groups. Overall, 0.2% of participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%). The reasons for discontinuation were also balanced. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reason was previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AEs (0.1% in both treatment groups).

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. Overall, most participants were White (82.8%) and non-Hispanic/non-Latino (72.7%) (26.8% of Hispanic/latino ethnicity), median age was 52.0 years, and approximately 49% were female. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). In 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy).

Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. Obese participants made up 35.1% of the safety population. Overall, 120 subjects were HIV-positive and were evenly distributed between treatment groups.

Efficacy data and additional analyses

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

The first interim analysis for vaccine efficacy (VE) was conducted on 08-Nov-2020 by an IDMC. The data cut-off date was 04-Nov-2020, when a total of 94 confirmed COVID-19 cases were accrued. There were 4 COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the

placebo group. These data gave a vaccine efficacy of 95.5% (95%CI: 88.8%, 97.5%) among participants without evidence of infection up to 7 days after Dose 2, and a >99.99% posterior probability for the true vaccine efficacy greater than 30% conditioning on available data. Participants included in the first interim analysis were also included in the final analysis.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was high, 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after dose 2 was 94.2%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively) with a posterior probability (VE≥30%/data) of >99.99%.

Slightly more subjects in the placebo group had symptoms of COVID-19 without being a confirmed case by PCR. This is also reflected in slightly more subjects in the placebo arm with result not available from the swab. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with the available data, assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavourable for efficacy results of the study. 500 imputations were performed that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level. VE after imputation was over 80% also with up to 15-fold increase of positivity rate applied to the BNT162b2 group. Hence, there is no concern that this slight imbalance has introduced any significant bias to the results presented below.

The 2-dose schedule is considered justified both based on immune responses and on the actual efficacy results. In dose 1 all-available efficacy (mITT) population, regardless of evidence of infection before or during the vaccination regimen, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group (n=21,314 subjects) compared to 275 cases in the placebo group (n=21,258 subjects). Notably, in the BNT162b2 group, most cases (36/(50)) occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after dose 1 but before dose 2.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverge with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months post-dose 2, the BNT162b2 cumulative curve is stable which would not suggest waning protection. A longer follow-up is necessary to investigate the duration of the efficacy of the vaccine in protecting against the disease.

For both primary endpoints, no clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%. Efficacy was consistent across relevant subgroups.

The results in elderly are of great importance, as increasing age is an identified risk factor for severe disease and death. The results from this study are therefore reassuring suggesting a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9). There was no indication of

decreasing efficacy in subjects ≥75 years although the number of cases was small (0 in the vaccine group and 5 in placebo). In addition, the number of subjects >85YOA is very limited (5 subjects) hence the impact of immunosenescence on vaccine efficacy in these very old individuals remain uncertain.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for participants at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, obese with body mass index (BMI) ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, hypertension) was 95.3%, as compared with 94.7% for those not at risk. VE for participants ≥65 years of age and at risk was 91.7%, as compared with 100% for those ≥65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. The VE by comorbidity status are as follows: cardiovascular (VE 100.0 (-0.8, 100.0)), Chronic pulmonary disease (93.0 (54.1, 99.8)), diabetes (94.7 (66.8, 99.9)), Hypertension (95.4 (82.6, 99.5)).

Severe disease cases were uncommon in the study: 1 case in the vaccine group and 4 cases in the placebo group (one case in the all evaluable population) after 7 days post second vaccination. None of the severe cases were baseline positive for SARS-CoV-2.

In the evaluable efficacy population, subjects without evidence of prior SARS-CoV-2 infection, the estimated VE against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%: 96.3%). The posterior probability for the true VE greater than 30% is 74.29% (7 days) and 74.32% (14 days), which did not meet the pre-specified success criterion for this endpoint, therefore no reliable conclusion can be drawn at this stage. While data on severe COVID-19 are limited, the experience with other vaccines (rotavirus and influenza vaccines with known efficacy against mild disease but better efficacy against severe disease) coupled with the high observed vaccine efficacy observed for BNT162b2 on all COVID-19 cases in populations with any comorbidity gives reassurance that the vaccine is likely to prevent severe disease. However, a precise estimate of its protective effect is presently lacking. The final study report may include additional data to the extent that the study is continued in a randomised fashion with a placebo group.

The second primary endpoint -VE in participants with and without prior evidence of SARS-CoV-2 infection- yielded similar results as the one in the population excluding those without evidence of prior infection. However, analysis is largely driven by events in subjects without evidence of prior infection, and therefore does not provide additional information.

It is not possible to conclude on vaccine efficacy in subjects with prior COVID-19, or signs of infection with SARS-CoV2 because only a small number of subjects were found to be seropositive at baseline (approximately 550 in each vaccine and placebo group), and only 2 cases of disease were reported in this subset (1 in each group). Further data may become available as the trial proceeds, but it is unlikely that the study will be able to deliver conclusive evidence for a number of reasons (e.g. it is very likely that the number of subjects seropositive will remain limited, and that there will be a lower incidence of disease in seropositive placebo recipients compared to seronegative placebo recipients due to existing partial protection). The extent of additional protection in seropositive subjects is presently uncertain. Effectiveness studies may give us some information on this regard.

Genome sequencing of the SARS-CoV-2 strains in the BNT162b2 vaccine and placebo groups has not been performed. However, this work is planned by the Applicant.

The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This correspond to about 1.5 months of median follow-up time duration after completion of the full vaccination regimen. Therefore, available efficacy data are limited in term of follow-up duration, and the efficacy of the vaccine over longer-time remains unknown. Data are expected to become available post-authorisation.

Immune responses in terms of neutralising antibodies were measured in the phase 1 and 2 part of the study. Overall, the immune responses measured in the phase 1 and 2 part of the pivotal study are consistent and in line with the phase 1 study BNT162-01 results. As expected, both neutralising antibody levels and S-protein binding antibody levels were higher in the youngest age stratum compared to the older age stratum. Serum titres in vaccinated subjects were numerically higher compared to human convalescent sera, up to 1 month after dose 2. There is presently no established correlate of protection.

Very limited results by baseline serostatus were provided, but updated immunogenicity data is expected to become available.

Cell mediated immune responses were demonstrated in the phase 1 part of the study as well as in the other phase 1/2 study BNT162-01, but in a small cohort of subjects only. A clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED.

In total 14 adolescents aged 12-15 years were included in the vaccine group and 13 in the placebo group, and 52 adolescents aged 16-17 years in the vaccine and 55 in the placebo group. Vaccine efficacy could not be estimated for these subjects as no cases of disease were reported. No immune response data are available. However extrapolation of efficacy is possible from young adults because, from an immune system perspective, adolescents do not differ from young adults, thus there are no reasons to believe that the vaccine will not be as efficacious at least in the age subgroup proposed for the current indication (>16 years).

At cut-off date (14-Nov-2020), 120 subjects HIV positive were vaccinated with BNT162b2. Immunogenicity and efficacy data are not available at this time but will be provided post-authorisation.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Excellent vaccine efficacy (preventing symptomatic COVID-19) was shown in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%), which was consistent across relevant subgroups. It is likely that the vaccine also protects against severe COVID-19, though these events were rare in the study, and statistically certain conclusion cannot be drawn. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

The candidate vaccine BNT162b2 at 30 µg given twice 21 days apart was assessed a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and a Phase 1/2/3 study (C4591001) was initiated shortly afterwards in the United States (US). Hence, the safety data base for BNT162b2 constitutes of two Phase 1 studies (BNT162-01 and C4591001) and one Phase 2/3 study still ongoing (C4591001).

The cut-off for safety data included in this assessment is 14 November 2020.

The two Phase 1 trials (BNT162-01 and C4591001) are described in previous sections. Study C4591001 was initially started as a Phase 1/2 study in the USA and was then amended to expand to a global Phase 3 study.

Phase 2/3 of Study C4591001 included subjects that were stratified into two age groups: 18-55 years and >55-85 years. The Phase 3 part however was subsequently amended (6 Sept 2020 protocol amendment) to include subjects from 16 years of age in the younger age group (and then from 12 years of age) and subjects >85 years of age in the older age group.

AEs were collected during the Phase 2/3 study from the signing of the informed consensus document through and including 1 month after Dose 2 (visit no. 3). In addition, in all follow-up visits where blood samples for immunogenicity data are taken, any AEs and SAEs as appropriate occurring up to 48 hours were recorded after each visit. Immunogenicity follow-up is planned to occur during that period with visits 1-month, 6-months, 12-months and 24-months post the first vaccination. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. SAEs are recorded for up to 6 months after Dose 2 (ongoing at the time of this submission). In addition, any potential COVID-19 illness will lead to extra visits followed by convalescent visits. At the cut-off date 14-Nov-20, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall the study enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up.

The assessment is based on the following safety data (cut-off date 14 Nov 2020):

- Phase 1: i) Study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=18); ii) Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=0).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536). This subset constitutes the core safety data set in this assessment.
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up. In this population, the total number of subjects 16-17 years were 283 (N=138 BNT162b; N=145 placebo) and 100 participants were 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group). HIV-positive subjects (BNT162b2 N=99, placebo N=97) were included in this summary but not included in the analyses of the overall study objectives.
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Among these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).

- Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events, and antipyretic/pain medication usage for 7 days after each dose by using an e-diary. Eight subjects aged 16-17 years were included in this subset (BNT162b2 N=5; placebo N=3).

2.6.1. Patient exposure

Distribution and Exposure were presented for the population with median follow up of 2 months and for the whole population. Of the 37,796 subjects in the group with median follow up of 2 months who were randomized in the study before 9 October 2020, 90 participants (0.2%) were excluded from the safety population (89 did not receive study intervention and 1 did not provide informed consent).

		BNT162b2 N = 18904	**Placebo N = 18892**
		N (%)	**N (%)**
Median follow up 2 months (at least one month after dose 2)	Randomized	18904 (100%)	18892 (100%)
	Vaccinated with Dose 1	18858 (99.8%)	18849 (99.8%)
	Vaccinated with Dose 2	18553 (98.1)	18534 (98.1%)
HIV positive		59	61
Follow up ≥ 2months after dose 2		9531 (50.5%)	9536 (50.6%)
Follow up ≥ 10 to < 12 weeks after dose 2		2853 (15.1%)	2809 (14.9%)
Follow up ≥ 12 to < 14 weeks after dose 2		382 (2.0%)	398 (2.1%)

For Dose 1, three participants randomized to the placebo group received BNT162b2, and two participants randomized to the BNT162b2 group received placebo. For Dose 2, four participants randomized to the placebo group received BNT162b2, and five participants randomized to the BNT162b2 group received placebo.

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the BNT162b2 (93.1%) and placebo (92.9%) groups.

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cut-off.

In total 1145 individuals of the safety population were SARS-CoV-2 seropositive at baseline.

A high exposure rate of 99.8% to the first dose was reached in both vaccine and control arm and a small number of individuals were withdrawn after the first dose, leading to a high rate of exposure to the second dose in both study arms (98.2% and 98.1%). Reasons for withdrawals (1.0% and 1.4%, respectively) were in most cases withdrawals by the participant, or loss to follow-up.

There were no clinically meaningful differences in the safety population by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Table 14 Safety Population, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis

Baseline SARS-CoV-2 Status		Vaccine Group (as Administered)		
		BNT162b2 (30 µg)	Placebo	Total
		n[a]	n[a]	n[a] (%)
Positive	Randomized[b]			1148
	Vaccinated	557	588	1145 (99.7)
	Safety population	557	588	1145 (99.7)
	HIV-positive	12	8	20 (1.7)
	Excluded from safety population			3 (0.3)
	Reason for exclusion			
	Subject did not receive study vaccine			3 (0.3)
Negative	Randomized[b]			35764
	Vaccinated	17885	17858	35743 (99.9)
	Safety population	17884	17858	35742 (99.9)
	HIV-positive	43	50	93 (0.3)
	Excluded from safety population			22 (0.1)
	Reason for exclusion			
	Subject did not receive study vaccine			21 (0.1)
	Did not provide informed consent			1 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (07:27)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adsl s003 saf pop bs p3

The disposition, exposure and withdrawal profile of the whole study population was comparable to the group that was randomised before 9 October 2020 with median follow up of 2 months.

Among the 37,706 subjects with a median follow-up of 2 months, 50.6% had ≥2 months duration of follow-up after Dose 2 and 91.6% had a duration of follow-up time of ≥1 month after Dose 2. Around 3000 individuals have already a follow of at least 10 weeks after dose 2. Updates, including additional safety data as well as assessment of the differences in safety profile in the longer follow-up compared to the initial safety dataset, if any, shall be provided when more mature data will be available.

Six-months post Dose 2 follow-up data from the first ~6000 subjects are expected by the end of February 2021 and this will allow a relevant discussion on the safety profile versus the initial dataset.

Based on the population with a median follow up of 2 months, demographic characteristics are considered well balanced between vaccine and placebo arm. Most included subjects were white (83%), with a median age of 52 years. A balanced distribution is seen regarding gender (51% male, 49%

female). The younger and older age groups were 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Of note, 35% of individuals were obese in both study arms. Across both treatment groups, 20.7% had any comorbidity.

The number of subjects with any Charlson co-morbidity diagnoses was balanced in both study arms (20%). Most prevalent were the diagnoses diabetes mellitus (7.8%) and COPD (7.8%) followed by subjects showing any type of malignant disease (3.9% in vaccine and 3.5% in placebo group). Other diagnoses were abundant with ≤ 1% in both study arms (population with a median follow up of 2 months). In the population with a follow-up ≥2 months, Charlson co-morbidity diagnoses was similar.

The demographic distribution was somewhat different when comparing seropositive and seronegative individuals, observing a median age of 43 years in seropositive and of 52 years in seronegative individuals. Furthermore, the seropositive group covered a higher proportion of obese individuals (42.2% versus 34.7%). Demographic characteristics in the whole population were comparable to those seen in the population with a median follow up time of 2 months.

2.6.2. Reactogenicity

Reactogenicity was evaluated in a subset of the Phase 2/3 study of 8,183 subjects (BNT162b2 n=4093; placebo n=4090) from both age groups (16 to 55 and >55 years of age) that received BNT162b2 or vaccine according to the proposed dosing regimen. Of note, the number of subjects aged 16-17 years included in this subset was limited (n=8; BNT162b2 n=5; placebo n=3). After each dose, the subjects reported any local reactions, systemic events, including antipyretic/pain medication usage for 7 days, by using an e-diary (cut-off date 14 Nov 20).

Local reactions

The most commonly reported local reaction among the subject that received BNT162b2 was pain at the injection site, which occurred slightly more common among subjects 16-55 years (N=2291 [83.1%] post Dose 1; N=2098 [77.8%] post Dose 2) compared to those >55 years of age (N=1802 [71.1%] post Dose 1; N=1660 [66.1%] post Dose 2). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at a lower frequency (16-55 [14.0% and 11.7%]; >55 [9.3% vs 7.7%]).

There was no difference in frequency of redness and swelling at injection site after the two doses of BNT162b2. Redness occurred in about 5-7% in both age groups (16-55 [4.5% after Dose 1, 5.9% after Dose 2]; >55 [4.7% after Dose 1, 7.2% after Dose 2]). Swelling was reported also in about 5-7% of the subjects in both age groups (16-55 [5.8% after Dose 1, 6.3% after Dose 2]; >55 [6.5% after Dose 1, 7.5% after Dose 2]). In the placebo group, redness and swelling were reported infrequently in both age groups (≤1.2%).

Overall, the majority of local reactions were mild or moderate in severity, no Grade 4 reactions were reported. Severe local reactions (≤0.7%) were reported infrequently in the BNT162b2 group after either dose and was more commonly reported in the younger group. Across age groups, local reactions for the BNT162b2 group after either dose had a median onset between 1-3 days (Day 1 was the day of vaccination), with a median duration of 1-2 days.

No clinically meaningful differences in local reactions were observed by baseline SARS-CoV-2 status subgroups. However, since the baseline SARS-CoV-2 positive subgroup included very few participants (vaccinated n=154; placebo n=164), these results should be interpreted with caution.

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population

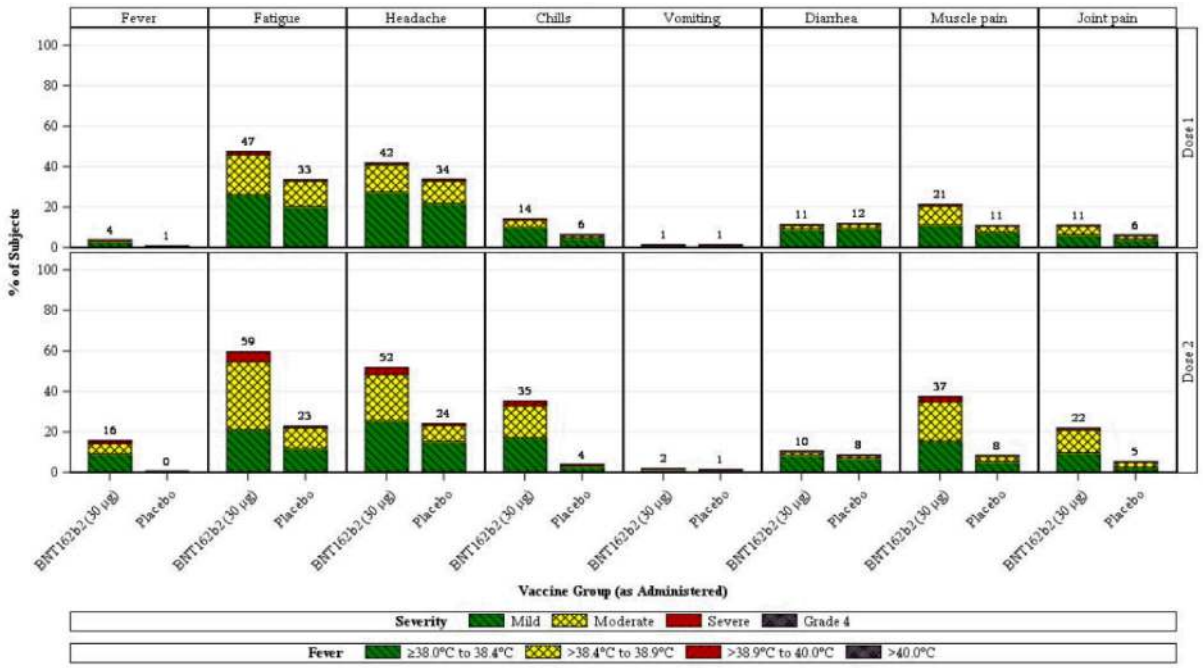
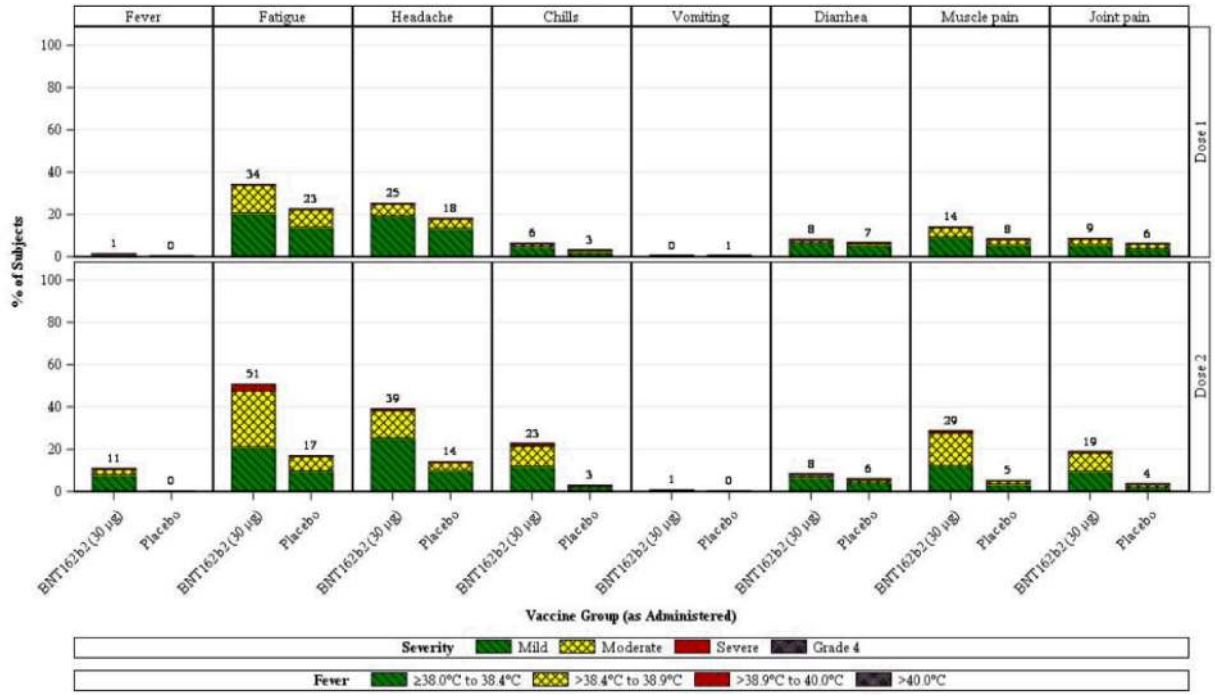


Table 16 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group >55 Years – Reactogenicity Subset for Phase 2/3 Analysis–Safety Population



Systemic events were generally reported more frequently in the BNT162b2 group than in the placebo group, for both age groups and doses. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was 2-3 days, with a median duration of 1 day.

Systemic events were generally increased in frequency and severity in the younger age group compared with the older age group, with frequencies and severity increasing with number of doses (Dose 1 *vs* Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were: fatigue, headache, muscle pain, chills, joint pain and, fever.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%). Of note, medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.8% to 22.0%).

No clinically meaningful differences in systemic reactions were observed by baseline SARS-CoV-2 status subgroups, however as mentioned data in baseline SARS-CoV-2 positive subjects are limited.

Overall, the reported reactogenicity is in line with what can be expected from any vaccine. The local and systemic reactions were transient and of short duration, the majority were mild to moderate at intensity and the reactions were milder among older subjects (>55 years).

2.6.3. Adverse events

In the subset of participants randomised before 9 October 2020 with Median 2 Months of Follow-Up After Dose 2 (N= 37,586; from Dose 1 to 1 month after dose 2) and the subset of participants with at least 2 Months of Follow-Up After Dose 2 (N=19,067; from dose 1 to data cut off 14 November 2020), the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cut-off date for all enrolled participants (N=43,252; from dose 1 to data cut-off 14 November 2020). Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events (see above). This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group (26.7%) compared with the placebo group (12.2%).

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs.

Table 17 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to date cutoff date (14 Nov 2020) – Subjects with 2 months follow-up time after dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Adverse Event	BNT162b2 (30 µg) (N[a]=9531) n[b] (%)	Placebo (N[a]=9536) n[b] (%)	Total (N[a]=19067) n[b] (%)
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related[c]	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related[c]	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:28)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 all 2mpd2 p23 saf

Overall, in participants with 2 months follow up after dose 2, 21.4% / 12.6% (vaccine/placebo) and 13.6%/3.6% experienced at least 1 AE and 1 related AE, respectively. It is noted that the frequency of AEs and related AEs is lower compared to individuals with a median follow up of 2 months (27%/12.5% and 20.8%/5.1%).

The frequency of individuals experiencing AEs were slightly higher in the younger compared to older individuals (29.3% and 23.8% vaccine arm; 13.2% and 11.7% placebo arm). SAEs and deaths were however balanced in both study arms in both age groups.

The frequency of immediate AEs after dose 1 was low in participants with median 2 months of follow-up after Dose 2 (0.4%) and the whole population (≤0.5%), belonging mostly to the SOC general disorders and administration site conditions, primarily injection site reactions. No participant reported an immediate allergic reaction to vaccine.

Severe AEs, SAEs, AEs leading to discontinuation, and deaths were reported by ≤1.1%, 0.6%, 0.0%, and 0.0%, i.e. low and equally distributed in both study arms. No differences vs. the whole population were seen according to age groups.

The rate of AEs and related AEs was slightly higher in the SARS-CoV-2 negative group compared to SARS-CoV-2-positive individuals. Stratification according to serostatus in the safety group median follow up 2 months reveals overall very low numbers of severe AEs, SAEs and deaths.

Table 18 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month after Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subject for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Positive

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=545) n[b] (%)	Placebo (N[a]=580) n[b] (%)
Any event	120 (22.0)	57 (9.8)
Related[c]	90 (16.5)	26 (4.5)
Severe	8 (1.5)	2 (0.3)
Life-threatening	2 (0.4)	0
Any serious adverse event	4 (0.7)	1 (0.2)
Related[c]	0	0
Severe	2 (0.4)	1 (0.2)
Life-threatening	2 (0.4)	0
Any adverse event leading to withdrawal	2 (0.4)	1 (0.2)
Related[c]	0	0
Severe	0	0
Life-threatening	1 (0.2)	0
Death	1 (0.2)	0

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 pd2 bs p3 saf

Table 19 Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Negative

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=17841) n[b] (%)	Placebo (N[a]=17808) n[b] (%)
Any event	4837 (27.1)	2253 (12.7)
Related[c]	3742 (21.0)	911 (5.1)
Severe	205 (1.1)	105 (0.6)
Life-threatening	16 (0.1)	20 (0.1)
Any serious adverse event	97 (0.5)	80 (0.4)
Related[c]	3 (0.0)	0
Severe	54 (0.3)	47 (0.3)
Life-threatening	16 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	31 (0.2)	24 (0.1)
Related[c]	13 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	1 (0.0)	4 (0.0)
Death	0	2 (0.0)

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_pd2_bs_p3_saf

There were 19,067 participants with at least 2 months follow-up time after Dose 2, and similar to the 37,586 participants randomised before 9 October 2020 with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cut-off date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo).

In the younger versus older BNT162b2 age groups, AE SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)

- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

Most often occurring events by PT comprised vaccine typical reactions such as injection site pain, fever, fatigue as well as myalgia and arthralgia. Lymphadenopathy occurred in 0.4% in the ≥ 2 months follow up subset (0% in placebo arm), or 0.3% of cases in the whole population (0% in placebo arm). Nausea also occurred in 0.6% more cases in the vaccine compared to placebo arm.

Related AEs belonged overall to the same SOCs as described above, i.e. general disorders and administration site conditions (3426 cases, 20.8%), musculoskeletal reactions (1148 cases, 6.1%), and nervous system disorders (979 cases, 5.2%) and occurred overall more often in the vaccine than in the placebo arm (median follow up 2 months). Severe AEs occurred more often in the vaccine arm (1.2% vs. 0.6%) in the subset with a median follow up time of 2 months, reflecting a similar SOC pattern.

The following specific observations are made based on PTs:

Numerical disbalances are observed for several hypersensitivity terms ((drug)hypersensitivity/ immunisation events; 5/3 cases ≥ 2 months group, 13/6 cases whole population, 6/1 cases deemed related in the whole population, 4 cases deemed severe (whole population), in the SOC immune system disorders).

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study, 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and, among those, two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. The participant who received BNT162b2 had a history of allergy to tree pollen. This participant reported Drug hypersensitivity and Urticaria on the day of Dose 1. Both AEs were of moderate severity and lasted one day. The participant did not receive Dose 2 of the vaccine. The participant who received placebo had an allergy to shellfish and iodine. This participant reported Allergy to vaccine and Pharyngeal swelling 1 day after Dose 1. Both events were of moderate severity and lasted 13 days and 10 days, respectively. This participant did not receive Dose 2 of study intervention.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine.

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole population)). However, none of the cases considered related to study drug treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm, which where however balanced in frequency between vaccine and placebo arm.

An imbalance in PT connected to sleep disturbances was noted in the whole population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus the placebo arm).

A slight imbalance of hyperhidrosis/night sweats was noted in the whole population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole population).

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole population).

Stratification according to age did not reveal meaningful differences in the types of AEs.

A stratification according to serostatus was performed in individuals with a follow up of at least one month (median FUP 2 months) and ≥2 months. Most abundant SOCs are similar to the SOCs identified in the general population with ≥2 months follow-up. No additional safety concerns are detected when stratifying according to serostatus.

2.6.4. Serious adverse event/deaths/other significant events

SAEs

This section presents the SAEs reported up to the data cut-off (14-nov-20).

Among the 19,067 subjects (BNT162b2 n=9531; placebo n= 9536) with ≥2 months of follow-up post Dose 2, small percentages of subjects in the 30 µg BNT162b2 group (56 [0.6%]) and the placebo group (53 [0.6%]) reported any SAEs. Subjects in both the BNT162b2 group and placebo group, respectively, reported SAEs at similar rates for the observed SOCs. A similar frequency was observed for the entire study population and no clinically meaningful differences in SAEs were observed by age, baseline SARS-CoV-2 status, ethnicity, race or sex subgroups.

Among all included subjects (BNT162b2 n=21720; placebo n=21728) three SAEs were reported in the SOC immune system disorders. One SAE of anaphylactic reaction (related to bee sting) and one drug hypersensitivity (related to treatment with doxycycline) was reported in the BNT162b2 group. In addition, one SAE of anaphylactic shock (related to an ant bite) was reported in the placebo group.

In the subset of individuals aged 16-17 years old, one SAE (facial bone fracture) was reported.

After the cut-off date and up to 5-Dec-20, additional 22 SAEs have been reported (blinded data).

SAEs related to study intervention

Up to the cut-off date, four of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention. One event of lymphadenopathy and one event of shoulder injury due to incorrected administration were considered related to BNT162b2.

It is not agreed that the event of ventricular arrythmia and the event of pain in the lower back/extremities/and radicular paraesthesia have been convincingly demonstrated to be related to

study intervention, since the subjects had underlying conditions that could have caused the two SAEs, there is little biological plausibility, and the overall numbers of reported events do not allow for a causal inference.

Death

Six events of death (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention, which is agreed since other pre-existing diseases were more likely to have caused death than the vaccine. After the cut-off date and up to 5-Dec-20, one additional event of death due to aortic rupture were reported (data blinded).

2.6.5. Laboratory findings

Laboratory results are available for the two Phase 1 studies, but not for the Phase 2/3 trials. This is considered acceptable. Except for minor transient decrease in lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

2.6.6. Safety in special populations

No clinically meaningful differences in AEs were observed by age, country (mostly Argentina, Brazil, USA), ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino), gender and race (With, Black or African American, all other races) subgroups.

Pregnancy

At the time of the data cut-off in the Phase 2/3 study (14 Nov 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes. Thus, data on pregnancy are very limited at this stage.

Elderly

The Phase 2/3 study included >40% of subjects >55 years of age. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). No differences in AE frequency were detected among subjects >70 years of age compared to the older age group >55 year. Thus, no specific safety concern is anticipated for the elderly.

Immunocompromised individuals

Per protocol, participants with chronic stable HIV infection were defined as HIV disease with a documented viral load <50 copies/mL and CD4 count >200 cells/mm3 within 6 months before enrolment, and on stable antiretroviral therapy for at least 6 months. Stratification by CD4 count, efficacy and immunogenicity data are not available at this time but will be provided post-authorisation.

Safety data are available for 196 participants with stable HIV infection. The most frequent AEs in the BNT162b2 group were reported in the General Disorders and Administrative Site Conditions SOC including injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

Assessment of paediatric data on clinical safety

Paediatric individuals age 16 to 17 years of age are included in the Phase 2/3 study that constitutes the safety database in this assessment. The population of subjects aged 16-17 years are limited (n=283). No additional or new AEs were observed compared to adults).

There were no participants in the 16 to 17 years of age group with ≥2 months of safety follow-up at the time of the data cut-off (14 November 2020). The longest duration of follow-up in this age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study.

The reactogenicity subset of ~8000 participants (n=4093 BNT162b2; n=4090 placebo) contributing e-diary data included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) include reactogenicity data (local reactions and systemic events) collected via e-diary up to the safety cut-off date of 14 November 2020. The reported adverse events were primarily reactogenicity events with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

In the reactogenicity subset including individuals aged 12-15 years and the 8 individuals aged 16-17 years, the most frequently reported systemic reaction in both treatment groups were fatigue (59.2% in the BNT162b2 group and 25.5% in the placebo group), followed by headache (57.1% BNT162b2, 43.1% placebo). Fever ≥38°C was reported for 26.5% more participants who received BNT162b2 over placebo; two (4.1%) of these participants reported severe fever (>38.9°C to 40.0°C).

2.6.7. Safety related to drug-drug interactions and other interactions

Interaction studies with other vaccines have not been performed, which is acceptable given the need to use the vaccine in an emergency situation. The Applicant will conduct a study post-authorisation as indicated in the RMP (see section 2.7).

2.6.8. Discontinuation due to adverse events

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn from the study because of AEs. The results were similar to the AEs leading to withdrawal in the group randomised before 9 October 2020 with median follow up of 2 months. Among 19,067 participants with at least 2 months of follow-up time post Dose 2, 1 participant in the BNT162b2 group and no participants in the placebo group had an AE leading to withdrawal from the study.

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal. Among all 43,448 participants, no clinically meaningful differences in AEs leading to withdrawal were observed by age or other subgroups.

2.6.9. Post marketing experience

Post-marketing data are not yet available as the vaccine has not been approved in any country at the time of the data cut-off (14-Nov-20). After the cut-off date, it is noted that several countries have recently authorised the vaccine for emergency use (e.g. UK, Canada, US). Two cases of anaphylactoid

reaction out of 138,000 persons vaccinated have been reported in individuals carrying Epipen after initiation of vaccination in one country, which resolved with standard therapy. One case of anaphylaxis was reported in another country (unknown denominator) in a subject without known history of allergies, which required ICU and was then resolved. Post-marketing safety data are expected with the next monthly summary safety report.

2.6.10. Discussion on clinical safety

The safety database for BNT162b2 constitutes of two Phase 1 studies (BNT162-01[2] and C4591001[3]) and one Phase 2/3 study (C4591001) which is still ongoing. The cut-off date for safety data included in this assessment is 14 November 2020.

Up to the cut-off date ~44,000 subjects had been recruited and received at least one dose of either BNT162b2 (n=21,720) or placebo (n=21,728). The core safety database of this assessment constitutes of ~19,000 participants who have been followed ≥2 months after the 2nd dose of BNT162b2 (n=9531) or placebo (n=9536). The Applicant has also presented data from a subset of ~38,000 subjects randomised before 9 October 2020 with a median follow-up period of 2 months after Dose 2 of BNT162b2 (n=18,860) or placebo (n=18,846).

Demographic characteristics are considered well balanced between vaccine and placebo arm (median follow up 2 months). Subjects were mostly white (83%) and had a median age of 52 years. The younger and older age groups included 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Gender was balanced (51% male). Of note, 35% of individuals were obese in study arms. The demographic distribution was different between seropositive and seronegative individuals, with a median age of 43 years in seropositive and of 52 years in seronegative subjects. Furthermore, the seropositive group covered a higher rate of obese individuals (42.2% versus 34.7%). Demographic characteristics in all participants were roughly comparable to those with median follow up of 2 months.

Charlson co-morbidity diagnoses were balanced in both study arms (20%). Most prevalent co-morbidities were diabetes (7.8%), COPD (7.8%) and malignant disease (3.9% in the vaccine arm and 3.5% in the placebo arm). Other diagnoses accounted for ≤ 1% of subjects in both study arms (median follow up of 2 months).

In the Phase 2/3 study reactogenicity was evaluated in a subset of 8,183 subjects who received BNT162b2 (n=4093) or placebo (n=4090) according to the proposed dosing regimen. The number of subjects aged 16-17 years included in the reactogenicity subset was small (n=8; BNT162b2 n=5; placebo n=3). After each dose, all subjects were asked to report any local reactions, systemic events, and antipyretic/pain medication usage for 7 days, by using an e-diary.

Pain at the injection site was the most common local reaction reported in the vaccine group, slightly more frequently reported among subjects 16-55 years (~80%) compared to >55 years (~70%). In the placebo group 8-14% reported pain at injection site. In the vaccine group redness and swelling were overall reported at a frequency of 5-7% in both age groups (vs. placebo 0-1%). Use of antipyretic/pain medication was more common after Dose 2 than after Dose 1 in both age groups, and overall slightly lower among subjects >55 years regardless of the dose (younger group: 28% after dose 1 vs 45% after dose 2; older group: 20% vs 38%). The use of antipyretic/pain medication was less common in the placebo group (younger group: 34% after dose 1 vs 23% after dose 2; older group: 23% vs 18%).

[2] Phase I: End of study 28 days after Dose 2.
[3] Phase I: participants enrolled in Phase1 in groups that do not proceed to Phase 2/3 (i.e. other doses than 30 µg) may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

Among the systemic reactions, headache and fatigue were the most common events, and the frequency was higher after Dose 2 compared to Dose 1 (16-55 YOA [47% vs 59%]; >55 YOA [34% vs 51%]). Fever also occurred more frequently after Dose 2 (16-55 YOA [4% vs 16%]; >55 YOA [1% vs 11%]). None of the subjects >55 YOA in the placebo group reported events of fever and 1% of the subjects aged 16-55 years reported fever after the first dose.

Overall, the local and systemic reactions were transient and of short duration (resolved within few days after vaccination), the majority were of mild to moderate intensity, and milder and of slightly lower frequency among older subjects (>55 years of age).

In the group of 19,067 participants with 2 months follow up after dose 2, 21.4% and 12.6% (vaccine vs placebo) of the subjects reported at least one AE. 13.6%/3.6% reported at least 1 related AE. Rates were lower compared to the whole enrolled trial population (26.7% (vaccine) and 12.2% (placebo)).

AEs in subjects with a follow up of at least 2 months belonged most often to the SOCs "General disorders and administration site conditions" (11.9% vs 2.9%), "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%), occurring more often in the vaccine than in the placebo arm. PTs comprised most often vaccine typical reactions, i.e. injection site pain, redness and swelling, fever, chills, fatigue, headache as well as myalgia and arthralgia and malaise. Nausea also occurred more often in the vaccine arm (79 cases, i.e. 0.8%, in vaccine vs. 21 cases, i.e. 0.2%, in placebo). Lymphadenopathy was seen in 0.4% subjects in the vaccine arm (38 cases) vs. 0% in the placebo arm (3 cases), or 0.3% of cases in the whole population (0% in placebo arm).

Severe AEs were reported by a small number of subjects (≤1.1%) and equally distributed between the study arms. No differences were seen between age groups. Frequencies are comparable in the whole enrolled trial population and when stratifying according to serostatus.

Numerical imbalances are observed for several hypersensitivity/immunisation reaction preferred terms (5/3 cases in the ≥ 2 months follow up subset, 13/6 cases in the whole enrolled trial population subset, 4 cases deemed severe (whole enrolled trial population), in the SOC immune system disorders).

Lymphadenopathy, nausea, and hypersensitivity are reported more often with the vaccine arm. For these items there is a reasonable possibility of a causal relation to vaccination and they are as such included in the SmPC section 4.8.

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and among those two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. There are incoming reports of anaphylactoid reactions from ongoing vaccination campaigns. A warning is included in the SmPC addressing the need of adequate emergency material in place at the vaccination site, which is common practice with any vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

Four cases of peripheral facial paralysis were observed in vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole enrolled trial

population, however the case of paresis was not considered for this calculation). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician. Taken together, this was considered to indicate there is a reasonable possibility of a causal relation to the vaccine, and to justify inclusion of peripheral facial paralysis (Bell´s palsy) in the SmPC 4.8 with a frequency as 'rare'.

An imbalance in PT connected to sleep disturbances was noted in the whole enrolled trial population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus in the placebo arm). The occurrence of insomnia may plausibly be due to e.g. local/systemic reactogenicity that may occur after vaccination. The CHMP agreed to include insomnia in section 4.8. of the SmPC.

A slight imbalance of hyperhidrosis/night sweats was noted in the whole enrolled trial population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole enrolled trial population). These events may be plausibly associated to the injection of BNT162b2 and should therefore be included in the SmPC section 4.8.

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole enrolled trial population). In addition to pain at injection site, which was commonly reported, pain in the extremity is also considered plausibly related to the vaccination and should therefore be included in the SmPC section 4.8.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole enrolled trial population)), however these are considered not related to study treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm. These were numerically balanced in frequency between vaccine and placebo arm. Autoimmune events will be monitored post-authorisation as described in the RMP.

SAEs occurred at a low frequency in both BNT162b2 and the placebo group (0.6%, 56 cases in vaccine vs. 53 cases in placebo) in subjects with ≥2 months of follow-up post Dose 2, and a similar frequency was observed in the total study population. One SAE of lymphadenopathy and one SAE of shoulder injury were considered related to study intervention. No cases of related SAEs were reported in the adolescent group (only one case of facial bone fracture). Six events of death (2 in the BNT162b2 group and 4 in the placebo group) have been reported in the entire study population, all deemed unrelated to the vaccine.

The rate of subjects discontinuing participation in the study due to AEs was low in both study arms (0.2%/0.1%).

The subgroup of seropositive subjects is limited in size (n=545 BNT162b2; n=580 Placebo). A stratification according to serostatus for AE investigation was specifically performed in individuals with a follow up of at least one month (median Follow up 2 months) and ≥2 months. Most reported SOCs are similar to those identified in the ≥ 2 months population. AE rate in seropositive individuals was lower (22%) compared to seronegative individuals (27%) and no specific safety concern is detected in this subpopulation.

23 participants reported pregnancies in the safety database, nine of them were withdrawn from the study due to the pregnancy status. These participants will be followed up for pregnancy outcomes.

The Applicant has not provided a specific analysis of elderly individuals > 70 years included in the development program. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). Thus, no specific safety concern is anticipated for the elderly.

Data on immunocompromised individuals are limited, which was raised as missing information in the RMP and will be further followed up. 196 participants with stable HIV infection were included in the trial and reported AEs that were mostly reactogenicity-related with no SAEs. No specific safety concern is detected in this subpopulation.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics as applicable.

Assessment of paediatric data on clinical safety

The longest duration of follow-up in the 16-17 years of age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study, albeit is numerically lower (11.6%/4.8%, vaccine/placebo).

The reactogenicity subset included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) show reactogenicity events (local reactions and systemic events) with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

Overall, the safety of BNT162b2 in individuals 16-17 years of age is extrapolated from young adults in general.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.6.11. Conclusions on the clinical safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off (14-Nov-20) included 43,448 subjects who received either two doses of BNT162b2 30µg (n=21 720) or placebo (n=21 728). Overall, the reported reactogenicity profile are in line with any authorised vaccine. In addition, the frequency of reported AEs and SAEs were low. The emerging safety profile is presently considered favourable. Long term safety data, interaction with other vaccines, data on use in pregnancy and other subgroups (e.g. frail subjects, or subjects with pre-existing autoimmune diseases) are missing at this stage.

The lack of long-term follow up renders the data provided non-comprehensive. Therefore, the delivery of the final C4951001 study report, including a 2-year follow up of the studied population, is classified as a specific obligation in the context of a conditional marketing authorisation.

The plan for the generation of further safety data post authorisation is described in the section below.

2.7. Risk Management Plan

Safety Specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breast feeding Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long term safety data

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the UK and US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for Comirnaty. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post-authorisation safety study.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the PASS.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is

requested. The Applicant commits to conduct a study of the co-administration of Comirnaty with inactivated quadrivalent influenza vaccine.

Data from use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- A **web-based AE reporting portal** will be available for vaccine providers (*e.g.* pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- **Signal detection activities** for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA Vaccine will include routine and specific review of AEs consistent with the AESI list provided in the RMP.
- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.
- Regulatory authority **safety alerts monitoring**, to detect and further investigate potential signals being raised on other areas outside of EU.
- A specific adverse reaction **follow-up questionnaire** intended to capture clinical details about the nature and severity of COVID-19 illness particularly in relation to potential cases of vaccine lack of effect or VAED.

- In addition to routine 6-monthly PSUR production, monthly summary safety reports will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:
    - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
    - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
    - Interval and cumulative number of reports per HLT and SOC;
    - Summary of the designated medical events;
    - Reports per EU country;
    - Exposure data (including age-stratified);
    - Changes to reference safety information in the interval, and current CCDS;
    - Ongoing and closed signals in the interval;
    - AESI reports – numbers and relevant cases;
    - Fatal reports – numbers and relevant cases;
    - Risk/benefit considerations.
- The submission of monthly reports complements the submission of PSURs (requested initially every six months). The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).
- Joint adverse event and product complaint (including available batch/lot information) trending reviews will be conducted routinely by the Applicant.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability from manufacturing to vaccination administration site is crucial to ensure maintenance of the cold-chain as well as for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The Applicant’s proposal to ensure traceability include:

- SmPC 4.4 labelling to raise HCP awareness regarding the need to clearly record the name and batch of the vaccine to improve traceability;
- a tracking device on every vaccine shipping container that provides real-time monitoring of GPS location and temperature 24 hours per day, 7 days per week;
- vaccine carton labelling also containing a 2-D barcode which has the batch/lot and expiry embedded within
- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card and peel-off labels (stickers with brand name and lot/batch numbers), acknowledging that each Member State will decided if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the Applicant's commitment that by 31 January 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

- Space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine, and keep it thereafter;
- QR code that links to additional information;
- Adverse event reporting information.

Additional pharmacovigilance activities

The Applicant proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study addressing co-administration with another vaccine) and 5 non-Interventional studies (4 safety and 1 effectiveness):

Study (*study short name, and title)* **Status *(planned/on-going)***	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2				
C4591001 *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Category 3				
C4591011	Assessment of occurrence of safety events of interest, including severe or	Anaphylaxis	Interim reports submission:	30-Jun-2021

Planned	atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		31-Dec-2021 30-Jun-2022 31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591012 *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591010 *Planned*	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review:	31-Jan-2021
			Final CSR submission:	31-Mar-2024

C4591015 *Planned*	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission: Final CSR submission:	28-Feb-2021 30-Apr-2023
C4591014 *Planned*	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	-	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022
C4591018 *Planned*	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission: IA submission:	28-Feb-2021 31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022
ACCESS/VAC4EU *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders	Protocol submission: Final CSR submission:	28-Feb-2021 31-Jan-2024

		Long term safety data.		
Co-administration study with seasonal influenza vaccine *Planned*	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

Non-Interventional Post Approval Safety Studies (4)

The Applicant proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 has been provided.

Additionally, Pfizer, on behalf of the Applicant, will sponsor one or more PASS using secondary electronic health records data sources in Europe based on a master surveillance protocol developed through the ACCESS project.

Two additional studies will be conducted using US data:

- 1 study using secondary data from EHR of active military and their families (C4591011),
- 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) have been provided.

Interventional studies (6)

The Applicant proposes 6 interventional studies, of which 2 are ongoing and 4 are planned.

- **Study C4591001** is an ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. At the time of the data cut-off date in Study C4591001 (14 November 2020), a total of 21,720 participants received at least one dose of the candidate vaccine.
- **Study BNT162-01 Cohort 13** is an ongoing multi-site (Germany), Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in 30 immunocompromised adults.
- **Study C4591015** is a planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID 19 mRNA vaccine.
- **Study C4591018** is a planned study of BNT162b2 in 100 adults receiving a stable dose of immunomodulators for the treatment of stable rheumatoid arthritis (RA), in two cohorts (50 tofacitinib, 50 TNF inhibitors). Subjects will be studied for safety, immunogenicity by neutralizing antibody titer, and evidence of asymptomatic infection by N-antigen antibodies.

- A planned **Phase II safety and immunogenicity study** (Safety and immunogenicity in high risk adults) in up to 150 immunocompromised adults (with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments.
- **Co-administration study with seasonal influenza vaccine** study investigating the safety and immunogenicity of Comirnaty and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Non-Interventional PASS in Pregnancy

The Applicant's proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be very limited; therefore, initially this information will derive from the 4 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in the preceding section. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The Applicant will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. The applicant's commitment and considerations are noted to evaluate pregnancy outcomes in a PASS using established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. Further feasibility analyses are awaited with RMP updates post-approval.

Non-Interventional Post-Approval Effectiveness study (1)

The Applicant will conduct at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. These studies will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups. The studies proposed below are under evaluation as potential commitments; studies are presented by geographical area (US and EU).

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The Applicant included a discussion on potential medication errors which is endorsed:

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID-19 vaccines are available, confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC and further materials for healthcare providers which will be made available to the Member States to be integrated in the national campaign for communication, as needed.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centres will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card will be provided with the pre-printed manufacturer name, dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines.
- Peel-off labels with lot/batch number

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those MSs where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Summary of additional risk minimisation measures

None proposed.

The Applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Important Potential Risks		
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Missing information		
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: No risk minimisation measures.	Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan **version 1.0** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, During the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

The following exemptions from labelling and serialization requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[4] document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

US packaging specific derogations (valid for December ’20 and January ‘21)

All EU Members States (MSs), as well as Norway and Iceland, have agreed to grant a temporary

[4] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

exemption to allow the placing in the EU market of the US packaging, under the following conditions:

a. The validity is only temporary and the MAH shall switch to the EU labelling requirements by February ’21;

b. The US pack will have included a Quick Response (QR) code which the vaccine recipient could scan and gain access to the package leaflet (PL) in his/her national language;

c. The MAH shall supply a separate printed PL in the national language(s) of those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine.

EU packaging specific derogations (from February ’21 onwards)

a. Outer and immediate labelling will be provided in English only.

The MAH shall provide outer and immediate labelling in all EU languages by 2nd Q 2022. This exemption is justified on the deep-frozen storage/shipping requirements and the necessity to label batches ahead of time. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

b. A printed package leaflet will be provided in the national language(s) for those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine. In addition, a QR code printed on the outer label and the PL will provide access to the package leaflet in the national language(s).

The MAH shall provide a printed package leaflet in all EU languages by 2nd Q 2022.

The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

c. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

d. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch from US packaging to EU compliant packs in February 2021.

Exemption from the obligation of serialisation

US packaging specific derogations (valid for December ’20 and January ‘21)

a. It is acceptable that the US pack will be placed in the EU market without serialisation according to the EU FMD requirements. Only the Global Trade Item Number (GTIN) will be common for US & EU and this will be printed on the US pack.

EU packaging specific derogations (from February until March ’21)

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from February until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February ‘21 and a second by 1st of March ‘21 referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Safe Handling Guidelines for Dry Ice
- Shipping and Handling Guidelines Brochure
- Preparation and Administration Video
- Storage and Handling Video
- Returning the Thermal Shipping Container video
- How to prepare and Administer Poster
- Traceability and vaccination reminder card
- Returning the thermal Shipping Container brochure
- Dry Ice Replenishment Brochure
- Link to Adverse Event Reaction Reporting

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

As of 1 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

Comirnaty is intended for active immunisation against SARS-CoV-2, thereby preventing COVID-19.

3.1.2. Available therapies and unmet medical need

There is currently no approved vaccine in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

3.1.3. Main clinical studies

The clinical development consists of one FIH phase 1 study (BNT162-01) in younger and older adults (18-55 years and 56-85 years) comparing 4 vaccine candidates, and one pivotal clinical study, C4591001 (or BNT162-02).

The pivotal study is a phase 1/2/3 placebo-controlled, randomised, observer-blind, dose finding, multicentre study performed in the US (start date 4 May 2020), Argentina, Brazil, Turkey, Germany, and South Africa, to evaluate the safety, immunogenicity and efficacy of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy adults. The phase 1 part of the study was designed for dose evaluation of 2 vaccines: BNT162b1 and BNT162b2 in younger (18-55 years) and older (65-85 years) adults. The Phase 2 part was designed to confirm safety and immunogenicity of the selected vaccine, BNT162b2, in the first 360 subjects enrolled in the Phase 2/3 part of the study.

The Phase 2/3 part of the study was designed to enrol up to 43,998 subjects (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (within 19 to 42 days), for an efficacy assessment in addition to safety and exploratory immunogenicity assessments.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test (NAAT) in subjects without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed ≥7 days after Dose 2), and in subjects with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The study was event-driven, i.e. the final efficacy analysis was to be triggered by 162 cases; in practice 170 cases were reached.

3.2. Favourable effects

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS-CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS-CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86.7% (95% CI 68.6, 95).

The efficacy analyses in the all-available efficacy population (including participants who had protocol violations), showed consistent results with those in the primary analysis population. The efficacy analyses using CDC defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

The VE in each demographic subgroup analysed, as defined by age (including subjects >65 years), sex, race, ethnicity, and country and in individuals with comorbidities including obesity, diabetes, hypertension and cardiopulmonary diseases was >90%. In the obese population, VE was 95.4% (CI 95% 86.0%, 99.1%).

VE among 65-74-year-olds was 92.9% (CI95% 53.1%, 99.8%). VE among >75-year-olds was 100% (CI95% -13.1%, 100.0) with 0 cases in the vaccine group and 5 cases in the placebo group. VE among >65 years and at risk of severe COVID-19 was 91.7% (95% 44.2%, 99.8%).

Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, but the number of cases after second dose was very low, 1 case in the vaccine group and 4 cases in placebo group. Counting cases from after dose 1, there were 1 case in the vaccine group and 9 cases in the placebo group.

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral responses after vaccination with 2 doses of BNT162b2 at 30 µg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years), and both in terms of neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a marked boosting effect in both younger and older adults. Responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data.

Study BNT162-01 provides evidence for T cell-mediated immune response, with antigen-induced IFNγ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of vaccine. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults.

The immunogenicity results are only considered supportive at this stage, as no correlate of protection has been established. The immune responses support the need for two doses, as neutralising antibody

levels increased substantially following the second dose compared to the first dose. Cell mediated immune responses were demonstrated in very few subjects in phase 1 but confirm a Th1 dominated cytokine pattern.

3.3. Uncertainties and limitations about favourable effects

Based on the available limited data, no reliable conclusion on the efficacy of the vaccine against severe COVID-19 can be drawn from 7 days after the second dose (secondary endpoint). The estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4%, with a large and negative lower bound CI (95% CI: -124.8%; 96.3%). Only a limited number of events occurred at the cut-off date of analysis (1 and 4 cases in the vaccine and placebo groups respectively). The posterior probability for the true vaccine efficacy ≥ 30% (74.29%) did not meet the pre-specified success criterion. Consequently, the efficacy against the severe disease across subgroups, notably certain populations at high-risk of severe COVID-19 cannot be estimated (elderly and subjects with comorbidities).

Efficacy against asymptomatic infection is not available but, notwithstanding all the limitations, will be assessed through seroconversion of N-binding antibodies in BNT162b2 and placebo recipients who did not experience COVID-19.

The pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from subjects who would be infected after vaccination. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies.

Duration of protection has currently been followed up for approximately 100 days after dose 1. Data on longer term protection are anticipated to the extent that the ongoing phase 3 study can continue as planned with a placebo group. The assessment of efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

There are very limited or no data in immunocompromised subjects and in pregnant women. Efficacy in subjects aged 16-17 years is extrapolated from young adults as no cases of disease were reported in this small group at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group, to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

3.4. Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty.

In Study C4591001, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older. Reactogenicity was evaluated in a subset of 8183 subjects (n=4093 vaccinated; n=4090 placebo) up to 7 days after each dose.

Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups.

Regarding AEs, at least one AE was reported in 21% of the vaccinated subjects and in 13% of the placebo arm. The frequency of severe AEs was low (<1%) in both study arms. The most frequently reported SOC were "General disorders and administration site conditions (11.9% vs 2.9%)", "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%). PTs comprised mainly of vaccine typical reactions such as injection site pain, headache, fever, fatigue, malaise as well as myalgia and arthralgia.

For subjects with a follow-up of ≥2 months, SAE were reported at a low frequency (0.5-0.6%) in both the vaccine and the placebo group, with no clinically meaningful differences by age, baseline serostatus, ethnicity, race or sex. Lymphadenopathy (0.4% with vaccine vs 0.0% with placebo, or 0.3% of cases in the whole population 0% in placebo arm) and nausea (0.8% with vaccine vs 0.2% with placebo) were reported to occur more often in the vaccine group compared to the placebo grouping the whole enrolled trial population. Numerical imbalances in reporting were observed for insomnia, injection site pruritus and pain in extremity. Since these are supported by a biologically plausible relation to vaccination, these AEs are reflected in the SmPC.

Acute peripheral paralysis was reported in 4 vs. 0 cases (vaccine vs placebo) in the whole study population, of which 2 cases were deemed related to study treatment (see section 2.6.10). For acute peripheral paralysis, there is a reasonable possibility of a causal relation to vaccination and should therefore be included in the SmPC.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. Three reports of anaphylaxis were identified during vaccination campaigns by the time this report was written.

Few cases of hypersensitivity/immunisation reaction events have been observed with the vaccine (13 vs 6 cases) in the whole study population. Hypersensitivity should be annotated in the SmPC, section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

AEs were slightly lower in subjects seropositive to SARS-CoV-2 at baseline (22% vs. 27% in seronegatives), however the number of such subjects was limited (vaccinated n=558; placebo n=590).

Data on immunocompromised individuals is limited, as only 196 participants with stable HIV infection were included in the study. No specific safety concern was detected.

Data from exposure during pregnancy is very limited. Up to the cut-off date 23 pregnancies have been reported in the Phase 2/3 trial and will be followed up for outcome.

Multiple long-term pharmacoepidemiology safety studies are planned to be conducted in order to confirm the safety profile in the already studied population as well as in a broader population including pregnant, immunocompromised and very elderly subjects.

There is no data available on interaction with other vaccines given in co-administration.

In the Phase 2/3 study, the total number of included subjects aged 16-17 years was smaller compared to other age groups (n=138 BNT162b; n=145 placebo), however no safety concerns were identified.

Uncertainties remain regarding causality association of acute peripheral paralysis to vaccination due to the limited number of cases, which are consistent with background rates. Nevertheless, facial paralysis will be included as an adverse event of special interest (AESI) for pharmacovigilance monitoring and in the active surveillance study protocols.

While apart from facial paralysis, whose aetiology is currently unknown, no possible autoimmune adverse events where identified as causally related to vaccination, rare events of this nature cannot be excluded based on the size of the available data set.

There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines, including Comirnaty, and the characterisation of the immune response does not indicate a risk profile in this regard (Th1 skewed).

This vaccine contains two new components (cationic lipid ALC-0315 and PEGylated liquid ALC-0159) in the LNP, for which there is limited experience. Some uncertainties remain regarding the ALC-0315 long half-life. Regarding PEG related toxicity which is known to depend on the dose, dose frequency, duration of treatment and molecular weight of the PEG protein, immunogenicity is not expected to be an issue due to the low molecular weight of this PEG (<2KDa). The scientific data available at this stage do not raise noticeable concerns regarding immunogenicity or immunotoxicity of the PEG, but current evidence is not definitive.

3.6. Effects Table

Table 20 Effects Table for Comirnaty intended for active immunisation to prevent COVID-19 caused by against SARS-CoV-2 in individuals 16 years of age and older (data cut-off: 14 Nov 2020)

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy	First COVID-19 occurrence from 7	**% (95% CI)**	**95.0** (90.0, 97.9)			

Effect	Short Description	Unit	BNT162b2 (30 µg)		Placebo		Uncertainties / Strength of evidence	References
	days after Dose 2, without prior SARS-COV-2, **overall**	**Cases/** Number of subjects at risk for the endpoint	**8/** 17411		**162/** 17511		Robust data with similar efficacy confirmed in all age sub-groups (16-64YOA, >65YOA, 65-74YOA, >75YOA)	Evaluable efficacy population (7 days post dose 2) - Study C4951001
	Patients aged ≥65	**%** **(95% CI)**	**94.7** (66.7, 99.9)					
		Cases/ Number of subjects at risk for the endpoint	**1**/3848		**19**/3880			
Unfavourable Effects								
Lymphadenopathy		% (denominator)	0.3% (n=21621)		0% (N=21631)		Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants[1]
Facial paralysis/facial paralesis		Number of cases	4		1			
Hypersensitivity/immunisation reaction		Number of cases	13		6			
			Post dose 1	**Post dose 2**	**Post dose 1**	**Post dose 2**	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
Pain at injection site	16-55 years	%	83%	78%	14%	12%		
	>55 years		71%	66%	9%	8%		
Headache	16-55 years		42%	52%	34%	24%		
	>55 years		25%	39%	18%	14%		
Fatigue	16-55 years		47%	59%	33%	23%		
	>55 years		34%	51%	23%	17%		

Abbreviations:
COVID-19: Coronavirus disease, SARS-CoV-2: Severe Acute Respiratory Syndrome, CI: Confidence Interval
[1] HIV-positive subjects were not included in the analyses of the overall study objectives.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, substantial efficacy in preventing symptomatic COVID-19 infection has been demonstrated, as well as an acceptable safety profile in a large phase 3 study. Uncertainties relate to the characterization of active substance and finished product. Given the comparable immunogenicity from 10 to 30µg doses, an impact on efficacy of the acceptance of somewhat lower levels of intact mRNA in the commercial product is not considered likely. Furthermore, based on low levels and biological plausibility, an impact of mRNA impurities on safety is deemed unlikely (see section 3.7.3).

Due to the limited extent of safety follow-up, the delivery of final data from the full 2-year follow up in the pivotal clinical trial are considered important to confirm the current knowledge.

With regards to the balance of efficacy and safety benefits and risks, it is overwhelmingly positive for subjects at risk of severe COVID-19, including the elderly and those with comorbid conditions, which are known to increase the risk of complication and death due to infection.

Uncertainties concerning the pharmaceutical characterization of the commercial product are compatible with a positive benefit/risk balance. This pertains not only to adults but, by extrapolation, to individuals 16-17 years of age.

Data are limited in individuals seropositive against SARS-CoV-2 at baseline. Available data however do not indicate any specific safety concerns, and efficacy is anticipated also in this subset.

There are no data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

Based on biological plausibility no risk in breastfeeding is anticipated.

While there was no indication of an excess risk of severe allergic reactions such as anaphylaxis in the clinical study program, three post marketing cases, of which 2 in patients carrying adrenaline pens and one in a person with no known history of allergies, have been reported during vaccination campaigns, and all resolved with standard treatment. Hypersensitivity to the active substance or to any of the excipients is a contraindication. However, there is presently no substantial evidence of a negative benefit/risk balance in a subject with severe allergy to substances absent in the vaccine. For all subjects, the vaccine should be administered in settings where resuscitation facilities are available, as specified in the SmPC and in line with other vaccines. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19.

Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned.

3.7.2. Balance of benefits and risks

Overall, the available data are supportive of a positive B/R in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation in the context of a conditional MA, including further characterisation of the active substance and finished product, the continuation of the pivotal study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine (Process 1). The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities.

Data demonstrates the presence of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are not sufficiently characterised, and although the limited data provided for protein expression does not fully address uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein, the amount of any such proteins, is expected to be too low to elicit an immune response of biological relevance.

Indeed, considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell it cannot be excluded that different proteins than the intact full-length spike will be expressed. The risk of unwanted immunological events is considered low based on the following observations and considerations:

- Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
- The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA able to be translated into a specific protein or peptide.
- The level of any individual fragment of mRNA species would anyway be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the truncated proteins would be non-significant.

Also, lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

Regarding the proposed control strategy for active substance and finished product, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Considering the above and the current public health emergency, the characterisation of the active

substance and finished product are considered acceptable, and the proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA.

Therefore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the Applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between March and July 2021.
Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomized, placebo-controlled, observer-blind study C4591001 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of Comirnaty.

- Unmet medical needs will be addressed

There is no approved or widely available COVID-19 vaccine, and COVID-19 remains associated with substantial morbidity and mortality. While care for patients who have COVID-19 has improved over time and with clinical experience, no medications to cure COVID-19 are available and there remains an urgent need for a prophylactic vaccine during the ongoing pandemic.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence including the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit/risk balance of Comirnaty is positive.

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Comirnaty is favourable in the following indication:

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Productie 16

← News

EMA starts second rolling review of a COVID-19 vaccine

6 October 2020

News Human COVID-19 Medicines Vaccines

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EMA's human medicines committee (CHMP) has started a 'rolling review' of data on a vaccine for COVID-19 known as BNT162b2, which is being developed by BioNTech in collaboration with Pfizer.

The start of the rolling review means that the committee has started evaluating the first batch of data on the vaccine,

which come from laboratory studies (non-clinical data). This does not mean that a conclusion can be reached yet on the vaccine's safety and effectiveness, as much of the evidence is still to be submitted to the committee.

The CHMP's decision to start the rolling review of BNT162b2 is based on preliminary results from non-clinical and early clinical studies in adults which suggest that the vaccine triggers the production of antibodies and T cells (cells of the immune system, the body's natural defences) that target the virus.

Large-scale clinical trials involving several thousands of people are ongoing, and results will become available over the coming weeks and months. These results will provide information on how effective the vaccine is in protecting people against COVID-19 and will be assessed once they are available. All the available data on the safety of the vaccine as well as on its quality (such as its ingredients and the way it is produced) will also be reviewed.

The rolling review will continue until enough evidence is available to support a formal marketing authorisation application.

EMA will complete its assessment according to its usual standards for quality, safety and effectiveness. While the overall review timeline cannot be forecast yet, the process should be shorter than a regular evaluation due to the time gained during the rolling review.

How is the vaccine expected to work?

BNT162b2 is expected to work by preparing the body to defend itself against infection with the coronavirus SARS-CoV-2. The virus uses proteins on its outer surface, called spike proteins, to enter the body's cells and cause disease. BNT162b2 contains the genetic instructions (mRNA) for the spike protein and is covered in small fats (lipid particles) that prevent the mRNA from being degraded. When a person is given the vaccine, their cells will read the genetic instructions and produce the spike protein. The person's immune system will then treat this protein as foreign and produce natural defences — antibodies and T cells — against it. If, later on, the vaccinated person comes into contact

with SARS-CoV-2, the immune system will recognise the virus and be prepared to attack it: antibodies and T cells can work together to kill the virus, prevent its entry into the body's cells and destroy infected cells, thus helping to protect against COVID-19.

What is a rolling review?

A rolling review is one of the regulatory tools that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency. Normally, all data on a medicine's effectiveness, safety and quality and all required documents must be submitted at the start of the evaluation in a formal application for marketing authorisation. In the case of a rolling review, EMA's human medicines committee (CHMP) reviews data as they become available from ongoing studies, before a formal application is submitted. Once the CHMP decides that sufficient data are available, the formal application should be submitted by the company. By reviewing the data as they become available, the CHMP can reach its opinion sooner on whether or not the medicine or vaccine should be authorised.

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EUROPEAN COMMISSION

Summary of European Union decisions on marketing authorisations in respect of medicinal products from 21 December 2020 to 21 December 2020

(Published pursuant to Article 13 or Article 38 of Regulation (EC) No 726/2004 of the European Parliament and of the Council [1]*)*

(2020/C 447 I/01)

— **Issuing of a marketing authorization** (Article 13 of Regulation (EC) No 726/2004 of the European Parliament and of the Council): **Accepted**

Date of the decision	Name of the medicinal product	INN (International Non-Proprietary Name)	Holder of the marketing authorization	Number of the entry in the Community Register	Pharmaceutical form	ATC code (Anatomical Therapeutic Chemical Code)	Date of notification
21.12.2020	Comirnaty	COVID-19 mRNA Vaccine (nucleoside modified)	BioNTech Manufacturing GmbH An der Goldgrube 12, 55131 Mainz, Deutschland	EU/1/20/1528	Concentrate for dispersion for injection	J07BX	21.12.2020

Anyone wishing to consult the public assessment report on the medicinal products in question and the decisions relating thereto is invited to contact:

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1083 HS Amsterdam
NETHERLANDS

[1] OJ L 136, 30.4.2004, p. 1.

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Productie 18

EMA/333964/2020

Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines

1. Background

Since its emergence in 2019, the SARS-Cov2 virus has spread to almost every country making the COVID-19 pandemic a global health crisis.

COVID-19 vaccines once available are expected to play a major role in the control of the pandemic. While developed at unprecedented speed, they will only be authorised by European Union (EU) authorities if their benefits outweigh their risks based on data on efficacy, safety and quality.

During the development phase of any medicine, a limited number of selected participants are included in clinical trials and followed up for a relatively short duration under controlled conditions. As a result, certain side effects, particularly rare or very rare ones, only emerge during real life use in many different people. It is therefore essential to closely monitor the safety and effectiveness of any medicine after it is authorised.

The uptake of COVID-19 vaccines once authorised is anticipated to be very high which may lead to a high volume of suspected adverse reaction reports and other safety data. Thus, the prompt detection and evaluation of new information on the benefit-risk balance of these vaccines, timely communication and a high level of transparency will be key to protect public health and ensure the public's trust in the vaccines and in the regulatory system.

In view of the public health urgency and the extensive vaccination campaigns foreseen worldwide, the European Medicines Agency (EMA) and the national competent authorities (NCAs) in EU member states have prepared themselves for the expected high data volume by putting in place this pharmacovigilance plan specific for COVID-19 vaccines. This is to ensure that all new information collected post-marketing will be promptly reviewed and any emerging new information will be shared with the public in a timely manner. The plan builds on the well-established pharmacovigilance system of the EU regulatory network and the experience gained during the 2009 (H1N1) flu pandemic while taking into account the current specificities of the COVID-19 pandemic.

2. Scope

The present document provides an overview of the activities the EU regulatory network (EMA and NCAs) will conduct once COVID-19 vaccines are authorised.

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The legal provisions on pharmacovigilance[1] and the extensive guidance developed by EMA in collaboration with NCAs set out in the good pharmacovigilance practices (GVP), apply to all medicinal products authorised in the EU, including COVID-19 vaccines.

This document focusses on the activities planned specifically for COVID-19 vaccines. The established processes and requirements for pharmacovigilance in general are briefly noted where relevant to provide context.

3. Objectives

The main objectives of this plan include:

- Active collection of data on rare potential risks;
- Rapid detection, prioritisation and assessment of emerging safety information derived from spontaneous reporting systems, observational studies and other data sources;
- Prompt evaluation of the impact of detected safety issues on the benefit-risk balance of the vaccines, taking into account exposure and effectiveness data;
- Active surveillance of vulnerable populations, such as pregnant women and older vaccinees;
- Engagement and collaboration with stakeholders including vaccinees and healthcare professionals, marketing authorisation holders (MAHs) and international partners;
- Prompt and effective communication of new information arising from the above activities.

4. Roles and responsibilities

The respective roles and responsibilities of MAHs, NCAs, the EMA and its scientific committees, including the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP), in the conduct of pharmacovigilance activities for medicinal products authorised in the EU are defined in the legislation and detailed in the respective GVP modules.

As part of its response to the COVID-19 pandemic, the Agency has established a COVID-19 EMA pandemic Task Force (COVID-ETF), whose main purpose is to draw on the expertise of the EU medicines regulatory network and ensure a fast and coordinated response to the COVID-19 pandemic. Amongst other activities, the task force will support the regulatory activities of member states and the European Commission and contribute to the PRAC activities on emerging safety concerns related to COVID-19 vaccines. The COVID-ETF includes experts from the Agency and its scientific committees.

Patients and healthcare professionals are regularly involved in EU pharmacovigilance processes and have representatives in the PRAC. They will also have representatives in the COVID-ETF meetings, to provide input and bring views from their community on specific aspects of EMA's work during the pandemic.

[1] Directive 2001/83/EC, Regulation (EC) No 726/2004, Commission Implementing Regulation (EU) No 520/2012

5. Activities

5.1. Risk management plan

The good pharmacovigilance practices include detailed requirements and guidance on the principles of risk management (GVP Module V) with a link to the format of the risk management plan (RMP template) as well as pharmacovigilance requirements for vaccines (GVP P.I).

In addition, core RMP requirements for COVID-19 vaccines have been developed to facilitate and harmonise the preparation of RMPs by companies and their evaluation by assessors. The 'coreRMP19' addresses the planning of the post-authorisation safety follow-up of COVID-19 vaccines by MAHs, while acknowledging uncertainties in the pandemic setting and recommending ways to prepare for pharmacovigilance activities.

5.2. Periodic safety reports

Periodic safety update reports (PSURs) are submitted by MAHs for evaluation by regulatory authorities at 6 months intervals in the first years of authorisation of any medicinal product and with a decreasing frequency thereafter (see GVP Module VII).

For COVID-19 vaccines, MAHs will be expected to submit to the Agency monthly summary safety reports in addition to regular PSURs. These will include, among others, information on reported suspected adverse reactions, including adverse events of special interest (AESIs), and sales data. The minimum elements to be addressed in these reports are listed in the coreRMP19.

5.3. Collection of exposure data

A timely availability of aggregated exposure data for each COVID-19 vaccine will be essential for several pharmacovigilance activities including observed-to-expected analyses. Member states will be gathering this data in various manners, for instance by implementing national health data registers to collect information on individual vaccinations. EMA will collect and compile this data from Member States.

An important requirement for the safety monitoring of all biological medicines in the EU (see GVP P.II: Biological medicinal products) is the need for product and batch traceability during clinical use. The traceability requirement covers the release by the manufacturer, the entire distribution chain and the actual vaccination. The use of traceability tools such as stickers should be described in the RMP (see coreRMP19). Their implementation is to be agreed at national level.

5.4. Observational research

Post-authorisation safety studies (PASS) are conducted by MAHs voluntarily or upon request from the regulatory authorities (see GVP Modules V and VIII). For COVID-19 vaccines, the need for observational PASS studies will be carefully considered as routine activities and ongoing or planned clinical trials may not be sufficient to provide adequate data to further characterise identified and potential risks and investigate missing information. Further recommendations are outlined in the coreRMP19.

EMA has contracts in place with academic and private partners to support the readiness of research networks to perform observational research, including on COVID-19 treatments and vaccines.

The ACCESS project ('vACCine Covid-19 monitoring readinESS') focuses on data sources and epidemiological methods to monitor the safety, effectiveness and coverage of COVID-19 vaccines. The project involves 22 research centres in Europe and its main objectives are to:

- Identify and characterise a Europe-wide network of data sources that could provide a continuous monitoring of the coverage, safety and effectiveness of COVID-19 vaccines and be used to investigate specific research questions on COVID-19 vaccines;
- Provide background rates of AESIs and other relevant conditions;
- Set up a network for the timely monitoring of coverage, safety and effectiveness of COVID-19 vaccines and the investigation of specific research questions including feasibility analyses.

The ACCESS project is supported by an EMA Advisory Group composed of members of the ECDC, PRAC and CHMP. The common protocols for safety studies and the network of data sources developed by ACCESS will be available to MAHs and other stakeholders for joint PASS studies. Vaccine-specific protocols submitted by applicants/MAHs will have to be endorsed PRAC and CHMP.

The CONSIGN ('COVID-19 infectiOn aNd medicineS In preGNancy') project will collect data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. The project will be carried out in collaboration with the ConcePTION consortium, which was established under the EU Innovative Medicines Initiative (IMI), the International COVID-19 and pregnancy registry (COVI-PREG) project and the International Network of Obstetric Survey Systems (INOSS) network.

In addition to these initiatives, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) may support the development and dissemination of good methodological practices for COVID-19 studies. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology highlights relevant aspects for COVID-19 observational studies. Researchers should register their pharmacoepidemiological studies and make study protocols and reports public in the European Union electronic register of post-authorisation studies (EU PAS Register), to ensure transparency on the various research efforts.

Several NCAs will also conduct pharmacoepidemiological studies on COVID-19 vaccines at national level and will register these in the EU PAS Register.

EMA, ECDC and many national governments are working to secure public funding for vaccine safety monitoring studies. Information on studies that are initiated will be available on the EU PAS Register.

5.5. Spontaneous reporting of suspected adverse reactions

The regulatory requirements for the collection, data management and submission of individual reports of suspected adverse reactions associated with medicinal products are addressed in GVP Module VI. With respect to vaccines, there are also specific recommendations in GVP P.I.

The Agency has also published detailed guidance on individual case safety reports (ICSRs) in the context of COVID-19, which takes into account the guidance regarding COVID-19 related terms published by the Maintenance and Support Services Organization of the Medical Dictionary for Regulatory Activities (MedDRA MSSO) and the implementation of the updated MedDRA 23.0 containing additional COVID-19 related terms.

Upon authorisation, COVID-19 vaccines will be subject to additional monitoring, which aims at enhancing the reporting of suspected adverse reactions.

The quality and completeness of the information in ICSRs are important for any meaningful causality assessment and will be crucial in this context of mass vaccination. Beyond the minimum criteria required for ICSR validation (see GVP VI.B.2), reports should ideally contain precise information on demographics, vaccine brand, batch number, vaccination and reaction dates, outcome, concomitant drugs etc.

EMA and NCAs will encourage timely submission of ICSRs.

The submission of ICSRs with AESIs, or fatal or life-threatening reactions in a shorter timeframe than 15 days should be considered when feasible.

5.6. Signal management

The roles and responsibilities, processes and requirements for signal management in the EU are described in GVP Module IX. The module also includes provisions for emerging safety issues (ESIs) i.e. those safety issues considered by MAHs to require urgent attention by the competent authorities. Methodological aspects of signal detection from spontaneous reports are discussed in the module's addendum. The Agency has also published scientific guidance on screening for adverse reactions in EudraVigilance.

GVP P.I outlines specific considerations for signal detection in mass vaccination campaigns, with a discussion on the caveats of traditional disproportionality methods and on observed-to-expected analyses. It is anticipated that a high volume of ICSRs related to COVID-19 vaccines will be sent to spontaneous reporting systems, including EudraVigilance, with a relatively short lag after the vaccination campaigns start. Routine signal detection methods may be insufficient to screen such a volume of data efficiently and effectively. EMA and NCAs, within PRAC's signal management review technical working group (SMART WG), are testing several methodologies to address these challenges.

In line with the prioritisation principles outlined in GVP Module IX, timelines should be expedited as much as possible throughout the management of potential signals for COVID-19 vaccines, although this should not be at the expense of a thorough evaluation. For instance, the 30-day timeframe for the confirmation of a validated signal may need to be shortened to allow for discussion of the signal at the forthcoming PRAC meeting. Similarly, shorter than usual timetables for assessment by PRAC (e.g. 30 days) may be warranted for some signals. The COVID-ETF will support the PRAC by providing rapid advice on new safety issues related to COVID-19 vaccines.

5.7. Exchange of information

Within the EU regulatory network, the European Pharmacovigilance Issues Tracking Tool (EPITT) is the established tool to communicate on signals that may warrant evaluation by PRAC (see GVP Module IX) and to support rapid exchange of information on other safety concerns through the Rapid Alert (RA) and Non-Urgent Information (NUI) System (see EU regulatory network incident management plan). In the context of the pandemic, RAs and NUIs will be the preferred channels to timely exchange of further information on batch related issues, national communications, or any concern that may not warrant a regulatory action but could have an impact on the vaccination programmes due to public perception.

The Agency will engage with EU networks of patients, consumers and healthcare professionals, for example through EMA's Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP), and will disseminate any relevant information on COVID-19 vaccines to their organisations. NCAs may also interact at national level with patients' and healthcare professionals' organisations.

The Agency has regular interactions with regulators in countries outside the EU, e.g. US FDA and Health Canada, and international public health organisations, such as WHO. Discussions on specific safety topics will take place as necessary and in compliance with the confidentiality agreements in place. In addition, the International Coalition of Medicines Regulatory Agencies (ICMRA) provides a framework for exchanging information on COVID-19 related initiatives and best practices across worldwide stakeholders. Its vaccines and surveillance working group has developed a COVID-19 pharmacovigilance network to share knowledge, experience and communication on pharmacovigilance planning activities, as well as emerging data on the safety and effectiveness of vaccines, once deployed.

Exchanges between MAHs, Rapporteurs at EMA committee level and EMA will take place whenever warranted to discuss any emerging information on the benefit-risk balance of the vaccines.

5.8. Communication and transparency

A detailed overview of established EMA transparency practices in relation to medicinal products is provided in the Guide to information on human medicines evaluated by EMA. The Agency also publishes descriptive information on suspected adverse reactions reported to EudraVigilance for all medicines authorised in the European Economic Area (EEA). The Agency operates the Early Notification System and circulates to NCAs and international partners safety communications agreed at EMA Committees under embargo ahead of publication. Lines-to-take are also developed to address anticipated media queries.

In addition to these, the Agency has put in place Exceptional transparency measures in relation to COVID-19 vaccines and treatments approved or under evaluation. These include the publication of the full RMPs for these products.

The scope of the meeting Highlights from the PRAC, has also been extended to include information on other safety procedures involving COVID-19 treatments and vaccines, including signals, PSURs, PASS and RMPs.

The Agency will publish regular pharmacovigilance updates on the approved COVID-19 vaccines, with the latest information. The format and contents will be developed in collaboration with NCAs through PRAC.

Patients', consumers' and healthcare professionals' organisations will be consulted during the preparation of some of these communication materials and pre-user testing will be considered.

NCAs may have webpages or websites dedicated to the pandemic, with information on suspected adverse reactions reported for COVID-19 vaccines in their territories.

5.9. Capacity building

In order to continuously achieve a high quality and fit-for-purpose safety monitoring and risk management of the COVID-19 vaccines, NCAs and supporting EMA staff should have the necessary expertise at their disposal. To support and reinforce the knowledge of assessors and staff who will be involved in these activities, the Agency, in collaboration with NCAs, have set up a dedicated training programme. The training builds on the scientific and regulatory experience gained by EMA and NCA experts through procedures for COVID-19 related products where a pharmacovigilance assessment was performed. The training recordings and presentations will be made available on the EU Network Training Centre (EU NTC) Learning Management System platform.

List of abbreviations

ACCESS: vACCine Covid-19 monitoring readinESS

AESI: adverse event of special interest

CHMP: Committee for Medicinal Products for Human Use

CONSIGN: COVID-19 infectiOn aNd medicineS In preGNancy

COVID-19: Coronavirus disease 2019

COVID-ETF: COVID-19 EMA pandemic Task Force

COVI-PREG: International COVID-19 and pregnancy registry

ECDC: European Centre for Disease Prevention and Control

EEA: European Economic Area

EMA: European Medicines Agency

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EPITT: European Pharmacovigilance Issues Tracking Tool

ESI: emerging safety issue

EU: European Union

EU NTC: EU Network Training Centre

EU PAS Register: European Union electronic register of post-authorisation studies

FDA: Food and Drug Administration

GVP: Good pharmacovigilance practices

HCPWP: Healthcare Professionals' Working Party

HRA: health regulatory authority

ICMRA: International Coalition of Medicines Regulatory Authorities

ICSR: individual case safety report

IMI: Innovative Medicines Initiative

INOSS: International Network of Obstetric Survey Systems

MAH: marketing authorisation holder

MedDRA: Medical Dictionary for Regulatory Activities

MSSO: Maintenance and Support Services Organization

MS: Member State

NCA: national competent authority

NUI: non-urgent information

PASS: post-authorisation safety study

PCWP: Patients' and Consumers' Working Parties

PRAC: Pharmacovigilance Risk Assessment Committee

PSUR: periodic safety update report

RA: rapid alert

RMP: risk management plan

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SMART WG: Signal Management Review Technical Working Group

US: United States

WHO: World Health Organization

Productie 19

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

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Summary

Background The first COVID-19 vaccine outside a clinical trial setting was administered on Dec 8, 2020. To ensure global vaccine equity, vaccine targets were set by the COVID-19 Vaccines Global Access (COVAX) Facility and WHO. However, due to vaccine shortfalls, these targets were not achieved by the end of 2021. We aimed to quantify the global impact of the first year of COVID-19 vaccination programmes.

Methods A mathematical model of COVID-19 transmission and vaccination was separately fit to reported COVID-19 mortality and all-cause excess mortality in 185 countries and territories. The impact of COVID-19 vaccination programmes was determined by estimating the additional lives lost if no vaccines had been distributed. We also estimated the additional deaths that would have been averted had the vaccination coverage targets of 20% set by COVAX and 40% set by WHO been achieved by the end of 2021.

Findings Based on official reported COVID-19 deaths, we estimated that vaccinations prevented 14·4 million (95% credible interval [CrI] 13·7–15·9) deaths from COVID-19 in 185 countries and territories between Dec 8, 2020, and Dec 8, 2021. This estimate rose to 19·8 million (95% CrI 19·1–20·4) deaths from COVID-19 averted when we used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19·8 million of 31·4 million) during the first year of COVID-19 vaccination. In COVAX Advance Market Commitment countries, we estimated that 41% of excess mortality (7·4 million [95% CrI 6·8–7·7] of 17·9 million deaths) was averted. In low-income countries, we estimated that an additional 45% (95% CrI 42–49) of deaths could have been averted had the 20% vaccination coverage target set by COVAX been met by each country, and that an additional 111% (105–118) of deaths could have been averted had the 40% target set by WHO been met by each country by the end of 2021.

Interpretation COVID-19 vaccination has substantially altered the course of the pandemic, saving tens of millions of lives globally. However, inadequate access to vaccines in low-income countries has limited the impact in these settings, reinforcing the need for global vaccine equity and coverage.

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Introduction

The first COVID-19 vaccine was delivered outside of a clinical trial setting on Dec 8, 2020.[1] By Dec 8, 2021, 55·9% of the global population was estimated to have received at least one dose of a COVID-19 vaccine, 45·5% estimated to have received two doses, and 4·3% estimated to have received a booster dose.[2] Despite the incredible speed with which COVID-19 vaccines were developed in 2020 and subsequently distributed during 2021, more than 3·5 million deaths due to COVID-19 have been reported globally since the first vaccine was administered.[2]

Understanding the global impact of vaccination on the course of the COVID-19 pandemic is challenging given the heterogeneous access to vaccines coupled with different levels of transmission and ongoing non-pharmaceutical interventions across countries. In the early months of 2021, the impact of vaccination would have been minimal because of the delay in developing the infrastructure for a widespread vaccination campaign, the need for a delayed two-dose regimen in some jurisdictions to ensure maximum protection,[3] and the delay in the development of antibodies following vaccination. Additionally, as vaccine supply was constrained, most countries opted to prioritise vaccination in high-risk populations, including health-care workers and older people. Such strategies would have generated direct protection but would have had comparatively less impact on SARS-CoV-2 transmission. However, from mid-2021 onwards those countries with access to plentiful vaccine supply opted for mass vaccination of the adult population, later including children and subsequent boosting to maintain high levels of protection given the waning in vaccine efficacy and the emergence of new variants of

Research in context

Evidence before this study

We searched PubMed up to April 26, 2022, without any date limits or language restrictions, using the search terms "vaccin* AND impact AND (death* OR live*) AND (estimat* OR evaluat*) AND (COVID-19 OR SARS-CoV-2)". We found eight published studies that estimated the impact of COVID-19 vaccination, including deaths averted from vaccination. None of the studies considered the global impact of COVID-19 vaccination, focusing instead on specific regions (Italy, California, North Carolina, Stockholm, subsets of states in the USA, New York City, and the WHO European Region). Furthermore, the study focusing on the WHO European region only quantified the direct impact of vaccination and did not estimate the indirect effects (ie, decreasing infection risk of both vaccinated and unvaccinated susceptible individuals).

Added value of this study

This mathematical modelling study advances previous work both in terms of scale (number of regions modelled) and in terms of quantifying both the direct and indirect impact of COVID-19 vaccination globally. We estimated the impact of vaccination up to Dec 8, 2021, by fitting COVID-19 transmission models to both reported deaths and excess mortality during the pandemic as a proxy for deaths due to COVID-19. This study is, to the best of our knowledge, the first to use excess mortality estimates in this way, allowing for the impact of COVID-19 vaccination to be estimated more accurately in countries with weaker surveillance systems.

Implications of all the available evidence

The results highlight the substantial impact that vaccination has had on the trajectory of the COVID-19 pandemic. They also illustrate the broader impact of COVID-19 vaccination in terms of allowing countries with high vaccine coverage to relax interventions. Furthermore, the findings highlight the importance of equitable access to vaccines, particularly in low-income regions, where substantially more lives could have been saved if the vaccination targets set out by the COVID-19 Vaccines Global Access (COVAX) Facility (20% coverage in COVAX Advance Market Commitment countries by the end of 2021) and WHO (40% coverage in each country by the end of 2021) had been reached.

concern. This approach has resulted in vast inequalities in global vaccine distribution.[4]

To reduce inequality, a fair allocation mechanism for COVID-19 vaccines was developed through the COVID-19 Vaccines Global Access (COVAX) facility, with a key target of achieving 20% vaccine coverage for the countries covered by its Advance Market Commitment (AMC) through COVAX-secured doses by the end of 2021.[5] WHO expanded this target by setting a global strategy to achieve 70% coverage in all countries by mid-2022, with an interim target of 40% coverage by the end of 2021.[7] However, as a result of numerous challenges, particularly the constrained vaccine supply to COVAX (exacerbated by some countries obtaining a greater proportion of the global vaccine supply, pharmaceutical companies not meeting their contractual obligations to COVAX, and unpredictable delays in supply including vaccines with brief expiry windows), these targets were not reached in many lower-middle-income countries and low-income countries.[6] Vaccine uptake has also been suboptimal in many countries because of vaccine hesitancy.[7] This considerable heterogeneity in vaccination coverage has resulted in continued reliance on non-pharmaceutical interventions for pandemic management in some countries[8] but concomitantly enabled other nations to relax interventions as a route out of the pandemic.[9]

Quantifying the impact of vaccination is further challenged by the incomplete picture of the COVID-19 pandemic that is obtained from reported deaths. In many countries, vital registration systems are incomplete and therefore only a fraction of deaths are routinely reported. However, even in countries with complete vital registration systems, it is difficult to accurately define the cause of death in individuals who present with multiple morbidities. Excess all-cause mortality (the difference between the observed and expected number of deaths in non-pandemic years) has therefore been used to quantify the impact of the COVID-19 pandemic.[10] Although the exact contribution of COVID-19 to excess mortality is unknown, the strong temporal correlation observed globally between reported COVID-19 mortality and excess mortality provides evidence that excess mortality is an informative indicator of pandemic-related mortality.[11] Robust vital registration systems do not exist in many parts of the world, with WHO estimating that 40% of global deaths that occurred in 2020 were unregistered,[12] and therefore data on excess mortality are not available for every country. Model-based estimates have therefore been developed to obtain a more complete estimate of the pandemic to date. One set of estimates produced by *The Economist* uses a range of socioeconomic and epidemiological data to infer excess mortality.[13] Although the precise estimates differ between research groups[14] and WHO,[15] they all suggest a substantially larger number of COVID-19 deaths than have been reported to date.

We aimed to quantify the global impact of the first year of COVID-19 vaccination and estimate the number of deaths from COVID-19 averted in 185 countries and territories, both from the direct protection of vaccinated individuals and from the indirect protection of all individuals living in vaccinated environments due to the reduction in risk of infection. Additionally, we aimed to quantify the impact that a more equitable global vaccination campaign, meeting the vaccination targets set by COVAX of 20% vaccination coverage of the eligible population by the end of 2021, could have had in COVAX

AMC countries. We also aimed to quantify the impact of achieving the WHO target of 40% coverage by the end of 2021 in all countries.

Methods

Transmission model fitting

For this mathematical modelling study, we used a previously published COVID-19 transmission model[16,17] and fitting framework[18] to obtain profiles of the COVID-19 pandemic in each country and thus estimate the counterfactual scenario in which vaccines are not delivered. Briefly, the model is a population-based, age-structured susceptible-exposed-infectious-recovered-susceptible (SEIRS) model, which explicitly captures disease severity, passage through different indicated health-care levels, and the roll-out of vaccination. We incorporated country-level data on demography, age-based mixing patterns, and health-care capacity. We fit the model to officially reported COVID-19 deaths in each country, resulting in an inferred time-varying level of transmission, R_t, denoting the mean number of secondary infections in the absence of both infection-induced and vaccine-derived immunity. By fitting directly to mortality, we indirectly captured the impact that non-pharmaceutical interventions have had over the course of the COVID-19 pandemic.

Vaccination rates for first and second doses in each country were taken from Our World in Data[2] and the WHO dashboard. We assumed a vaccination strategy that first targets those most at risk (including health-care workers) and then iteratively distributes vaccines in descending age order. Vaccination was assumed to confer protection against SARS-CoV-2 infection and the development of severe disease requiring hospital admission,[3] and to reduce transmission from vaccine breakthrough infections (ie, we assumed vaccinated individuals who develop infection would be less infectious than unvaccinated individuals).[19] We inferred vaccine efficacy for each country on the basis of vaccine types known to be predominantly used in each country. We explicitly modelled the emergence of the delta (B.1.617.2) variant and its impact on vaccine efficacy, hospital admissions, and immune escape.[20,21] Any epidemiological differences associated with previous variants were assumed to be reflected by their effects on mortality,[22] which were subsequently captured by the estimated R_t trend. We fit the model to COVID-19 mortality in a Bayesian framework using a Metropolis-Hastings Markov Chain Monte Carlo-based sampling scheme. We used the resulting fit to estimate the time-varying reproductive number, R_t, and its associated uncertainty.

Complete details of the model, vaccination, variants, and model fitting are given in the appendix (pp 2–10). No ethical concerns were noted for this study, with all mortality data used based on nationally aggregated statistics; all datasets used were publicly available.

Excess mortality and COVID-19 mortality data

Because of the heterogeneity in death registration and certification worldwide, we also fit the model to all-cause excess mortality. For countries and time periods for which excess mortality had not been reported, we used model-based estimates of all-cause excess mortality, first produced by *The Economist*.[13] More details of the methodology are given in the appendix (p 2). Given the wide uncertainty in these model-based estimates of excess mortality in many parts of the world, we also presented the deaths averted as estimated by fitting to official reported COVID-19 deaths from the Johns Hopkins University COVID-19 Data Repository (appendix p 2). Importantly, these estimates based on official reported COVID-19 deaths represent the lower bound of deaths averted at the global level due to the considerable levels of under-reporting of COVID-19 mortality documented worldwide.[23]

For the **Johns Hopkins University COVID-19 Data Repository** see https://coronavirus.jhu.edu/map.html

Estimating deaths averted due to vaccination

The first vaccination outside a clinical trial setting was given on Dec 8, 2020. We introduced vaccination from this point onwards in the model and explored the impact of the first year of vaccination up to Dec 8, 2021. To quantify the impact of vaccination and its associated uncertainty, we took 100 draws from the estimated distribution of R_t and vaccine efficacy estimates for each country and simulated a counterfactual scenario in which no vaccines are available and the epidemic in each country follows the same R_t trend since the start of the pandemic; a counterfactual in which vaccines are delivered but there are no indirect effects (ie, they do not reduce SARS-CoV-2 transmission); and the observed scenario in which vaccines were delivered at the rates reported. The third scenario generated an estimate of the trajectory of the epidemic for our fitted model and hence closely matched reported COVID-19 or excess deaths or estimated excess deaths in each country. We calculated the deaths averted as a result of vaccination by subtracting the estimated COVID-19 deaths from the simulation with vaccines included (the observed scenario) from the estimated COVID-19 deaths under the first counterfactual scenario. This process is illustrated in the appendix (p 18), which shows the estimated deaths averted for the USA. Because of the difficulty in predicting how governments and populations would have responded, and how viral evolution would have progressed if vaccines had not been available, we made no attempt to adjust the R_t trends for further non-pharmaceutical interventions, changes in mobility, or development of variants that probably would have occurred differently in the absence of vaccination. To explore the impact of key model parameters on estimates of deaths averted, we did additional sensitivity analyses. These included characterising the effects of the assumed relationship between the infection fatality ratio (IFR) and age (appendix p 10), as well as the assumed degree of immune evasion exhibited by the delta variant (appendix p 7).

For the **WHO dashboard** see https://covid19.who.int/

See **Online** for appendix

	Total COVID-19 deaths	Vaccination coverage (%)	Estimated deaths averted by vaccinations		
			Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	5 469 000 (5 339 000–5 613 000)	38·30%	14 400 000 (13 650 000–15 900 000)	22·81 (21·63–25·18)	25·99 (24·64–28·69)
World Bank income group					
High-income countries	1 956 000 (1 892 000–2 032 000)	68·80%	6 353 000 (6 105 000–6 604 000)	52·6 (50·54–54·67)	36·67 (35·23–38·11)
Upper-middle-income countries	2 287 000 (2 220 000–2 355 000)	50·10%	2 914 000 (2 785 000–3 047 000)	25·6 (24·47–26·77)	23·36 (22·33–24·43)
Lower-middle-income countries	1 188 000 (1 099 000–1 302 000)	29·80%	5 083 000 (4 379 000–6 628 000)	15·27 (13·16–19·91)	20·39 (17·57–26·59)
Low-income countries	36 520 (33 390–40 410)	3·57%	20 380 (17 680–23 870)	0·3188 (0·2766–0·3733)	2·965 (2·572–3·472)
WHO region					
African region	153 800 (145 100–164 700)	5·48%	97 190 (88 420–107 400)	0·8677 (0·7894–0·9589)	5·958 (5·420–6·584)
Region of the Americas	2 492 000 (2 418 000–2 576 000)	58·30%	3 813 000 (3 624 000–3 987 000)	37·46 (35·6–39·17)	29·28 (27·83–30·62)
Eastern Mediterranean region	318 700 (307 200–331 500)	28·10%	639 200 (581 600–707 700)	8·746 (7·958–9·684)	13·50 (12·28–14·95)
European region	1 628 000 (1 589 000–1 673 000)	56·50%	4 334 000 (4 214 000–4 487 000)	46·77 (45·48–48·42)	39·52 (38·43–40·92)
South-East Asian region	713 800 (635 900–807 000)	35·40%	3 913 000 (3 234 000–5 491 000)	19·61 (16·21–27·52)	21·63 (17·88–30·36)
Western Pacific region	149 000 (120 100–234 400)	62·40%	1 574 000 (1 267 000–1 839 000)	30·14 (24·26–35·21)	22·58 (18·18–26·38)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Vaccination coverage is the proportion of the population with a full dose in the modelled countries by Dec 8, 2021. Total deaths are all modelled deaths in the presence of vaccinations when fitted to reported deaths from the start of the pandemic up to Dec 8, 2021.

Table 1: **Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to officially reported COVID-19 deaths**

We also explored the impact of increasing vaccine distribution to meet WHO and COVAX targets. We modelled two scenarios in which the targets set by WHO to fully vaccinate 40% of the eligible population in each country and administrative region, and by COVAX to fully vaccinate 20% of the eligible population in AMC countries, by the end of 2021 had been reached. To do so, for countries in which these targets had not been met, we scaled the roll-out of vaccines across the year by a constant factor such that exactly the targeted amount of the population had received their second vaccine dose by our end date (Dec 8, 2021).

Statistical analysis

All analyses were done with R software (version 4.1.3), with all data, code, packages, and versions used available online at GitHub. This analysis covered 185 countries and territories with a population greater than 90 000 as reported in *World Population Prospects 2019*,[24] and that reported at least one death due to COVID-19 or 1 week of positive estimated excess mortality. We excluded China from our estimates because of its unique position as the origin of the detected epidemic and its large influence on estimates of deaths averted stemming from its population size.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Based on our model fit to officially reported COVID-19 deaths, we estimated that 18·1 million (95% credible interval [CrI] 17·4–19·7) deaths due to COVID-19 would have occurred without vaccinations worldwide during the first year of the COVID-19 vaccination programme (Dec 8, 2020, to Dec 8, 2021). Of these, we estimated that vaccination prevented 14·4 million (95% CrI 13·7–15·9) deaths due to COVID-19, representing a global reduction of 79% of deaths (14·4 million of 18·1 million) during the first year of COVID-19 vaccination (table 1). These estimates of vaccine impact do not account for the potential under-ascertainment of deaths related to COVID-19.

Using our model fit to predicted and reported excess mortality (appendix p 23), we estimated that 31·4 million (95% CrI 30·6–32·1) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination, with 19·8 million (95% CrI 19·1–20·4) deaths averted, corresponding to 63% (19·8 million of 31·4 million) of total deaths (table 2). The difference between vaccine impact estimates based on excess mortality and official deaths due to COVID-19 was greatest in low-income regions, with approximately ten times more deaths estimated to have been averted in low-income countries when relying on excess mortality estimates (appendix pp 13, 19).

Using our model fit to excess mortality, we estimated that most deaths averted were due to the high levels of individual-level direct protection conferred by vaccination, with 79% (15·5 million of 19·8 million) of deaths averted through direct protection (figure 1A). Vaccine impact was also conferred through reducing the levels of burden placed on health-care systems, reducing the number of days that health-care capacity would have been exceeded and therefore contributing to an overall lower fatality rate from infection (appendix p 20). Throughout 2021, vaccine impact changed over time and space. Vaccine impact was

	Total excess deaths	Estimated deaths averted by vaccinations		
		Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	17 990 000 (17 610 000–18 530 000)	19 810 000 (19 130 000–20 380 000)	31·21 (30·14–32·1)	35·68 (34·47–36·71)
World Bank income group				
High-income countries	2 503 000 (2 412 000–2 609 000)	8 004 000 (7 644 000–8 438 000)	66·18 (63·20–69·77)	46·14 (44·07–48·64)
Upper-middle-income countries	4 717 000 (4 611 000–4 827 000)	4 230 000 (4 051 000–4 384 000)	36·97 (35·40–38·31)	33·71 (32·28–34·94)
Lower-middle-income countries	9 688 000 (9 329 000–10 170 000)	7 401 000 (6 841 000–7 655 000)	22·23 (20·55–23·00)	29·69 (27·44–30·71)
Low-income countries	1 087 000 (1 068 000–1 106 000)	180 300 (171 400–188 900)	2·711 (2·576–2·840)	26·23 (24·93–27·48)
WHO region				
African region	1 614 000 (1 580 000–1 652 000)	466 400 (446 300–487 000)	4·164 (3·985–4·348)	28·59 (27·36–29·85)
Region of the Americas	3 354 000 (3 260 000–3 456 000)	4 469 000 (4 233 000–4 728 000)	43·89 (41·57–46·43)	34·31 (32·50–36·29)
Eastern Mediterranean region	2 310 000 (2 248 000–2 376 000)	992 800 (938 800–1 066 000)	13·58 (12·85–14·59)	20·97 (19·83–22·52)
European region	3 448 000 (3 347 000–3 568 000)	5 811 000 (5 551 000–6 187 000)	62·30 (59·51–66·33)	52·63 (50·28–56·04)
South-East Asian region	6 741 000 (6 398 000–7 247 000)	5 658 000 (5 114 000–5 858 000)	27·99 (25·3–28·98)	31·29 (28·28–32·39)
Western Pacific region	518 700 (489 200–547 800)	2 429 000 (2 266 000–2 617 000)	46·31 (43·21–49·91)	34·74 (32·42–37·44)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Total deaths are all modelled deaths in the presence of vaccinations when fitted to excess mortality from the start of the pandemic up to Dec 8, 2021.

Table 2: **Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality**

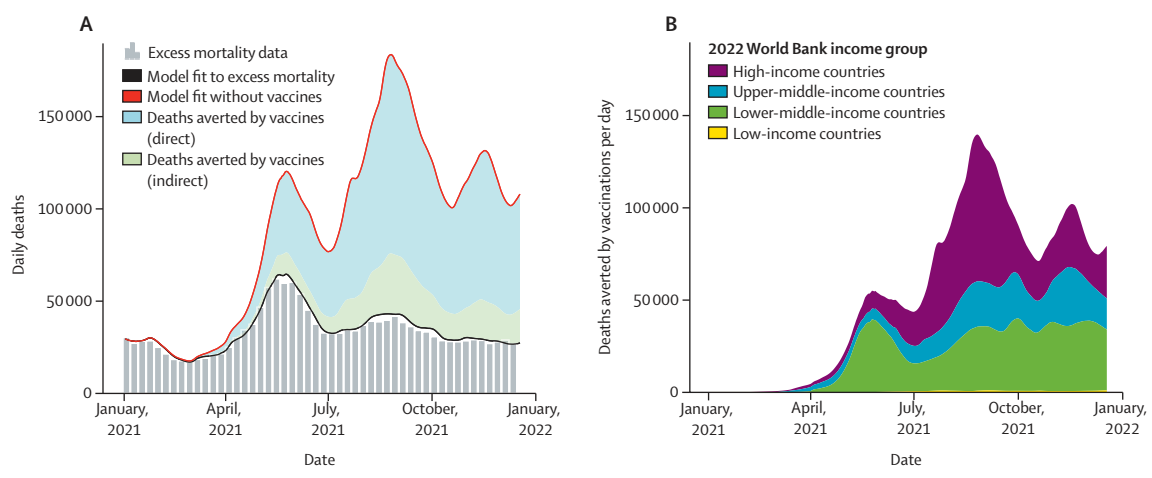

Figure 1: **Global COVID-19 deaths averted due to vaccination based on excess mortality**
(A) Median number of daily COVID-19 deaths based on excess mortality estimates (grey vertical bars) in the first year of vaccination. The baseline estimate of daily COVID-19 deaths from the model fit to excess mortality is plotted with the solid black line and the counterfactual scenario without vaccines is plotted with a red line. The gap between the red and black line indicates the deaths averted due to vaccination, with the proportion of total deaths averted by direct protection conferred by vaccination shown in blue and indirect protection shown in green. (B) Median number of daily deaths averted per day as per 2022 World Bank income group.

initially concentrated in lower-middle-income countries (figure 1B), resulting from the significant epidemic wave in India as the delta variant emerged. This was subsequently followed by vaccine impact being concentrated in high-income countries that were then either able to relax interventions due to high vaccination coverage (eg, the UK), or that did not implement further restrictions despite the spread of the more virulent delta variant in the second half of 2021.

Overall, estimated deaths averted per capita were highest in high-income countries, reflecting the earlier and wider roll-out of vaccination campaigns (table 2, figure 2; appendix p 13). We estimated that substantially more deaths were averted in the WHO European region. This was due to both the greater number of vaccinations administered in these regions and the higher levels of vaccine coverage achieved before the arrival of the delta variant.

The estimated number of deaths averted per vaccine administered was notably higher in high-income countries and upper-middle-income countries, in part due to greater access to the more efficacious mRNA vaccines (table 2;

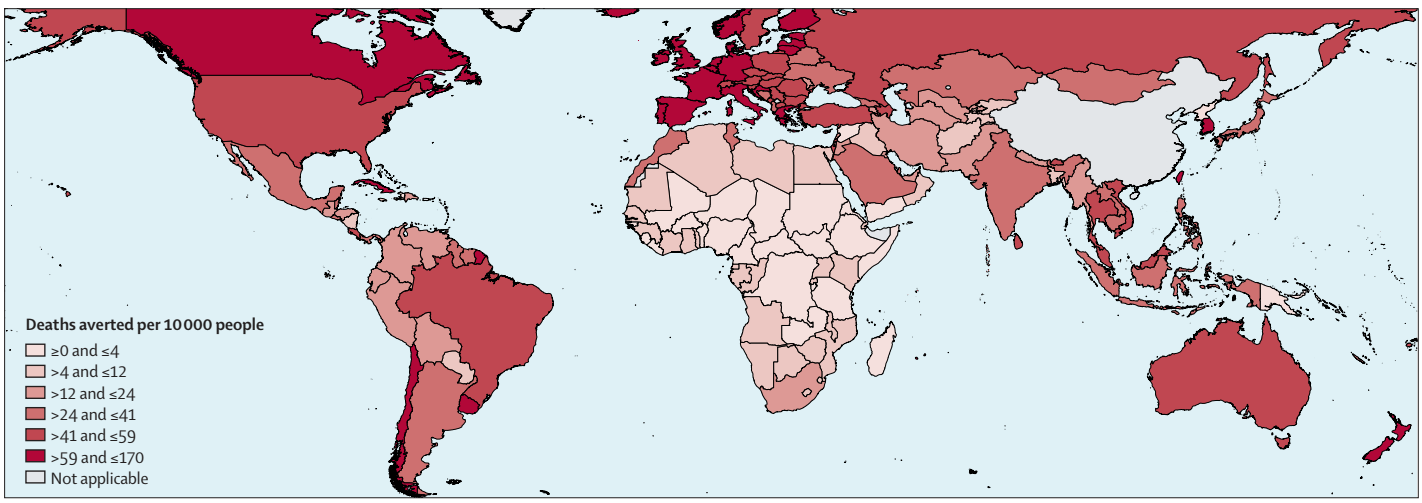

Figure 2: **Median deaths averted by vaccinations per 10 000 people by country in the first year of COVID-19 vaccination**
Estimates of deaths averted were based on model fits to excess mortality and were binned within seven equal quantiles starting at 0 deaths averted. Deaths averted listed as not applicable for China because of its exclusion from our analysis, due to its unique position as the origin of the detected epidemic and large influence on estimates of deaths averted stemming from its population size.

appendix p 14). Across the geographical regions, the estimated number of deaths averted per vaccine administered was estimated to be significantly higher in the European region and significantly lower in the Eastern Mediterranean region, reflecting disparities in access to different vaccine types (appendix p 14) coupled with very high predicted excess mortality in several countries in the Eastern Mediterranean region (table 2). The disparity in the number of deaths averted per vaccine between the European region and the Western Pacific region, despite access to similar vaccine types, reflects the zero-COVID strategy adopted by some countries in the Western Pacific region, such as New Zealand, which resulted in smaller epidemics predicted in the no-vaccine counterfactual (table 2; appendix p 13). Conversely, we estimated the greatest vaccine impact to have occurred in high-income countries that did not pursue a zero-COVID strategy (appendix p 13), reflecting how maximising vaccination coverage was leveraged to re-open the economy, resulting in increased transmission and subsequently higher inferred R_t trends. When viewed across income strata, a linear log–log relationship was observed between per-capita deaths averted and vaccines administered (figure 3), with low-income countries estimated to have a lower vaccine impact resulting from lower vaccine coverage. This relationship was weakest within high-income countries, as all high-income countries had high levels of vaccinations per capita, with the variation in deaths averted explained by other heterogeneities in their epidemics, such as pursuing zero-COVID strategies.

For the 83 COVAX AMC countries modelled, using our model fit to excess mortality, we estimated that 17·9 million (95% CrI 17·2–18·5) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination. We estimated that vaccinations averted 7·4 million (95% CrI 6·8–7·7) deaths, 41% (7·4 million of 17·9 million) of the deaths that would have occurred in COVAX AMC countries. Notably, the shortfall of the COVAX target in several regions was estimated to have resulted in an additional 156 900 (95% CrI 147 800–165 400) deaths (table 3). Although these deaths constituted a small proportion of the total deaths averted globally, these avertable deaths were concentrated in 25 low-income countries, which we predict would have averted an additional 81 750 (95% CrI 75 430–88 200) deaths across low-income countries by reaching 20% coverage, representing an additional 45% of deaths averted (table 3).

We found that 96 countries and administrative regions were below the WHO target of 40% vaccination coverage by the end of 2021. Had this target been met, we estimated that 599 300 (95% CrI 577 700–622 400) additional deaths would have been averted (table 3). The majority of these deaths occurred in lower-middle-income countries and the African and Eastern Mediterranean regions, although the largest proportional increase was seen in low-income countries, with the averted deaths making up a 111% increase in estimated deaths averted by vaccinations (table 3).

Our vaccine impact estimates were dependent on the assumed level of immune escape shown by the delta variant and the assumed relationship between age and the IFR. In the scenario in which the epidemic wave caused by the delta variant was comparable to previous waves and neither reached herd immunity nor resulted in health-system capacity being breached, our estimates of vaccine impact were unchanged regardless of the assumed level of immune evasion associated with the delta variant (appendix p 21). However, in scenarios in which the introduction of the delta variant produced a significantly larger wave that resulted in herd immunity being reached in the counterfactual, increased immune escape associated with the delta variant resulted in an

increased number of averted deaths due to the larger effective size of the susceptible population. In sensitivity analyses in which the relationship between age and IFR was changed, we estimated that vaccine impact would be greater in scenarios with higher IFRs, reflecting the higher number of deaths that could be averted by vaccination (appendix p 22).

Discussion

The high individual-level protection against severe disease and mortality due to COVID-19, as well as the population-level benefit afforded by mild protection against SARS-CoV-2 infection (before the emergence of the omicron [B.1.1.529] variant), conferred by vaccination, has fundamentally altered the course of the COVID-19 pandemic. Directly measuring the impact of vaccination programmes on COVID-19 mortality is not possible as the counterfactual (ie, without vaccinations) cannot be observed. Mathematical models are a valuable tool for quantifying the impact of vaccination campaigns on epidemic dynamics.[25] We evaluated the impact of the first year of COVID-19 vaccination, revealing how vaccinations have more than halved the potential global death toll due to COVID-19, with an estimated 19·8 million deaths from COVID-19 averted as a result of vaccination, based on excess mortality estimates of the impact of the pandemic. These reductions were concentrated in high-income countries that relied on their vaccination programmes to relax interventions and allow SARS-CoV-2 transmission to increase as they moved into a new stage of the pandemic.

In low-income countries, particularly countries that did not reach the 20% targets set out by COVAX, vaccine impact was substantially lower, with vaccine impact estimated to have been almost doubled if the targets had been reached. If the 40% target, per country, from WHO had been met, we estimated a further increase in deaths averted, mainly focused in lower-middle-income countries and low-income countries. A limitation of our assessment of the COVAX and WHO targets is the timeframe of our analysis, as these targets were set to be reached by the end of 2021, whereas our modelling endpoint was Dec 8, 2021, to align with 1 year since the start of public vaccination. Hence, some countries might have moved closer to achieving the targets, or achieved them, by the end of the year. However, any recent vaccination drives would have had consequently negligible impact given the delay in developing protection and insufficient impact on COVID-19 dynamics.

Deriving estimates of vaccine impact is heavily dependent on the counterfactual scenario chosen. In our counterfactual, we assumed the same time-varying levels of SARS-CoV-2 transmission as estimated in our model fits. Consequently, the largest impact was observed in countries that delivered the most vaccinations to date and simultaneously relaxed interventions, allowing SARS-CoV-2 transmission to increase. However, several countries with slower vaccination roll-out as well as countries adopting a zero-COVID strategy maintained stronger interventions to suppress transmission and thus observed smaller impacts of their vaccination programmes as a result. As these countries start to reopen, we predict that vaccine impact estimates would increase in line with increasing levels of SARS-CoV-2 transmission.

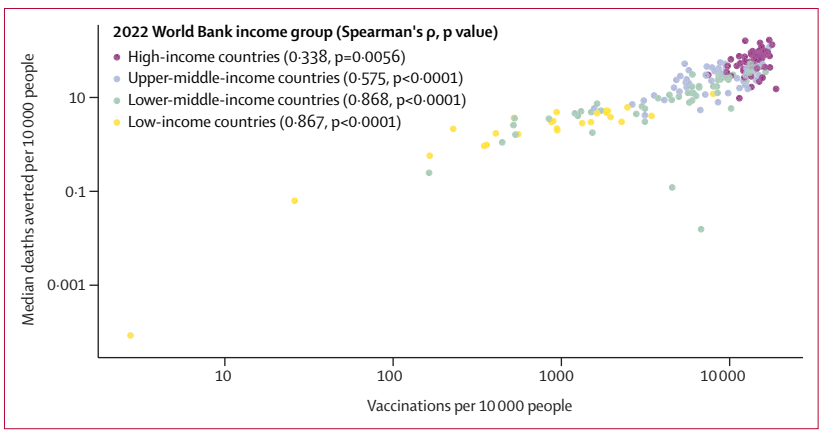

Figure 3: **Median deaths averted by vaccinations per 10 000 against vaccinations per 10 000 for each country**
All measures are on the log-scale. Spearman's rank correlation coefficient (Spearman's ρ) is also given for each income group with a p value based on the Z score against a null hypothesis of no correlation. Countries that did not deliver any vaccinations or had no deaths averted are not included.

Under-ascertainment of COVID-19 mortality is a known issue that has hindered our understanding of the pandemic.[23] In this analysis, we consequently focused on fitting to all-cause excess mortality, which provides a more complete description of the pandemic.[15] However, even when relying on model fits based on reported COVID-19 deaths, we estimated that more than 14 million deaths were averted by COVID-19 vaccination. The discrepancy between vaccine impact estimates based on excess mortality and COVID-19 deaths was concentrated in settings with lower death registration and certification. This substantial discrepancy underpins the crucial need for continued investment in civil registration and vital statistics to prevent biases in mortality reporting further minimising the perceived impact and necessity of vaccination in settings with lower reporting of deaths. In countries with more complete reporting systems, our estimates were broadly comparable to other endeavours focused on officially reported COVID-19 deaths and on understanding the direct impact of vaccination on people older than 60 years in Europe.[26] We identified one study that estimated both the indirect and direct impact of vaccination, which again yielded estimates for vaccine impact in the USA that were similar to our impact estimates based on reported COVID-19 deaths.[27]

In our effort to provide impact estimates globally, we introduced various assumptions into our model. We were hindered by the global disparities in SARS-CoV-2 genomic surveillance and the absence of detailed vaccination data for the majority of countries. Consequently, key model

	COVAX target (20% of eligible population in COVAX Advance Market Commitment countries fully dosed)				WHO target (40% of eligible population fully dosed)			
	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)
Worldwide	41	4·15%	156 900 (147 800–165 400)	0·792% (0·744–0·843)	96	27·8%	599 300 (577 700–622 400)	3·03% (2·89–3·17)
World Bank income group								
High-income countries	..	..	..	..	1	0·00191%	20 (20–30)	0·000298% (0·000243–0·000342)
Upper-middle-income countries	..	..	..	..	27	6·1%	51 110 (47 860–66 690)	1·21% (1·12–1·58)
Lower-middle-income countries	16	4·28%	75 540 (68 640–80 380)	1·02% (0·923–1·13)	41	39·7%	347 500 (330 300–363 300)	4·71% (4·43– 5·11)
Low-income countries	25	253%	81 750 (75 430–88 200)	45·2% (42·0–49·3)	27	1060%	200 000 (187 900–211 900)	111% (105–118)
WHO region								
African region	31	134%	132 700 (123 800–141 300)	28·4% (26·5–30·4)	44	631%	348 900 (330 200–370 000)	74·9% (70·7–78·8)
Region of the Americas	1	0·248%	1080 (850–1390)	0·0241% (0·0186–0·0308)	14	1·66%	6330 (5870–6840)	0·141% (0·129–0·155)
Eastern Mediterranean region	6	5·56%	20 850 (18 860–22 710)	2·09% (1·86–2·32)	13	61·6%	126 800 (118 900–134 600)	12·7% (11·6–13·7)
European region	..	..	..	..	13	3·05%	41 760 (38 110–46 160)	0·715% (0·644–0·799)
South-East Asian region	1	0·586%	1410 (50–2960)	0·0254% (0·000914–0·0532)	7	17·5%	70 420 (64 300–75 890)	1·25% (1·15–1·39)
Western Pacific region	2	0·302%	900 (610–1200)	0·0366% (0·0250–0·0492)	5	2·59%	4990 (4390–5730)	0·205% (0·178–0·237)

Data are n (95% credible interval [CrI]) or % (95% CrI). All percentages are reported to 3 significant figures. Increased vaccination coverage is defined as the percentage increase in the proportion of the population with a full dose in all modelled countries when meeting the respective targets. Countries are grouped by 2022 World Bank income group and WHO region. COVAX=COVID-19 Vaccines Global Access.
*In proportion to total deaths averted by vaccines, as shown in table 2.

Table 3: **Estimated increase in deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality had all countries met either of the COVAX or WHO vaccination targets**

inputs had to be created from working assumptions on which vaccines were delivered, how they were delivered, and when new variants of concern spread worldwide. We also assumed that the relationship between age and IFR was the same for each country. These assumptions would have affected our estimates of deaths averted, with sensitivity analyses showing that higher overall IFRs will increase the number of deaths that could be averted by vaccination. Our impact estimates were also limited by the inherent uncertainty in model-based estimates of excess mortality.[13] These estimates are likely to have underestimated or overestimated COVID-19 death tolls in many countries. Notably, our model fits were unable to recreate excess mortality death tolls in recent epidemic waves in Iraq and Sudan because of the depletion of the susceptible population. These discrepancies could have been due to multiple reasons, including overestimated excess mortality, proportions of excess mortality not due to COVID-19,[28] higher infection fatality rates by age in low-income settings than those estimated from high-income countries,[29] and lower vaccine effectiveness than assumed in our framework. Last, our impact estimates were dependent on the assumed degree of immune escape that each variant of concern exhibits.[20] If immune escape was higher than we assumed, more of the population would have been susceptible to re-infection and consequently more deaths from COVID-19 could have been averted by vaccination.

More broadly, our estimates should be considered in light of the considerable uncertainty inherent in estimating vaccine impact. Uncertainty in the true death toll of the pandemic, the circulating variants of concern and their immunological phenotypes, and the vaccines themselves administered in many countries vastly complicate efforts to derive accurate estimates of the impact of COVID-19 vaccines. However, the results of this analysis still provide a comprehensive and thorough assessment of the impact of COVID-19 vaccination, revealing the substantial impact that vaccines have had and the millions of lives that are likely to have been saved during the first year of vaccination. Despite this, more lives could have been saved if vaccines had been distributed more rapidly to many parts of the world and if vaccine uptake could have been strengthened worldwide. Reaching vaccination coverage targets and improving vaccine coverage globally is dependent on multiple factors and not solely dependent on improving

vaccine donations.[30] Vaccine intellectual property needs to be shared more quickly in the future, with more open technology and knowledge transfer surrounding vaccine production and allocation. Vaccine distribution and delivery infrastructure also needs to be scaled up worldwide and misinformation combatted to improve vaccine demand. Improvements must be made in all these areas to reach current vaccine targets and help ensure that vaccines are more equitably distributed in the future.

Contributors

OJW and ACG conceived the study with input from GB, ABH, PW, and JT. OJW and GB led the model fitting and counterfactual simulation analyses for the estimation of deaths averted. OJW and GB produced the first draft of the manuscript and have accessed and verified the underlying data. All authors read, contributed to, and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ACG has received personal consultancy fees from HSBC, GlaxoSmithKline, and WHO related to COVID-19 epidemiology and from The Global Fund to Fight AIDS, Tuberculosis and Malaria for work unrelated to COVID-19. ACG is a non-remunerated member of scientific advisory boards for Moderna and the Coalition for Epidemic Preparedness. ABH and PW have received personal consultancy related to COVID-19 work from WHO. All other authors declare no competing interests.

Data sharing

All data, codes, and supplementary tables used and generated by this study are available in a GitHub repository (version 1.0.1) or the Zenodo open repository. All estimates of deaths averted from vaccination are available in the appendix (p 13).

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For the **GitHub repository** see https://github.com/mrc-ide/covid-vaccine-impact-orderly

For the **Zenodo repository** see https://doi.org/10.5281/zenodo.6539545

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Productie 20

COVID-19-vaccinatie: BioNTech/Pfizer

Aan: de minister van Volksgezondheid, Welzijn en Sport
Nr. 2020/29, Den Haag, 24 december 2020

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inhoud

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samenvatting

Recent is het BNT162b2-vaccin tegen COVID-19 dat is ontwikkeld door BioNTech en Pfizer (merknaam *Comirnaty*) beoordeeld door het Europees geneesmiddelenagentschap (EMA) en goedgekeurd door de Europese Commissie. Dit betekent dat het in Nederland ingezet kan worden voor de bestrijding van de COVID-19-pandemie. De minister van Volksgezondheid, Welzijn en Sport heeft de Gezondheidsraad gevraagd te adviseren over de inzet van dit vaccin bij verschillende doelgroepen die in aanmerking komen voor vaccinatie. De Commissie Medische aspecten van COVID-19 heeft het vaccin beoordeeld aan de hand van de vaste criteria die de Gezondheidsraad gebruikt bij de advisering over vaccinaties.

Ziektelast van COVID-19 is groot

Het eerste criterium voor inzet van vaccinatie is dat er sprake moet zijn van een aanzienlijke ziektelast. Dat is bij COVID-19 duidelijk het geval. Tot half december zijn er bij de GGD 628.577 ziektegevallen en 10.168 sterfgevallen door COVID-19 bevestigd. Het risico op een ernstig ziektebeloop neemt toe bij mensen met een chronische aandoening en bij toenemende leeftijd. De gemiddelde leeftijd van patiënten op de verpleegafdeling was 67 jaar en op de IC 64 jaar. Verreweg de meeste sterfgevallen zijn te betreuren onder ouderen, van wie een groot deel woonachtig was in verpleeghuizen.

Vaccin werkt goed bij volwassenen, ouderen en medische risicogroepen

Een volgend criterium is dat vaccinatie werkzaam en effectief moet zijn. Het vaccin wordt in twee doses toegediend met ongeveer drie weken ertussen. De werkzaamheid van het BNT162b2-vaccin tegen COVID-19 is bepaald bij ruim 36.000 mensen, van wie de helft het vaccin ontving en de helft een placebo. Daaruit kwam naar voren dat de vaccinatie zowel volwassenen als ouderen en medische risicogroepen goed beschermt. Bij alle groepen lag de werkzaamheid ruim boven de 90%. Nog onbekend is hoe lang de bescherming duurt en in hoeverre vaccinatie ook verspreiding van het virus kan voorkomen.

Vaccin is voldoende veilig: bijwerkingen zijn doorgaans mild

Ook de veiligheid van vaccinatie is een belangrijk criterium. Het BNT162b2-vaccin is voldoende veilig en wordt goed verdragen. Net als alle geneesmiddelen, hebben ook vaccins bijwerkingen. De bedoeling van vaccinatie is om een reactie van het immuunsysteem op te wekken en dat gaat vaak gepaard met bijbehorende tijdelijke symptomen. Vaccinatie met het BNT162b2-vaccin geeft bij de meeste mensen bijwerkingen na zowel de eerste als de tweede dosis. De meest voorkomende waren

een milde tot matige pijn op de plaats van de injectie en vermoeidheid, hoofdpijn en spierpijn. De reacties kwamen vaker voor bij jongere mensen en vaker na de tweede dosis.
De meeste bijwerkingen waren binnen enkele dagen verdwenen.

Vaccinatie is aanvaardbaar: voordelen wegen op tegen nadelen

De commissie vindt dat de voordelen van vaccinatie (gezondheidswinst door bescherming tegen COVID-19) opwegen tegen de nadelen (bijwerkingen die doorgaans mild en kortdurend zijn). Daarmee is ook aan het criterium van aanvaardbaarheid voldaan. De kosteneffectiviteit van vaccinatie kan nog niet beoordeeld worden omdat daarover nog geen gegevens bekend zijn.

Advies: vaccin inzetten, primair bij ouderen vanaf 60 jaar

Vaccinatie met het BNT162b2-vaccin is werkzaam, voldoende veilig en aanvaardbaar voor volwassenen, ouderen en medische risicogroepen. De commissie adviseert daarom het BNT162b2-vaccin in te zetten bij publieke vaccinatieprogramma's gericht tegen COVID-19. Omdat het vaccin een boven verwachting hoge werkzaamheid heeft bij ouderen en de ziektelast als gevolg van COVID-19 het grootst is in deze groep, adviseert de commissie het BNT162b2-vaccin primair in te zetten voor ouderen vanaf 60 jaar, te beginnen bij de oudsten. Dit is in lijn met vaccinatiestrategie 1, zoals geformuleerd in het recente advies van de Gezondheidsraad over vaccinatiestrategieën. Met deze strategie wordt de meeste gezondheidswinst behaald en wordt daarnaast de toestroom van COVID-19-patiënten naar de ziekenhuizen tegengegaan, wat de druk op de zorg zal verminderen. Het BNT162b2-vaccin zou volgens de commissie beperkt ingezet moeten worden om zorgpersoneel in de langdurige zorg te vaccineren, namelijk zolang de medische risicogroepen die zij verzorgen niet zelf gevaccineerd kunnen worden. Ook zou het vaccin heel selectief in de curatieve zorg kunnen worden ingezet om de zorg in stand te houden op plaatsen waar acute gezondheidsschade optreedt door uitval van zorgmedewerkers. Volgens de commissie zou het vaccin van AstraZeneca uitkomst kunnen bieden voor vaccinatie van alle zorgmedewerkers, omdat dit vaccin volgens de huidige verwachting begin 2021 in een grote hoeveelheid van 4,5 miljoen doses zou kunnen worden geleverd.

01 inleiding

1.1 Aanleiding

Sinds begin 2020 is er sprake van een COVID-19-pandemie, veroorzaakt door het virus SARS-CoV-2. Het afgelopen jaar heeft biotechnologiebedrijf BioNTech in samenwerking met farmaceut Pfizer een vaccin ontwikkeld tegen COVID-19. Recent is dit zogeheten BNT162b2-vaccin (merknaam *Comirnaty*) beoordeeld door het Europees geneesmiddelenagentschap (EMA) en goedgekeurd door de Europese Commissie, waardoor het in Nederland ingezet kan worden voor de bestrijding van de pandemie.

1.2 Adviesvraag

Op 18 december 2020 vroeg de minister van Volksgezondheid, Welzijn en Sport (VWS) de Gezondheidsraad advies uit te brengen over de inzet van het BNT162b2-vaccin bij verschillende doelgroepen die in aanmerking komen voor vaccinatie. De adviesvraag staat op www.gezondheidsraad.nl.

Voor de beantwoording van deze en andere adviesaanvragen over medische aspecten rond COVID-19 heeft de voorzitter van de Gezondheidsraad een tijdelijke commissie geïnstalleerd, de Commissie Medische aspecten van COVID-19. De samenstelling van de commissie staat achter in dit advies. Het advies is getoetst door de beraadsgroep van de Gezondheidsraad en op 24 december 2020 aangeboden aan de minister van VWS.

1.3 Werkwijze

Bij advisering over vaccinaties hanteert de Gezondheidsraad een vast beoordelingskader (te vinden op www.gezondheidsraad.nl). Voor de beoordeling van de verschillende criteria baseert de commissie zich zoveel mogelijk op *peer-reviewed* publicaties uit wetenschappelijke tijdschriften. Daarnaast heeft zij beschikking over gegevens (zoals het *European public assessment report* (EPAR)) die door registratie-autoriteiten EMA en de Amerikaanse *Food and Drug Administration* (FDA) gepubliceerd zijn bij de registratie van het vaccin. Van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) zijn actuele gegevens verkregen over de epidemiologie van COVID-19 in Nederland.

De commissie heeft bekeken of er reden was om af te wijken voor Caribisch Nederland. Dat bleek niet het geval te zijn en daarom is de inhoud van dit advies ook voor Caribisch Nederland toepasbaar.

1.4 Leeswijzer

De commissie beschrijft in hoofdstuk 2 de actuele epidemiologische situatie van COVID-19 in Nederland en de doelgroepen die op basis van de ziektelast in aanmerking komen voor vaccinatie. In hoofdstuk 3 bespreekt de commissie de criteria werkzaamheid, effectiviteit, veiligheid, aanvaardbaarheid en kosteneffectiviteit van vaccinatie met het BNT162b2-vaccin. In hoofdstuk 4 formuleert de commissie haar qdvies en bespreekt zij implementatieaspecten.

Het kader voor advisering over vaccinaties

De Gezondheidsraad hanteert een vast kader voor de advisering over vaccinaties om te bepalen of een vaccinatie een plek in een publiek programma moet krijgen, als essentiële zorg kan worden aangemerkt, of individuele zorg is (voor eigen rekening).[1] Daarbij beoordeelt de raad of er sprake is van een aanmerkelijke ziektelast en of vaccinatie effectief, veilig, aanvaardbaar en doelmatig is. Is dat het geval, dan komt een vaccinatie volgens de Gezondheidsraad mogelijk in aanmerking voor invoering. Vervolgens is de vraag welke rol de overheid daarbij zou moeten spelen. Bij de bepaling welke overheidsbemoeienis aangewezen is, gelden twee uitgangspunten. De eerste is de taak die de overheid heeft in de bescherming van de bevolking en het maatschappelijk leven. Daaruit volgt dat de overheid een duidelijkere rol heeft naarmate een infectie door het besmettelijke karakter een belemmering kan vormen voor het maatschappelijke leven en individuen zichzelf moeilijk kunnen beschermen. Dan is er reden om een vaccinatie op te nemen in een publiek programma. Het tweede uitgangspunt is het streven van de overheid naar een rechtvaardige verdeling van zorg. Dat geldt wanneer sprake is van essentiële zorg, waarbij van belang is dat de groepen voor wie bescherming het meest urgent is ook daadwerkelijk beschermd worden.

02
ziektelast

Het aantal bevestigde COVID-19-ziektegevallen liep in de eerste weken van december 2020 fors op. Per week werden meer dan 55.000 bevestigde ziektegevallen gemeld. Ouderen vanaf 60 jaar hebben een sterk verhoogd risico op een ernstig beloop van COVID-19 en sterfte. Deze groep komt daarom als eerste in aanmerking voor vaccinatie.

2.1 Epidemiologische situatie

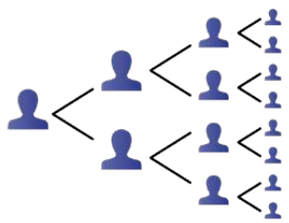
Sinds 27 februari 2020, toen het eerste ziektegeval van COVID-19 in Nederland werd bevestigd, is het totaal aantal ziektegevallen opgelopen tot 628.577 en het aantal sterfgevallen tot 10.168 (bij de GGD bevestigde gevallen; data van 15 december 2020, 10.00 uur).[2] Waar in november aanvankelijk een daling in het wekelijkse aantal bevestigde ziektegevallen te zien was, is dit aantal sinds begin december weer opgelopen. In de periode van 24 november tot 15 december 2020 steeg het aantal van ruim 36.000 naar ruim 58.000 bevestigde ziektegevallen per week. Ook het aantal afgenomen tests en het percentage positieve testuitslagen nam toe. De recente ziektegevallen kwamen in alle leeftijdsgroepen voor, maar bij kinderen jonger dan 10 jaar veel minder vaak. Het risico op een ernstig ziektebeloop neemt toe bij mensen met een chronische aandoening en bij toenemende leeftijd. De gemiddelde leeftijd van in het ziekenhuis opgenomen patiënten was op de verpleegafdeling 67 jaar en op de IC 64 jaar.[3,4] Verreweg de meeste sterfgevallen zijn te betreuren onder ouderen, van wie een groot deel woonachtig was in verpleeghuizen. Bijna 90% (n=9.135) van de bij de GGD bevestigde sterfgevallen betrof ouderen van 70 jaar of ouder. Na herstel van COVID-19 kunnen patiënten last houden van long-, hart- of neurologische klachten, zoals (extreme) vermoeidheid, hoofdpijn, spierpijn, hoesten, kortademigheid en cognitieve problemen. Dit kan ook voorkomen bij patiënten die een milde infectie hebben gehad en niet in het ziekenhuis opgenomen zijn geweest. Dergelijke langdurige klachten staan ook wel bekend als *long COVID*.[5] Er is nog veel onbekend over de ernst en duur van deze klachten en hoe vaak en bij welke patiënten deze optreden.

2.2 Doelgroepen voor vaccinatie

In november 2020 heeft de Gezondheidsraad geadviseerd welke groepen als eerste in aanmerking komen voor vaccinatie tegen COVID-19.[6] De raad beschreef verschillende strategieën (zie figuur 1), waarbij de keuze afhangt van de eigenschappen van het vaccin, de stand van wetenschap en de epidemiologische situatie. In de huidige omstandigheden komen ouderen vanaf 60 jaar als eerste in aanmerking voor vaccinatie, omdat deze groep duidelijk het hoogste risico heeft op (ernstige) ziekte en sterfte (strategie 1). Uit analyses van ziekenhuisgegevens blijkt dat het risico op sterfte vanaf 60 jaar sterk toeneemt; het risico voor 60-jarigen is 3 tot 5 maal hoger, voor 70-jarigen 7 tot 11 maal hoger en voor 80-jarigen en ouder 20 tot 40 maal hoger, ten opzichte van mensen jonger dan 50 jaar.[3] Ook wanneer gekeken wordt naar andere parameters van de ziektelast, zoals ‘verloren levensjaren’ en DALY’s (*disability adjusted life years*), is de ziektelast het grootst bij ouderen vanaf 60 jaar.[7-9] Dit kan verklaard

worden door de zeer hoge sterfterisico's bij ouderen. Door hen als eerste te vaccineren kan de meeste gezondheidswinst worden behaald en kan bescherming worden geboden aan de groepen die het meest kwetsbaar zijn. Deze doelstelling is ethisch te onderbouwen op grond van zowel het utiliteitsprincipe als rechtvaardigheidsoverwegingen.

Figuur 1: Vaccinatiestrategieën

	Doelstelling	Doelgroep	
1.	**Verminderen (ernstige) ziekte en sterfte als gevolg van COVID-19**		Groepen die op basis van persoonlijke kenmerken een verhoogd risico lopen op een ernstiger ziektebeloop en sterfte na virusbesmetting (gezondheidskundig kwetsbare groepen)
			Groepen die een verhoogd risico lopen om mensen uit medische risicogroepen te besmetten, ondanks preventieve maatregelen of omdat preventieve maatregelen niet beschikbaar of mogelijk zijn
			Groepen die een verhoogd risico lopen op virusinfectie door hun werk- of leefomgeving
2.	**Terugdringen verspreiding SARS-CoV-2**		Groepen die een verhoogd risico lopen om anderen te besmetten (‘risicovormers’)
3.	**Voorkomen maatschappelijke ontwrichting**		Groepen die van belang zijn voor het in stand houden van de zorg en het behoud van de vitale infrastructuur

03
vaccinatie met het vaccin van BioNTech/Pfizer

Vaccinatie tegen COVID-19 met het BNT162b2-vaccin is zeer werkzaam bij zowel volwassenen als ouderen en medische risicogroepen. Het vaccin is voldoende veilig en wordt goed verdragen. De commissie beoordeelt de nut-risicoverhouding van vaccinatie daarom als gunstig.

3.1 BNT162b2-vaccin

Het vaccin BNT162b2 (merknaam *Comirnaty*) dat door biotechnologie-bedrijf BioNTech en farmaceut Pfizer is ontwikkeld, is een mRNA-vaccin.[10] Dit houdt in dat het vaccin genetisch materiaal (*messenger* RNA, mRNA) bevat van SARS-CoV-2, het virus dat COVID-19 veroorzaakt.
Het mRNA codeert voor het *spike*-eiwit van het virus. De functie van dit eiwit is het binden van het virus aan receptoren van lichaamscellen. Wanneer dat lukt, kan het virus de cel binnendringen en zich vermeer-deren, wat vaak tot ziekte leidt. Het vaccin is gericht tegen dit *spike*-eiwit. Doordat het mRNA uit het vaccin ertoe leidt dat lichaamscellen tijdelijk het virale eiwit produceren, wordt er een immuunrespons opgewekt die sterk lijkt op een natuurlijke infectie. Hierbij worden neutraliserende antistoffen gevormd die aanhechting van het virus kunnen blokkeren en daarmee ziekte voorkomen. Daarnaast is na vaccinatie een sterke T-celrespons (CD4+ en CD8+) meetbaar, wat kan meehelpen om infectie te beperken en ziekte te voorkomen. Omdat het vaccin uitsluitend mRNA van een enkel eiwit bevat, kan het geen infectie of ziekte veroorzaken. Het mRNA wordt bovendien binnen enkele dagen door het lichaam zelf weer afgebroken.[11]

Het Pfizer-vaccin BNT162b2 is in Europa recent geregistreerd voor gebruik vanaf 16 jaar oud.[12] Het vaccin wordt in twee doses toegediend met een interval van drie weken. De samenstelling van het vaccin staat beschreven in de samenvatting van de productkenmerken (SmPC).[10]

3.2 Werkzaamheid en effectiviteit

De werkzaamheid van vaccins wordt bepaald in klinische studies door een gevaccineerde en ongevaccineerde groep met elkaar te vergelijken. In fase 1-2-trials wordt onderzocht of het vaccin een immuunrespons opwekt en of het veilig is. Is dat het geval, dan zal in een fase 3-trial in een grote groep mensen de werkzaamheid en veiligheid verder worden onderzocht. De effectiviteit van vaccinatie wordt bepaald nadat het vaccin beschikbaar is gesteld buiten een gecontroleerde onderzoekssetting, en wordt op twee niveaus beschreven:

- de reductie van de ziektelast binnen de gevaccineerde populatie,
- de reductie van ziektelast in de gehele populatie (populatie-effect), na invoering van een vaccinatieprogramma. Hiervoor wordt in de wetenschappelijke literatuur de term *impact* gebruikt.

De effectiviteit kan niet bepaald worden met de resultaten van de klinische trials, maar zal na invoering van een vaccinatieprogramma met vervolgonderzoek in de bevolking worden bepaald. De commissie beschrijft daarom in dit advies alleen de werkzaamheid.

3.2.1. Klinische trials

Momenteel zijn er nog verschillende fase 1-, 2- en 3-trials in uitvoering naar het BNT162b2-vaccin. Er zijn resultaten gepubliceerd van een fase 1-2-trial die bij 45 gezonde volwassenen tussen 18-55 jaar oud (gemiddelde leeftijd 37 jaar) en 45 gezonde volwassenen tussen 65-85 jaar oud (gemiddelde leeftijd 69 jaar) onderzocht of vaccinatie met twee doses van het BNT162b2-vaccin leidde tot een immuunrespons.[13] In zowel de jonge als de oudere leeftijdsgroep leidde vaccinatie na zeven dagen tot de productie van antistoffen en mogelijk ook tot T-celresponses. Van de fase 2-3-trials zijn gegevens beschikbaar over werkzaamheid van het vaccin tegen het optreden van COVID-19, ongeveer twee maanden na vaccinatie in ruim 36.000 mensen.[10,14] De gemiddelde leeftijd in zowel de vaccinatie- als controlegroep was 50 jaar. Ongeveer 7.700 mensen waren 65 jaar of ouder (ongeveer 20%) en de oudste deelnemer die het vaccin ontving was 89 jaar. Ongeveer 20% van de deelnemers had een (stabiele) onderliggende aandoening, meestal diabetes mellitus (8%) of een longziekte (8%). Er werden op basis van een PCR-test die werd gedaan bij mensen met klachten, 170 gevallen van COVID-19 vastgesteld: 162 in de controlegroep (n=18.325) en 8 in de vaccinatiegroep (n=18.198). Dit betekent dat de werkzaamheid van het vaccin 95% was (95% betrouwbaarheidsinterval (95%BI): 90,0-97,9%). In de leeftijdsgroep van 65 jaar en ouder (n=7.728) werden 20 gevallen COVID-19 vastgesteld: 19 in de controlegroep en 1 in de vaccinatiegroep. Dit betekent dat de werkzaamheid ruim 94% (95%BI: 66,7-99,9%) was. In de leeftijdsgroep van 75 jaar en ouder werd geen COVID-19 vastgesteld in de vaccinatiegroep en 5 gevallen in de controlegroep (werkzaamheid 100% (95%BI: -13,1-100,0)).
De werkzaamheid was ook hoog (meer dan 90%) bij mensen ouder en jonger dan 65 jaar uit medische risicogroepen. Het is nog niet bekend wat de duur van de werkzaamheid is, omdat het vaccin recent is ontwikkeld en de klinische trials nog in uitvoering zijn. Ook is nog niet bekend of het vaccin verspreiding kan voorkomen. De commissie acht het waarschijnlijk dat vaccinatie zou kunnen leiden tot minder verspreiding, geredeneerd vanuit de gedachte dat wanneer vaccinatie beschermt tegen ziekte, er minder virus aanwezig is in de neus- en keelholte, wat de mogelijkheid om het virus verder te verspreiden verkleint.

Betrouwbaarheidsinterval

Het betrouwbaarheidsinterval is van belang voor de zeggingskracht van een uitkomst, in dit geval de effectiviteit van vaccinatie. Hoe groter het interval, hoe groter de onzekerheid over het effect.

3.3 Veiligheid

Voor elk vaccin geldt dat het uitsluitend tot de markt wordt toegelaten indien EMA of het College ter beoordeling van geneesmiddelen (CBG) het vaccin als voldoende veilig heeft beoordeeld op grond van de resultaten uit klinische trials. Dat neemt niet weg dat vaccins, net als alle geneesmiddelen, bijwerkingen hebben. De bedoeling van vaccinatie is het

opwekken van een immuunrespons. Dit gaat vaak gepaard met bijbehorende tijdelijke symptomen die worden veroorzaakt door het immuunsysteem zoals pijn, roodheid en zwelling op de plek van de injectie (lokale reacties) en koorts, vermoeidheid, spierpijn en hoofdpijn (systemische reacties). Deze reacties worden aangeduid met de term reactogeniciteit. In zeldzame gevallen treden ernstiger symptomen op na vaccinatie. Om vast te stellen of een symptoom daadwerkelijk een bijwerking van een vaccin is, of aan toeval is te wijten, zijn klinische trials nodig waarbij een vergelijking wordt gemaakt met een placebo of controle-vaccin, of observationele onderzoeken met grote aantallen deelnemers.

3.3.1 Reactogeniciteit

Vaccinatie met het BNT162b2-vaccin geeft bij de meeste mensen na zowel de eerste als de tweede dosis één of meerdere lokale of systemische reacties. De meest voorkomende lokale reactie was in de fase 1-2-trial een milde tot matige pijn op de plaats van de injectie.[13] Dit werd gemeld door tenminste 83% van de deelnemers tussen 18-55 jaar oud en door 67% van de deelnemers tussen 65-85 jaar oud. De meest genoemde systemische reacties waren vermoeidheid, hoofdpijn en spierpijn. Ook deze werden vaker gemeld in de jongere groep dan in de oudere groep en bovendien vaker na de tweede dosis in zowel de jongere als oudere groep. Zo werd vermoeidheid na de eerste dosis door 42% van de jongere deelnemers en door 25% van de oudere deelnemers genoemd. Na de tweede dosis was dat door respectievelijk 75% en 42%. Dit beeld werd ook gezien in de fase 2-3-trial, waarin bij ruim 8.100 mensen (de helft in de vaccinatiegroep en de andere helft in de controlegroep) de reacties na vaccinaties zijn nagevraagd.[10,14] Pijn op de plaats van de injectie was de meest voorkomen lokale reactie (ongeveer 80%), vermoeidheid (ongeveer 60%), hoofdpijn (ongeveer 50%) en spierpijn (ongeveer 30%) de meeste voorkomende systemische reacties. Koorts kwam bij meer dan 10% van de deelnemers voor. De reacties kwamen vaker voor bij jongere mensen en vaker na de tweede dosis. In enkele gevallen was de systemische reactie zodanig dat het de dagelijkse activiteiten beïnvloedde. De meeste lokale en systemische reacties waren binnen enkele dagen verdwenen.

3.3.2 Ernstige symptomen

In de fase 1-2-trial zijn geen ernstige symptomen (*serious adverse events*) voorgekomen.[13] In de fase 2-3-trial werd in zowel de vaccinatiegroep als de controlegroep bij minder dan 1% van de ruim 19.000 mensen een ernstig symptoom gemeld.[10,14] In twee gevallen was een ernstig symptoom gerelateerd aan het op een verkeerde wijze toedienen van het vaccin: een schouderblessure en opgezette lymfeklieren (lymfadenopathie). Gedurende de trial zijn 6 mensen overleden: 2 in de vaccingroep (arteriosclerose, hartstilstand) en 4 in de controlegroep (hartinfarct, hersenbloeding, 2 oorzaken onbekend).[14] Geen van deze sterfgevallen werd veroorzaakt door het vaccin of de placebo. Omdat het vaccin kort geleden is ontwikkeld, zijn er nog geen gegevens over eventuele bijwerkingen op de lange termijn of eventuele zeer zeldzame ernstige bijwerkingen.

3.3.3 Contra-indicaties

Het BNT162b2-vaccin is gecontra-indiceerd voor mensen die overgevoelig zijn voor één van de bestanddelen van het vaccin. De bestanddelen en samenstelling van het vaccin staan beschreven in de samenvatting van de productkenmerken (SmPC).[10] Kort na de start van het vaccinatie-programma in het Verenigd Koninkrijk, werden drie meldingen gemaakt van anafylaxie.[11,15] Uit voorzorg is daarom in de productinformatie (SmPC) de aanbeveling opgenomen om de gevaccineerde gedurende 15 minuten na vaccinatie te observeren.

3.3.4 Speciale groepen

Zwangerschap en borstvoeding

De werkzaamheid en veiligheid van het BNT162b2-vaccin is nog niet onderzocht bij zwangere vrouwen. Om deze reden zou het vaccin niet gebruikt moeten worden in deze groep, totdat er meer onderzoeks-gegevens beschikbaar komen. Echter, in individuele gevallen is vaccinatie van zwangere vrouwen wel denkbaar. Uit pre-klinische trials (dierstudies in ratten) zijn geen aanwijzingen gekomen die duiden op directe of indirecte nadelige gevolgen van vaccinatie tijdens zwangerschap.[10] Wanneer de risico's van COVID-19 groter zijn dan de mogelijke nadelen van vaccineren, kan vaccinatie worden overwogen in overleg met de behandelend arts. Vrouwen die zwanger willen worden, kunnen wel gevaccineerd worden. Vrouwen bij wie achteraf is gebleken dat zij ten tijde van vaccinatie zwanger waren, worden zorgvuldig gemonitord door Bijwerkingencentrum Lareb. De commissie heeft geen redenen om vaccinatie bij vrouwen die borstvoeding geven af te raden. Hoewel er geen specifieke gegevens zijn over dit vaccin, kan er wel gekeken worden naar het gebruik van andere niet-replicerende ('dode') vaccins tijdens de borstvoeding. Op basis van theoretische gronden en opgedane ervaring, verwacht de commissie dat het BNT162b2-vaccin voldoende veilig is voor gebruik bij deze groep vrouwen.

COVID-19

De commissie adviseert om mensen die reeds een infectie met SARS-CoV-2 hebben doorgemaakt, ook te vaccineren. Het is namelijk niet duidelijk hoe lang bescherming na een eerder doorgemaakte infectie aanhoudt en hoe hoog het antistofniveau moet zijn om ziekte te voorkomen. In de fase 2-3-trial werd ook in een beperkt aantal mensen (ongeveer 1.100) die al een infectie hebben doorgemaakt en antistoffen hadden, een beschermend effect gemeten. Bij mensen met een beves-tigde infectie zou vaccinatie uitgesteld moeten worden tot herstel of tot tenminste vier weken na een positieve testuitslag. Hiermee wordt voor-komen dat er onduidelijkheid kan ontstaan over de oorzaak van eventuele klachten. Het is onwaarschijnlijk dat vaccinatie het beloop van een infectie verslechtert. Daarom is het niet nodig om voorafgaand aan vaccinatie te testen op de aanwezigheid van een infectie. Mensen met klachten passend bij COVID-19, zouden wel eerst getest moeten worden om te voorkomen dat zij het virus verspreiden op de vaccinatielocatie.

Immuunstoornissen

Bij mensen met ernstige immuunstoornissen, zoals aangeboren immuundeficiënties, stoornissen die ontstaan door immuunsuppresieve medicatie of een hiv-infectie, is de werking van het immuunsysteem tegen infecties verstoord, waardoor zij een hoger risico hebben op infectieziekten en op een ernstiger ziektebeloop. Bij deze groepen is daarom preventie van een infectie met SARS-CoV-2 belangrijk en dat kan met vaccinatie worden bereikt. Hoewel er geen onderzoeksgegevens beschikbaar zijn over deze groepen, wegen volgens de commissie de voordelen van vaccinatie op tegen de nadelen. De commissie adviseert dan ook deze groepen te vaccineren en zorgvuldig te monitoren. Voor zover mogelijk zou er ook gekeken moeten worden naar *vaccine-associated enhanced disease (VAED)*. Er bestaat een theoretisch risico dat door een suboptimale antistofproductie na vaccinatie een ernstiger beloop van COVID-19 of een verergering van de bestaande aandoening optreedt. Dit zou nader onderzocht moeten worden.

3.4 Aanvaardbaarheid

De aanvaardbaarheid van vaccinatie wordt bepaald aan de hand van de verhouding tussen de gezondheidswinst als gevolg van bescherming tegen ziekte (het nut) en gezondheidsverlies door eventuele nadelige gevolgen van vaccinatie (het risico). Vaccinatie met het BNT162b2-vaccin heeft bijwerkingen, maar deze zijn overwegend mild, van korte duur en van voorbijgaande aard. De commissie beoordeelt de vaccinatie dan ook als aanvaardbaar voor volwassenen, ouderen en medische risicogroepen: de gezondheidswinst door bescherming tegen COVID-19 weegt op tegen de bijwerkingen van vaccinatie.

3.5 Kosteneffectiviteit

Er zijn geen data beschikbaar over de kosteneffectiviteit van vaccinatie tegen COVID-19 met het BNT162b2-vaccin. De commissie kan er daarom geen uitspraken over doen.

04
advies

De commissie concludeert dat vaccinatie met het BNT162b2-vaccin werkzaam, voldoende veilig en aanvaardbaar is voor volwassenen, ouderen en medische risicogroepen. De commissie adviseert dan ook om dit vaccin in te zetten bij publieke vaccinatieprogramma's gericht tegen COVID-19. Omdat het vaccin een boven verwachting hoge werkzaamheid heeft bij ouderen en de ziektelast als gevolg van COVID-19 het grootst is in deze groep, adviseert de commissie het BNT162b2-vaccin primair in te zetten voor ouderen vanaf 60 jaar.

4.1 Vaccinatie met BNT162b2

De ziektelast van COVID-19 is zodanig hoog dat op termijn alle volwassenen in Nederland, inclusief Caribisch Nederland, vaccinatie aangeboden krijgen. Een vaccin dat in een publiek vaccinatieprogramma wordt gebruikt, moet voldoen aan de criteria uit het beoordelingskader voor vaccinaties. De commissie concludeert dat vaccinatie met het BNT162b2-vaccin voldoet aan de criteria voor werkzaamheid, veiligheid en aanvaardbaarheid. Het vaccin wekt bij volwassenen, ouderen en medische risicogroepen een immuunrespons op die beschermt tegen COVID-19. De bijwerkingen die optreden zijn mild, van korte duur en van voorbijgaande aard, zoals pijn op de plaats van de injectie en vermoeidheid. Omdat het vaccin kort geleden is ontwikkeld en recent is geregistreerd voor gebruik buiten een onderzoekssetting, zijn er nog geen gegevens beschikbaar over de duur van de werkzaamheid en de effectiviteit. Ook zijn er geen gegevens over de kosteneffectiviteit van vaccinatie. De commissie kan daarom over deze criteria vooralsnog geen uitspraken doen. Desondanks adviseert zij het BNT162b2-vaccin in te zetten bij publieke vaccinatieprogramma's gericht tegen COVID-19, gezien de maatschappelijke ontwrichting die het gevolg is van deze infectieziekte.

Sinds enige tijd circuleert er een besmettelijker variant van het SARS-CoV-2-virus in het Verenigd Koninkrijk. Deze variant is ook in Nederland aangetroffen. Er zijn geen aanwijzingen dat het BNT162b2-vaccin minder werkzaam is bij deze variant.

4.2 Vaccinatiestrategie

De Gezondheidsraad heeft in november 2020 geadviseerd welke groepen als eerste in aanmerking komen voor vaccinatie tegen COVID-19.[6]
Er zijn verschillende strategieën beschreven, waarbij de keuze afhangt van de stand van wetenschap en de epidemiologische situatie. De huidige epidemiologische situatie heeft geleid tot maatschappelijke ontwrichting. Door de grote toestroom van COVID-19-patiënten naar de verpleeg- en IC-afdelingen van de ziekenhuizen staat het zorgsysteem onder druk. Enerzijds door de hoeveelheid patiënten, anderzijds door de uitval van zorgpersoneel. Een lockdown is van kracht om verdere verspreiding van het virus en de toestroom van patiënten te verminderen. Het gevolg is dat er ook op andere terreinen (indirecte) gezondheidsschade wordt geleden als gevolg van het afschalen van reguliere zorg en bijvoorbeeld

het sluiten van het onderwijs. Daarnaast is er sprake van een grote maatschappelijke en economische impact.

4.2.1 Strategie 1: verminderen ernstige ziekte en sterfte als gevolg van COVID-19

De commissie stelt vast dat in de huidige situatie de ziektelast, uitgedrukt in ernstige ziekte, sterfte, verloren levensjaren en DALY's als gevolg van COVID-19, het hoogst is bij ouderen vanaf 60 jaar. Daarnaast stelt de commissie vast dat de werkzaamheid van het BNT162b2-vaccin in ouderen boven verwachting is. Gegeven de zeer goede werkzaamheid van het BNT162b2-vaccin in ouderen en de zeer hoge ziektelast in deze groep, adviseert de commissie dit vaccin primair in te zetten voor ouderen vanaf 60 jaar, te beginnen bij de oudsten. Dit is in lijn met vaccinatiestrategie 1, zoals geformuleerd in het recente advies van de Gezondheidsraad over vaccinatiestrategieën. Door het vaccineren van ouderen vanaf 60 jaar met het BNT162b2-vaccin wordt de meeste gezondheidswinst behaald en wordt daarnaast de toestroom van COVID-19-patiënten naar de ziekenhuizen tegengegaan, wat de druk op de zorg zal verminderen. Er worden volgens planning verspreid over 2021 ongeveer 8,4 miljoen doses van het BNT162b2-vaccin geleverd, wat voldoende is om ongeveer 4,2 miljoen ouderen te vaccineren.

Vanwege de kwaliteitsborging en praktische overwegingen zal het BNT162b2-vaccin vooral ingezet worden op centrale vaccinatielocaties. De commissie adviseert om ouderen zo veel mogelijk naar deze locaties te laten komen, ondanks de logistieke implicaties die dit met zich meebrengt. Voor verpleeghuisbewoners en anderen die niet naar centrale locaties kunnen komen, adviseert de commissie te zoeken naar logistieke oplossingen. Mocht dat onmogelijk blijken, verwacht de commissie dat het vaccin van fabrikant Moderna uitkomst kan bieden. Dat vaccin is ook een mRNA-vaccin waardoor de werkzaamheid in ouderen vermoedelijk hoog is. De fabrikant heeft een hoge werkzaamheid gerapporteerd en het vaccin wordt inmiddels in de VS gebruikt. Het vaccin wordt naar verwachting binnenkort geregistreerd in Europa en volgens planning in het eerste kwartaal van 2021 geleverd. Het vaccin wordt in kleine hoeveelheden verpakt en hoeft niet diepgevroren bewaard te worden, waardoor het beter decentraal inzetbaar is.

Tot het moment dat deze groepen zelf gevaccineerd kunnen worden, kan de ring van zorgmedewerkers om hen heen gevaccineerd worden. Begin januari zal het vaccinatieprogramma starten met het vaccineren van zorgmedewerkers van verpleeghuizen, kleinschalige woonvormen, gehandicaptenzorg, wijkverpleging en Wmo-ondersteuning, waarbij gebruikgemaakt wordt van het BNT162b2-vaccin. Omdat de commissie het waarschijnlijk acht dat het vaccin een effect heeft op verspreiding, kan hiermee enige mate van bescherming worden bereikt bij deze medische risicogroepen. Het BNT162b2-vaccin zou volgens de commissie beperkt ingezet moeten worden om zorgpersoneel in de langdurige zorg te vacci-

neren, namelijk zolang de medische risicogroepen die zij verzorgen niet zelf gevaccineerd kunnen worden. Dit past binnen vaccinatiestrategie 1, zoals geformuleerd in het recente advies van de Gezondheidsraad over vaccinatiestrategieën.

4.2.2 Strategie 2: terugdringen van verspreiding van SARS-CoV-2

Omdat er nog geen zekerheid is over de mate waarin het BNT162b2-vaccin verspreiding kan tegengaan, stelt de commissie vast dat er op dit moment niet ingezet moet worden op een vaccinatiestrategie die gericht is op het terugdringen van verspreiding. Wanneer blijkt dat een van de ingekochte vaccins virusverspreiding tegengaat, is het voorstelbaar om dat vaccin in te zetten voor deze strategie. Daarmee kan een reproductie-getal (R) lager dan 1 worden bereikt of behouden. Er is echter model-leringsonderzoek nodig om te bepalen welke groep of groepen dan gevaccineerd moeten worden, welk effect daarmee bereikt kan worden en op welke termijn. De commissie beveelt dan ook aan reeds nu te beginnen met dit onderzoek. Daarnaast kunnen vaccins die beschermen tegen verspreiding, ook worden ingezet voor ringbescherming rondom gezondheidskundig kwetsbare mensen die zelf niet gevaccineerd kunnen worden.

4.2.3 Strategie 3: voorkomen van maatschappelijke ontwrichting

De huidige epidemiologische situatie heeft geleid tot ontwrichting van de zorgsector. Door het vaccineren van zorgmedewerkers in de langdurige zorg, waar begin januari mee wordt gestart, kan uitval van zorgpersoneel worden voorkomen. Naast het verkrijgen van ringbescherming kan met het vaccineren van deze groep dus ook de zorg in stand gehouden worden. Dit laatste is passend bij vaccinatiestrategie 3, zoals beschreven in het recente advies van de Gezondheidsraad over vaccinatiestrategieën. Om de hoogste nood te verhelpen op plaatsen waar acute gezondheids-schade optreedt door uitval in de curatieve zorg, zou het BNT162b2-vaccin heel selectief ingezet kunnen worden voor zorgmedewerkers van bijvoorbeeld spoedeisende hulp en IC. Volgens de commissie zou het vaccin van AstraZeneca uitkomst kunnen bieden voor alle zorg-medewerkers. Het vaccin komt volgens de huidige leveringsschema's beschikbaar in het eerste kwartaal van 2021 en wordt direct in een grote hoeveelheid van 4,5 miljoen doses geleverd, waarmee ruim 2 miljoen mensen kunnen worden gevaccineerd.

4.3 Registratie

Een essentieel onderdeel van het vaccinatieprogramma tegen COVID-19 is volgens de commissie registratie van wie, wanneer, welk vaccin heeft ontvangen. Vooralsnog kan alleen het BNT162b2-vaccin toegediend worden, maar er zullen, als alles verloopt volgens planning, snel nieuwe vaccins bijkomen. Registratie is noodzakelijk om mensen uit te kunnen nodigen voor hun tweede dosis vaccin, maar ook om inzicht te krijgen in de vaccinatiegraad, effectiviteit, impact en veiligheid van de vaccins. Omdat de vaccins kort geleden zijn ontwikkeld, zijn er nog geen gegevens

over eventuele bijwerkingen op lange termijn of eventuele zeer zeldzame ernstige bijwerkingen. Monitoring en onderzoek van de veiligheid dienen dan ook te gebeuren.

4.4 Vooruitzichten

Hoewel vaccinatie een belangrijk middel is om het SARS-CoV-2-virus te bestrijden, zijn er op korte termijn geen grote effecten te verwachten voor de bevolking als geheel. Dit komt allereerst doordat er vooralsnog relatief weinig doses vaccin beschikbaar komen, waardoor slechts een klein deel van de bevolking gevaccineerd wordt. Daarnaast is nog niet duidelijk welk effect vaccineren heeft op de verspreiding van het virus.
Naarmate er meer groepen in de bevolking gevaccineerd zijn, is een groter effect te verwachten. Het is van belang om nauwgezet te monitoren en te onderzoeken hoe groot de effecten van de verschillende vaccins zijn op het reduceren van ziektelast en het voorkomen van verdere verspreiding van het virus.

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De Gezondheidsraad ontvangt de meeste adviesvragen van de bewindslieden van Volksgezondheid, Welzijn en Sport; Infrastructuur en Waterstaat; Sociale Zaken en Werkgelegenheid en Landbouw, Natuur en Voedselkwaliteit. De raad kan ook op eigen initiatief adviezen uitbrengen, en ontwikkelingen of trends signaleren die van belang zijn voor het overheidsbeleid.
De adviezen van de Gezondheidsraad zijn openbaar en worden als regel opgesteld door multidisciplinaire commissies van – op persoonlijke titel benoemde – Nederlandse en soms buitenlandse deskundigen.

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The Race to Develop the Pfizer-BioNTech COVID-19 Vaccine: From the Pharmaceutical Scientists' Perspective

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Abstract

At the outset of the coronavirus disease 2019 (COVID-19) pandemic, it was clear that a vaccine would be crucial for global health efforts. The Pfizer and BioNTech teams came together in a race against the virus, working to design, test, manufacture, and distribute a safe and efficacious vaccine in record time for people around the world. Here, we provide backstory commentary from the pharmaceutical scientist perspective on the challenges and solutions encountered in the development of the Pfizer-BioNTech mRNA COVID-19 vaccine (BNT162b2; b2; Comirnaty®; tozinameran). We discuss the foundational science that led to the decision to use an mRNA-based approach. We also describe key challenges in the identification of an optimal vaccine candidate and testing in clinical trials, the continuous efforts to improve the vaccine formulation in response to changing global health priorities and facilitate vaccine accessibility, and how vast quantities of vaccine doses were manufactured and safely delivered to every corner of the globe, all without compromising quality, science, and safety. The key to successfully delivering a safe and efficacious vaccine within nine months was a result of extraordinary, real-time, parallel effort and across-the-board collaboration between stakeholders on a global scale.

Keywords: Global Health, Lipid Nanoparticles, mRNA, Vaccine, Vaccine delivery

Abbreviations: CDMO, contract development and manufacturing organization; CMA, Conditional Marketing Authorization; COVID-19, coronavirus disease 2019; CTA, clinical trial applicatior EMA, European Medicines Agency; EUA, Emergency Use Authorization; GMP, Good Manufac

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Practice; IVT, *in vitro* transcription; mRNA, messenger RNA; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; FDA, Food and Drug Administration; WHO, World Health Organization

Introduction

Each stage of vaccine development, spanning pre-clinical and clinical research and testing, regulatory approvals, manufacturing, and successful distribution, has inherent challenges under the best of circumstances. These steps typically occur sequentially and usually take years to accomplish. During a pandemic, when *time is life* [1] and the need for an expedited and successful process is heightened, overcoming challenges in a safe and swift manner becomes a matter of great public health concern.

News broke of a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) spreading globally in late 2019, and the gravity of the subsequent disease it caused (coronavirus disease 2019, COVID-19) was soon realized in the subsequent months. On March 11, 2020, the World Health Organization (WHO) declared a pandemic, and on March 13, 2020, Pfizer announced their partnership with BioNTech to co-develop a messenger RNA (mRNA)-based vaccine to prevent COVID-19.[2, 3] Both companies, which had an existing partnership to develop an mRNA-based influenza vaccine, signed a letter of intent on March 17, 2020 to join hands in the race against the virus and immediately commence the joint COVID-19 vaccine development program (Project Lightspeed).[3, 4]

Here, from the pharmaceutical scientists' perspective, we describe some of the challenges encountered during the development of the Pfizer-BioNTech mRNA COVID-19 vaccine (BNT162b2; b2; Comirnaty®; tozinameran) on a hyper-expedited timeline (Fig. 1), and the solutions utilized to successfully bring the first COVID-19 vaccine (and the first mRNA-based vaccine) to patients within nine months without compromising quality, science, and safety. This endeavor is the result of an unprecedented effort by thousands of individuals working collaboratively across Pfizer and BioNTech, who continue to respond to the evolving global status of COVID-19.

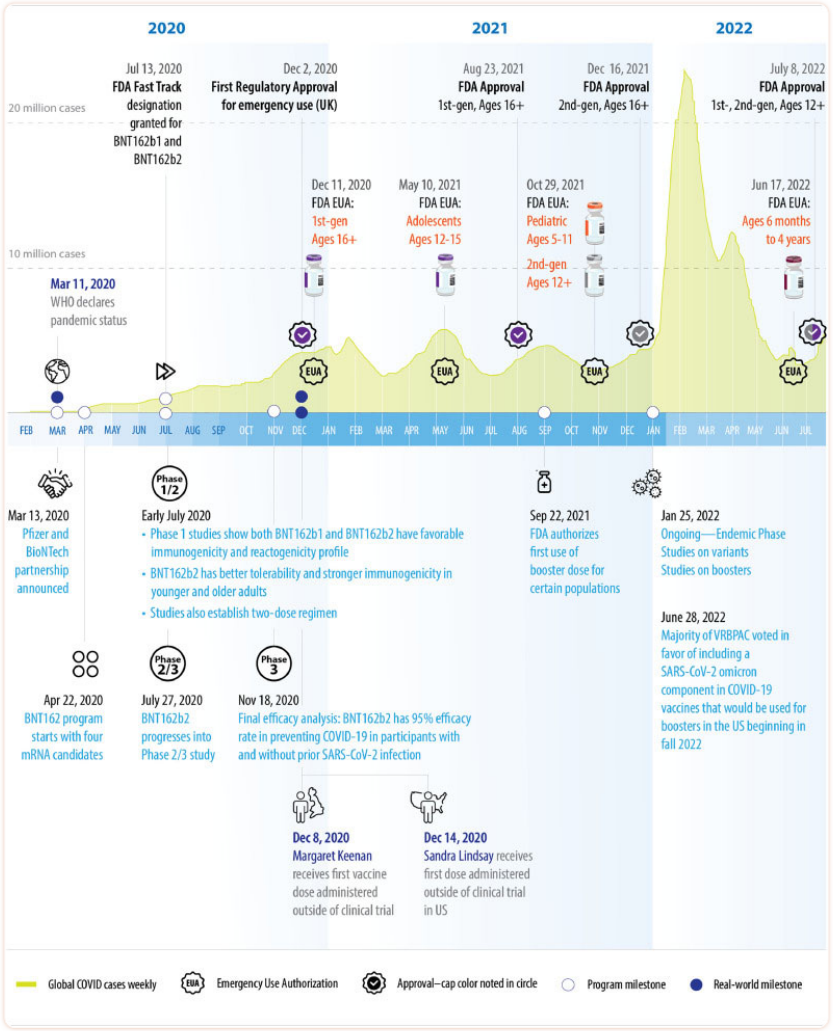

Fig. 1

Timeline of key events.[1,2,5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]

Figure shows US FDA milestones; other country approvals not shown for simplicity.

mRNA as the Vaccine Technology Platform of Choice for the Pfizer-BioNTech COVID-19 Vaccine

There are many available vaccine technology platforms which the vaccine development team could have explored, including adenovirus, recombinant proteins, conjugation, and mRNA.[1] mRNA vaccine technology quickly arose as the most viable path forward for COVID-19, as this approach has a more rapid manufacturing process and would enable a swifter response. While many think of mRNA-based vaccine technology as new, scientists have been studying this vaccine platform for decades prior to the breakthroughs brought about during the COVID-19 pandemic leading to the approvals of the first mRNA-based vaccines.[16] mRNA was discovered in 1947-1961, and its ability to be transported to mouse/human cells in liposomes to induce protein expression was discovered in the late 1980s. The therapeutic potential of mRNA was subsequently realized in a range of

applications, including viral vaccines in which mRNA is packaged in a viral vector.[17] As mRNA is structurally unstable and can easily be degraded by ubiquitous RNAase enzymes, mRNA-based vaccine technology has been continually refined, for example, the backbone of the mRNA molecules can be modified to improve stability. Some modified mRNA formats include nucleoside-modified mRNA, uridine-containing mRNA, and self-amplifying mRNA.[17, 18]

To achieve therapeutic effects, mRNA requires safe, effective, and stable delivery systems that protect it from degradation and allow for cellular uptake and release at the specific target cell. One such delivery system that has been successfully utilized are lipid nanoparticles.[17] Previous studies had indicated that modified mRNA encapsulated in a lipid nanoparticle delivery system mobilizes a broader range of immune responses (both humoral and cellular) compared to traditional vaccine platforms.[1]

Other advantages of using synthetic mRNA in a lipid nanoparticle delivery system as the vaccine platform include that it is chemically defined, minimizes risk of anti-vector immunity, permits quick modifications for new variants and boosters, and enables rapid development and quick production scaling compared to traditional vaccine technologies.[19] Part of this ability for rapid development/production was derived from (1) prior mRNA platform knowledge from an earlier collaboration between Pfizer and BioNTech for influenza, and (2) prior experience in manufacturing critical starting raw material (plasmid DNA) from Pfizer's Gene Therapy Program. With all advantages and challenges considered and fueled by the urgent need for a safe and effective COVID-19 vaccine in the face of increasing infection rates and death tolls, the Pfizer vaccine development team moved forward with an mRNA-based approach in partnership with BioNTech.

Challenges and Solutions in the Development of the COVID-19 Vaccine

Developing a vaccine for a novel virus involves many scientific challenges including scaling vaccine production for global distribution, overcoming complex regulatory interfaces, and logistical hurdles. For the development of Comirnaty®, the challenges were abundant, with key challenges including (1) the identification of an optimal vaccine candidate and testing in clinical trials on an expedited timeline, (2) continually updating the vaccine formulation to respond to changing global health priorities, (3) sourcing vast quantities of raw materials for manufacturing, and (4) ensuring quality control across all global sites. Throughout, effective collaborations with regulatory bodies were crucial for bringing the vaccine to patients quickly while prioritizing safety and regulatory compliance. Here, we describe the solutions utilized in collaboration with BioNTech and many key partners to develop, manufacture, and distribute Comirnaty®.

Identification of the Vaccine Candidate and Clinical Trial Challenges

To identify a single lead vaccine candidate more quickly, the team initially pursued a diverse set of four constructs in parallel, each representing different mRNA formats and target antigens.[1] In late April 2020, approximately one month after the partnership between Pfizer and BioNTech began, the phase 1/2 clinical trials were initiated in Germany (NCT04380701)[20] and the US (NCT04368728)[21] with the following constructs:

- BNT162b1 (b1): a nucleoside-modified mRNA targeting the smaller optimized receptor binding domain (RBD) from the spike protein of SARS-CoV-2.
- BNT162b2 (b2): a nucleoside-modified mRNA targeting the P2-mutated full spike protein (Fig. 2).

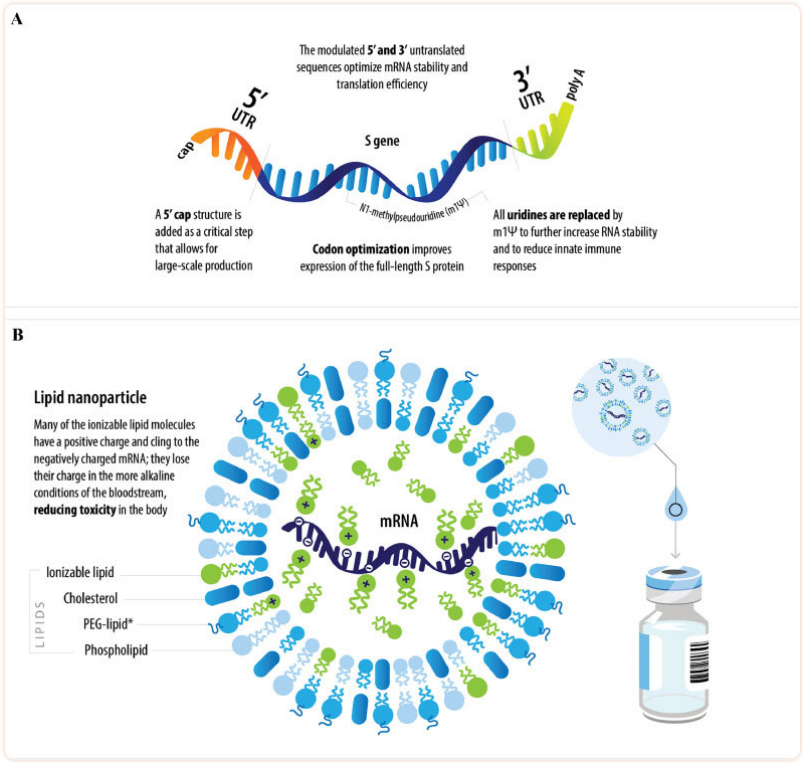

Fig. 2

Schematic of the BNT162b2 (A) mRNA and (B) lipid nanoparticle.

*Lipid attached to polyethylene glycol.

PEG, polyethylene glycol; S, spike; UTR, untranslated region.

- BNT162a1: an uridine-containing mRNA targeting the RBD from the spike protein.
- BNT162c2: a self-amplifying mRNA targeting the P2-mutated full spike protein.

The RBD-based candidates contain the domain of the spike protein that facilitates cellular attachment and is thought to be most important for eliciting antibodies that can inactivate the virus. The P2-mutated candidates encode a full-length spike with two-point mutations (proline substitutions) within the central helix; this mutation stabilizes the spike protein in a prefusion conformation for optimal expression and immunogenicity.[22] , [23] Each mRNA format is encapsulated in a lipid nanoparticle formulation (Fig. 2). In addition to these four diverse formats, different dose ranges were explored between 0.1 to 100 mcg depending on the type of construct.

Initial clinical data of the first vaccine candidate (b1) studied in the phase 1/2 trials were promising, and early predictions led to b1 being the anticipated candidate. However, emerging data on the second candidate b2 suggested it to have favorable reactogenicity in both younger and older participants in the phase 1 studies; earlier virus clearance and no evidence of virus in the lung in nonhuman primate challenge studies; and robust immunogenicity in both younger and older participants at the 30 mcg dose level.[24, 25] Based on these data, the team decided on July 27, 2020 to proceed with b2 at the dose of 30 mcg for the phase 2/3 study (NCT04368728).[24] Narrowing down to the b2 construct and 30 mcg dose was a data-derived decision, expedited by the strategy of pursuing multiple diverse options in parallel in early stages rather than working through candidates sequentially.

As the clinical trials progressed, vaccine supply challenges arose during the phase 3 trial, with a very tight hand-to-arm supply of clinical trial material. For example, there was only one contract development and manufacturing organization (CDMO) making lipid nanoparticles at the initiation of the phase 2/3 trial that had planned to enroll ~44,000 subjects. A typical expedited program development and manufacturing of phase 3 supplies can be 12 months or more depending on the molecule; for the COVID-19 vaccine, the timeline was ~4-5 months. Several mitigation approaches were used to ensure timely clinical supply, including: sourcing of drug substance and using PCR-based template for clinical trial materials from BioNTech; use of multi-dose vials in the trial to conserve doses; scaling out the lipid nanoparticle manufacturing process to ensure higher throughput; CDMO relationships to ensure back-to-back manufacturing slots for continuous clinical supply; ensuring availability of starting materials, critical raw materials, custom lipids, glass vials, etc., by undertaking at-risk large order contracts with vendors; multiple fill nodes within the Pfizer network to work around fill capacity constraints; use of Pfizer private jets to deliver samples, drug substance, and supply to clinical trial sites; and rapid turnaround on multiple round-the-clock amendments to clinical trial applications (CTAs) from regulatory authorities/Boards of Health.

Through use of these mitigation steps, coordinated collaboration, and prioritization of multiple stakeholders to ensure timely/adequate supplies, the clinical trials were successfully completed. On November 18, 2020, the results of the final efficacy analysis of the phase 3 study were announced: b2 met all primary efficacy endpoints with a favorable safety profile; the vaccine efficacy rate was 95% ($p<0.0001$) in participants without prior SARS-CoV-2 infection (first primary objective) and in participants with and without prior SARS-CoV-2 infection (second primary objective), measured from 7 days after the second dose.[14] The vaccine was shown to elicit both neutralizing antibody and cellular immune responses to the spike antigen, which may contribute to protection against COVID-19.[22] Based on these results, in December 2020, b2 became the first COVID-19 vaccine to be granted authorizations for emergency use. The first authorization was in the UK, followed shortly by the Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) and the Conditional Marketing Authorization (CMA) by the European Medicines Agency (EMA) (Fig. 1).[1, 26, 27]

Adapting Formulations to Evolving Global Health Priorities and Regulatory Interactions to Bring the Vaccine to Patients

The b2 vaccine is a white to off-white suspension for intramuscular injection (pH: 6.9-7.9).[7, 8, 9, 10, 22] It is formulated in lipid nanoparticles for delivery into host cells; the lipid nanoparticles are composed of four different lipids (ALC-0159, ALC-0315, cholesterol, and DSPC).[22] The vaccine formulations have evolved to address changing global health priorities and to simplify handling and storage to maximize vaccine availability and accessibility (Fig. 3). The cap colors for the multiple vaccine formulations now available were selected to help ensure vaccine administration sites differentiate between the formulations and intended patient group.

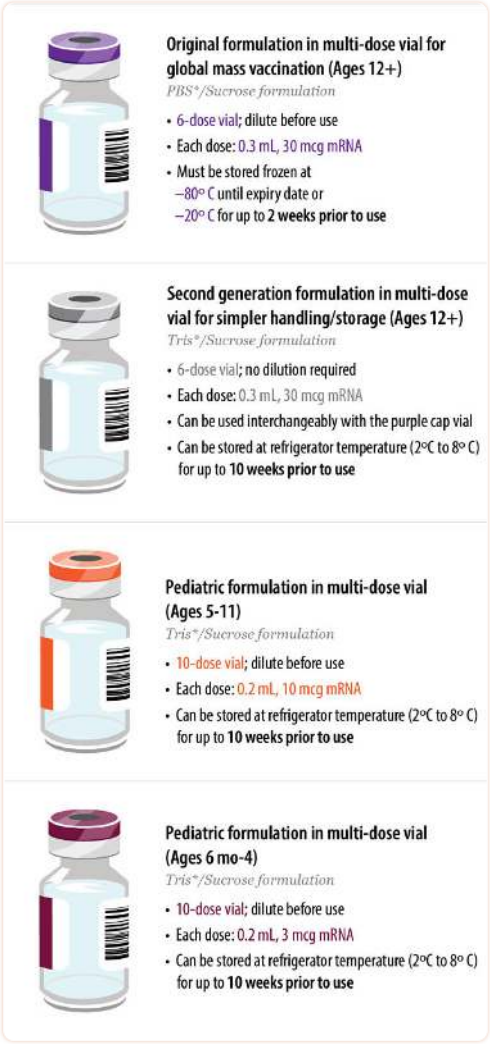

Fig. 3

Vaccine formulations evolved to address changing global priorities and needs.[7, 8, 9, 10]

*PBS and Tris are buffering agents that help maintain the pH and stability of the product.

The initial vaccine formulation uses a PBS (phosphate-buffered saline)/sucrose buffer to help maintain the pH and stability of the product, and is provided in 2 mL clear type I glass vials with a purple flip-off plastic cap and a stopper (synthetic bromobutyl rubber) with aluminum seal.[22] Prior to administration, the 0.45 mL vaccine concentrate requires dilution with sterile 0.9%

sodium chloride injection, USP. Each 0.3 mL dose contains 30 mcg of a nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2.[8] The vaccines are provided in multi-dose vials to maximize vaccine availability for mass global vaccinations.

The initial regulatory submissions took a conservative approach and indicated that each vial contained five doses of 0.3 mL.[25] To minimize potential wasted vaccine, this was later updated to six doses of 0.3 mL following feedback from frontline healthcare providers with the use of low dead-volume syringe/needle combination (with dead volume of no more than 35 μL) to enable the extraction of six doses per vial (this may not be possible with standard needles/syringes).[8, 22]

To ensure the quality and supply of the vaccines, a conservative approach was also taken for the initial global shipments following the initial authorizations in December 2020. Given the fragile nature of the mRNA vaccine, multi-dose vials were shipped in specially-designed thermal containers with real-time tracking during transport that can maintain ultra-low temperatures (-70°C ±10°C) for 10 days.[1] Initial authorizations required storage of undiluted frozen vials at ultra-low temperatures for up to 30 days, undiluted thawed vials at standard refrigerator temperature (2^0C to 8^0C) for up to 5 days, and diluted thawed vials at refrigerator temperature or room temperature for use within 6 hours. In February 2021, based on continuous stability data in efforts to increase/improve vaccine accessibility, the FDA authorized undiluted frozen vials to be transported and stored at -25°C to -15°C for up to 2 weeks, in addition to the ultra-low temperatures.[28] In May 2021, the FDA authorized longer storage of undiluted thawed vials at standard refrigerator temperatures, increasing from up to 5 days to up to 1 month.[8, 29] This would ensure the vaccine can be shipped and stored under increasingly flexible conditions and would also offer vaccine providers greater flexibility in how they manage their vaccine supply to remote areas.

To help simplify handling of the vaccine, a second-generation formulation of the vaccine was developed that does not require dilution prior to administration and allows for longer storage at standard refrigerator temperatures. The second-generation formulation (provided in multi-dose vials with gray caps) uses Tris (tromethamine) as the buffering agent, instead of PBS in the original purple cap formulation, and no longer contains sodium chloride and potassium chloride.[30] All other aspects, including the antigen and the lipids of the vaccine, remain unchanged. The Tris/sucrose formulation allows for longer storage at standard refrigerator temperatures: frozen vials can be thawed and stored at 2°C to 8°C for up to 10 weeks,[7] versus up to 1 month for the initial PBS/sucrose formulation.[8] Vials can also be stored at room temperature for up to 12 hours, versus 6 hours for the original PBS/sucrose formulation. The Tris/sucrose formulation was shown to be analytically comparable to the original PBS/sucrose formulation.[30] It received FDA authorization for emergency use in ages 12+ in October 2021 and received full FDA approval for ages 12+ in July 2022 (Fig. 1). The two formulations currently have the same FDA approvals and are approved to be used interchangeably for ages 12+.[7, 8]

The two pediatric formulations are based on the second-generation formulation using the Tris/sucrose buffer and require dilution with sterile 0.9% sodium chloride injection, USP to adjust dosage prior to administration.[9, 10] The orange cap vial for individuals aged 5 through 11 years was authorized for emergency use by the FDA in October 2021; each 0.2 mL dose contains 10 mcg of a nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2.[9] The maroon

cap vial for individuals aged 6 months through 4 years was authorized for emergency use by the FDA in June 2022; each 0.2 mL dose contains 3 mcg of the nucleoside-modified mRNA.[10] These pediatric vaccines are currently provided in multi-dose vials. Single-dose vials are being considered, so doses can be delivered on-demand at pediatrician offices.

Throughout the trials and development/refinement of the manufacturing process, a dialogue with various global regulatory agencies was crucial for ensuring vaccine deployment would not be stalled by regulatory roadblocks. Between April 2020 and April 2021 (the height of the pandemic), approximately 2100 queries were received from 24 markets. At the time of authoring this manuscript (July 2022), the number of queries have compounded to approximately 3255 from 49 markets. Innovative solutions were implemented to enable effective communication with FDA, EMA, and other health authorities, including proactive communications with health authorities, establishing rolling submission strategies with major health authorities, and aligning on a single, global EUA dossier applicable to most markets. In August 2021, Comirnaty® was approved in 70 global markets, and at the time of authoring this manuscript (July 2022) it has been launched in 186 markets globally.

Manufacturing, Distribution, and Quality Control on a Global Scale

It took approximately 3 months to transition from the first bench scale 10 mL *in vitro* transcription (IVT) reaction to the first production scale EUA drug product vial. In early 2021, following the initial authorizations, Pfizer had publicly committed to making 2.5 billion vaccine doses by the end of the year. For context, Pfizer's total vaccine production before COVID-19 was 200 million doses per year; the largest-volume vaccine before COVID-19 was the pneumococcal vaccine and it had taken a decade to reach the production levels at the time.[1] Preparations for large-scale manufacturing were made in parallel with preclinical research and clinical trials, even before the vaccine candidate was identified, in an effort to roll out the vaccine as quickly as possible.[1]

After careful assessment of complementary manufacturing capabilities and capacities across the network, the team devised a plan that would ensure safety and allow for optimal speed. Steps in the manufacturing of the mRNA drug substance and vaccine drug product are shown in Fig. 4 .[1] The plasmid DNA that would serve as the template for the mRNA in the vaccine is generated in Chesterfield St. Louis, Missouri, USA. Following subsequent purification steps, the purified template DNA is linearized and sent to Andover, Massachusetts, USA for the manufacture of the mRNA drug substance. At the Andover facility, the linearized template DNA is incubated with mRNA building blocks to create the mRNA drug substance, which is then purified and shipped for formulation and further processing to two of the largest sterile injectable manufacturing sites in the US (Kalamazoo, Michigan) and Europe (Puurs, Belgium). The use of two separate sterile injectable manufacturing facilities in separate countries was intentional, to build redundancy into the system in the event of interruptions at one facility, and as a precaution in the event of export restrictions. At the sterile injectable manufacturing facilities, the mRNA drug substance undergoes specialized mixing with raw materials to form the lipid nanoparticles and thus creating the vaccine drug product, which would be sterilized and filled into vials for inspection and packing into storage freezers.[1] In this multi-step commercial manufacturing process, the supply chain needed constant adjustment and recalibration to account for changing rate-limiting steps on a monthly basis. To

meet continued demand, the mRNA and lipid nanoparticle manufacturing process was expanded to include multiple manufacturing sites within the Pfizer and BioNTech networks, and additional partnerships with contract manufacturing organizations were established.

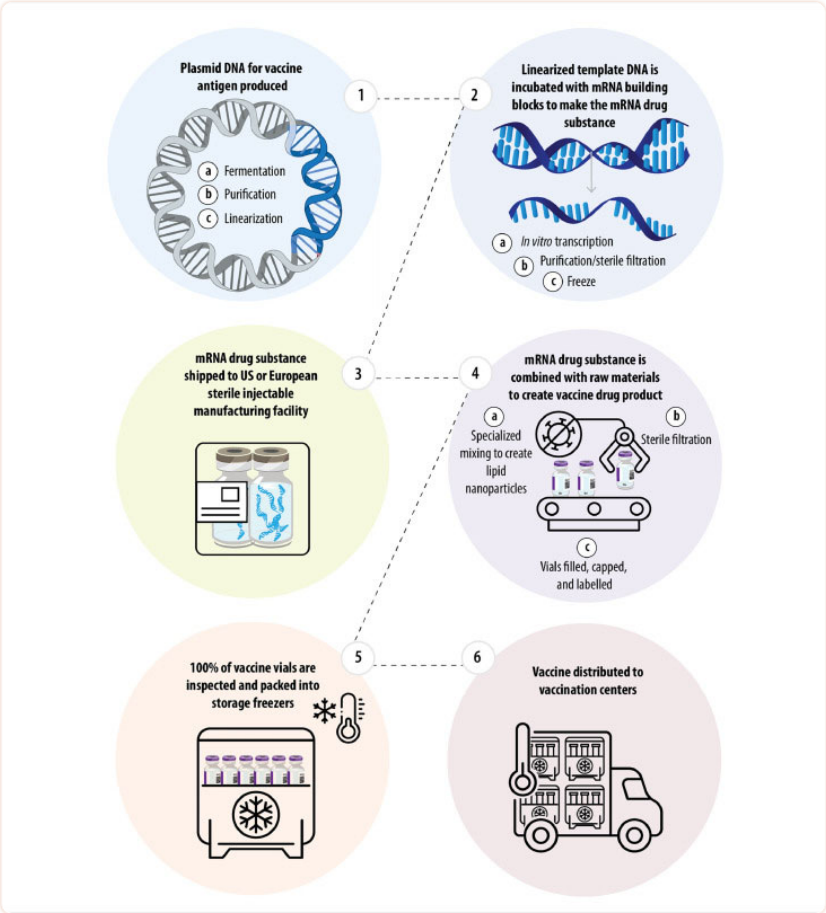

Fig. 4

Steps in the manufacturing of the mRNA drug substance and vaccine drug product.[1]

Ensuring the availability of the necessary quantity of raw materials/disposables needed for the mRNA, lipids, and other solutions for formulation at such a massive scale was a major concern. The four different lipids needed to synthesize the lipid nanoparticles (ALC-0159, ALC-0315, cholesterol, and DSPC) were a particular challenge to source, as two are proprietary and two are commodity. As these were new ingredients that were not used at scale in other vaccines, Pfizer began to produce the lipids internally to increase and ensure availability, in addition to production in close collaborations with the respective chemical companies. Obtaining vials and caps was also a challenge, with many vaccine suppliers vying for the same materials; leveraging existing relationships with suppliers was helpful in ensuring availability.[1]

In addition to the availability of raw materials at scale, focusing on Good Manufacturing Practice (GMP), the manufacturing team invented, designed, and ordered specialized formulation, storage, and transport tools, equipment, and software to prepare for the mass production/delivery of the first mRNA-based medical product.[1] Instrumentation was another challenge, as both analytical labs and mRNA process development labs had to be re-designed with key instrumentation and operational workflows managed under accelerated timelines.

It was also crucial to demonstrate appropriate and comparable product quality and stability across the global manufacturing network. A series of comprehensive comparability evaluations were executed to demonstrate comparable processes and product quality for materials manufactured across the global network. For example, computational fluid dynamics was utilized to conduct mixing similarly across different facilities. Drug substance and drug products manufactured at new sites and/or increased scale were demonstrated to be comparable to historical product lots through lot release data and heightened characterization testing. The active substance specifications contain tests for appearance, pH, content (RNA Concentration), Identity of Encoded RNA Sequence, RNA Integrity, 5'- Cap, Poly(A) Tail, Residual DNA Template, dsRNA, Bacterial Endotoxin and Bioburden.[31] The release and stability testing specifications for b2 finished product include tests for Appearance, Subvisible Particles, pH, Osmolality, LNP Size, LNP Polydispersity, RNA Encapsulation, RNA content, ALC-0315 content, ALC-0159 content, DSPC content, Cholesterol content, extractable volume, Lipid identities, Identity of encoded RNA sequence, Potency / in Vitro Expression, RNA Integrity, Bacterial Endotoxin, Sterility and Container Closure Integrity.[31] Stability data from lots manufactured across the global network informed appropriate product storage guidance which could be followed at all global sites.

Storage and transport of the vaccine at ultra-low temperatures was another challenge that required innovative solutions. The team would design and implement a temperature-controlled thermal shipper which could hold up to 5,850 vaccine doses in the size of a carry-on suitcase and record location, temperature, and light exposure in real time.[1] This logistical innovation could also serve as cold storage in settings without a suitable freezer. Pfizer also expanded 'freezer farms' at manufacturing plants around the world to house vaccine at appropriate temperatures;[1] this incredible effort involved significant innovations outside the scope of this article.

By the end of 2021, Pfizer had successfully manufactured over 3 billion vaccine doses, and more than 2.6 billion doses were delivered to 166 countries/territories.[32] At the time of authoring this manuscript (July 2022), 3.6 billion doses of the COVID-19 vaccine have been delivered to 180 countries and territories in every region of the world. Scaling up the manufacturing capabilities to hit these production targets was an enormous undertaking that required a dynamic and redundant supply chain, manufacturing precision, and unprecedented engineering and logistical efforts.

Conclusion and Future Outlook

In the first year of Comirnaty® rollout, it is estimated that the vaccine contributed to averting almost 9 million symptomatic cases, 700,000 hospitalizations, and over 110,000 deaths.[33] This was made possible by progressing our vaccine development program swiftly, going from the first 10

mL IVT reaction run to the first drug product lot with an EUA in 3 months (Fig. 5). Our team and collaborators did this while successfully ensuring the highest compliance and quality standards according to the normal vaccine development principles:[19]

1. The vaccine must be proven effective, meaning it can help prevent severe disease and hospitalizations in at least a majority of vaccinated people
2. The vaccine must be proven safe, with robust safety data generated from thousands of people
3. The vaccine must be consistently manufactured at the highest quality standards

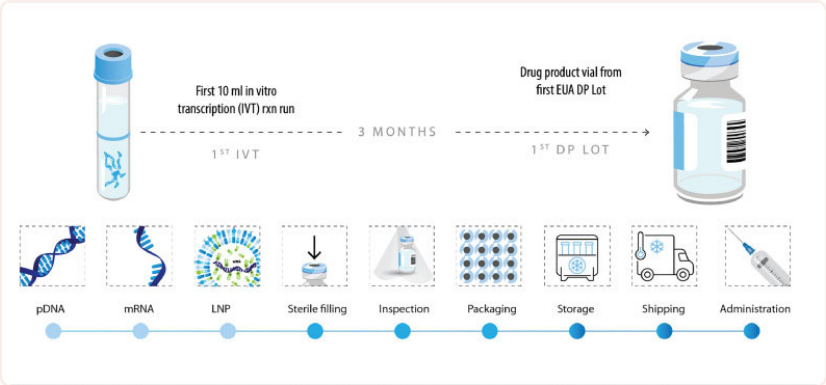

Fig. 5

The Comirnaty® development process was accelerated without compromising compliance or safety.

DP, drug product; EUA, Emergency Use Authorization; IVT, in vitro transcription; LNP, lipid nanoparticle; mRNA, messenger RNA; pDNA, plasmid DNA.

Throughout the process, a dialogue between the Pfizer-BioNTech development team, global regulatory agencies, and vaccine providers on-the-ground was crucial for raising practical challenges and addressing them appropriately. Such collaboration between scientific, medical, and policy stakeholders will remain essential as the pressing concerns of the COVID-19 pandemic continue to evolve. As SARS-CoV-2 transitions to an endemic virus, the healthcare system must adapt to a patient population with heterogeneous levels of prior immunity/exposure and the emergence of new viral variants. Ongoing studies aim to optimize booster vaccination strategies to continually offer all patients well-tolerated protection from severe COVID-19. As in the initial development of Comirnaty®, these ongoing/future studies will be built on a foundation of partnership across companies and countries, with a common goal of championing global health. We hope this collaborative spirit and transparent review of decision-making in the development of Comirnaty® proves useful to the broader scientific community for future vaccine development efforts.

Disclosures

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Productie 22

INSTITUT PASTEUR

DISCOVERY OF MESSENGER RNA IN 1961

NEWS | 2021.02.15

International

Since the beginning of the COVID-19 pandemic, words that just a year ago would have been the preserve of scientists have entered everyday language. One example is PCR, used for diagnostic tests. Another term that was once unfamiliar and is now on everyone's lips is messenger RNA, the miraculous molecule that has led to vaccines being administered to the general population less than a year after the start of the pandemic – bearing in mind that it previously took around a decade to develop a vaccine for a new disease. What exactly is this messenger RNA? Who discovered it, and when?

Our story starts sixty years ago, at the Institut Pasteur in Paris. For the past ten years, scientists had known that DNA, which makes up chromosomes, was the basis for heredity. Since 1953, based on their knowledge of the structure of DNA, identified by James Watson and Francis Crick, they had been aware that it carried a code determining the structure of proteins and that it was able to make an identical copy of itself with each cell division.

Regulation of gene expression

At the Institut Pasteur, a team including Jacques Monod, François Jacob and François Gros was looking into the mechanisms involved in reading genetic information. One question in particular caught their attention, and that was the regulation of gene expression. How was it that all the genes carried by the chromosome – in this case they were looking at a bacterium – were not expressed at the same time? For example, the enzymatic proteins needed to metabolize a sugar were only synthesized when that sugar was present in the culture medium.

Their research led them to the conclusion that the expression of the genes encoding these proteins was controlled by regulatory proteins whose activity was dependent on the presence of the sugar (the metabolite in figure 1 below). Jacob and Monod presented their findings in early 1961 in a seminal article (1) which earned them the Nobel Prize. They were particularly interested in the way in which the message carried by genes, by DNA, was transmitted to the protein synthesis site, on particles known as ribosomes.

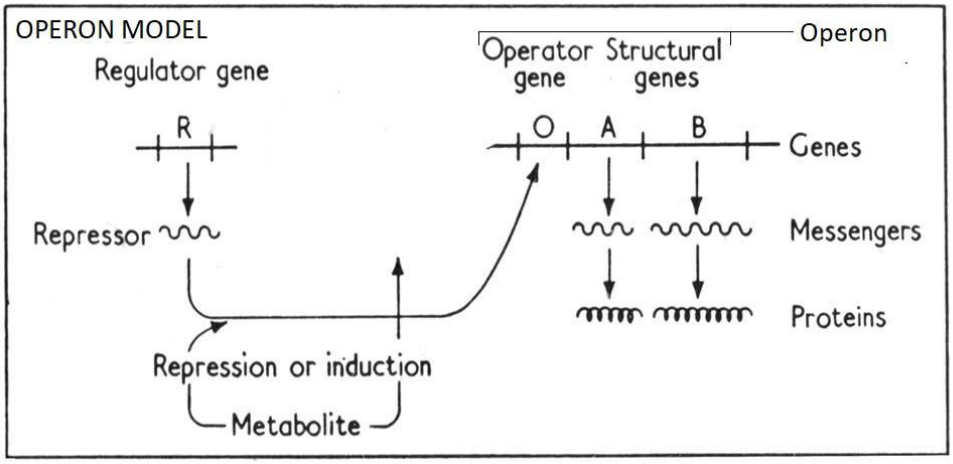


Figure 1 : The operon model. Credit : Institut Pasteur.

The hypothesis of messenger RNA

According to their theories, this transmission had to be performed by a type of RNA, which they termed "messenger RNA," a copy of the DNA sequence. Other theories had been put forward, including the idea that the DNA was directly read by ribosomes or that there were specific ribosomes for each gene. An experiment carried out by François Gros (see photo below) played a decisive role in confirming the

hypothesis of messenger RNA: when he added an RNA synthesis inhibitor to cultures, protein synthesis was immediately halted. This suggested that a type of RNA served as an intermediary in protein synthesis, and also indicated that this intermediary must be unstable, degraded by enzymes, because otherwise the protein synthesis would have continued for a while rather than stopping immediately.

The scientists now had to identify this messenger RNA – a particularly difficult task given its presumed instability.

François Gros in 1976 Credit: photo JP de Monceaux, Paris

Two similar experiments by François Gros and François Jacob on visits to US labs

François Gros explained (2) how he and François Jacob met in June 1960 in front of the central porch at the Institut Pasteur in Paris. They were both preparing to set off on short research trips to the United States – François Jacob to Matthew Meselson's laboratory at the California Institute of Technology in Pasadena, and himself to Jim Watson's lab at Harvard University. They had a brief discussion about the research they were intending to carry out during their research trips. While messenger RNA itself was not the immediate focus of their work, they would be looking into related subjects. And ultimately, in their respective laboratories, they both ended up proving the existence of messenger RNA. But for both scientists, the experience was anything but straightforward.

As François Gros described, "in Jim's laboratory, in the very austere Harvard University building flanked by two bronze rhinoceroses, there were some epic experiences! The laboratory was unbearably hot, the equipment virtually non-existent, the radiation counters were huge, antiquated, creaky machines. It wasn't unusual for our experiments to continue long into the night..."

François Jacob explained in his memoir *La statue intérieure* (The Statue Within) (3) that he was working with Sydney Brenner (from the Cavendish Laboratory at the University of Cambridge, who was also on a visit to Matthew S. Meselson's laboratory), with whom he had had many lively discussions in Britain and who had also come to spend the summer in Pasadena. " We were not succeeding. In vain did we try to check through the experiment, to modify it, to change a detail here and there. [...] But the gods were still against us. Nothing worked [in their bid to detect the elusive messenger RNA]. [...] There we were, collapsed on the sand, stranded in the sunlight like beached whales. My head felt empty. Frowning, knitting his heavy eyebrows, with a nasty look, Sydney gazed at the horizon without saying a word." It was a few days before the end of their stay. "Suddenly, Sydney gives a shout. He leaps up, yelling, "The magnesium! It's the magnesium!"." And he was right. Their experiments would only work by increasing the concentration of magnesium, since it stabilized the ribosomes.

Proof of the existence of messenger RNA

Back in Paris, François Gros and François Jacob were delighted to note that their results, obtained in laboratories some 5,000km apart, were very similar. The detection of messenger RNA required pulse labeling of growing bacteria with phosphate labeled with radioactive phosphorus, ^{32}P. Ultracentrifugation

experiments could then be used to find the ribosome-associated labeled RNA. Additional experiments, in particular showing that the RNA nucleotide sequence was complementary to the DNA sequences, enabled them to confirm that this RNA was indeed messenger RNA.

The articles published alongside each other in the same issue of *Nature* in May 1961 – François Gros was the first author of one article (4) and François Jacob the second author of the other (5) – officially marked the discovery of messenger RNA.

We can be sure that neither François Gros nor François Jacob could have imagined back in 1961 that, 60 years later, this highly unstable messenger RNA could be used to produce vaccines that are now being administered to the world's population to protect them against COVID-19. This was only made possible as a result of techniques developed by industry to stabilize the molecule, together with complex distribution processes, given the need to keep the vaccines at extremely low temperatures.

References:

1. Jacob F. and Monod J., "Genetic Regulatory Mechanisms in the Synthesis of Proteins," *J. Mol. Biol.* 3, 318-356 (1961).
2. Gros F., "L'Histoire du Messager." In *Hommage à Jacques Monod. Les origines de la biologie moléculaire.* Presented by André Lwoff and Agnès Ullmann. Éditions Études vivantes, Academic Press, 1980. pp. 121-128. English versions of this book were published in 1979 by Academic Press and in 2004 by the American Society of Microbiology.
3. Jacob F., *La Statue intérieure*. Odile Jacob (1987).
4. Gros F., Hiatt H., Gilbert W., Kurland C.G., Risebrough R.W. and Watson J.D., "Unstable Ribonucleic Acid Revealed by Pulse Labelling of Escherichia Coli," *Nature*, 190, 581-585 (1961).
5. Brenner S., Jacob F. and Meselson M, "*An Unstable Intermediate Carrying Information from Genes to Ribosomes for Protein Synthesis*," *Nature*, 190, 576–81 (1961).

Find out more about the discovery of messenger RNA:

https://webext.pasteur.fr/biblio/expos/operon/posters/expoOPERON6.pdf

For more information, please visit **Concernant la découverte de l'ARN messager :**

Productie 23

Our History

Based on profound scientific know-how, we are ushering in a new era of immunotherapy

For decades, most researchers overlooked messenger RNA (mRNA) because it was considered far too unstable, and no proper solution existed to administer or guide it to the right cells in the body. In early research, it was difficult to achieve the desired levels of immune response and the production of the targeted proteins was too low to make mRNA a suitable candidate for drug development and medical applications. Over more than 30 years, our co-founders defied conventional beliefs and achieved a series of scientific and technological breakthroughs to unlock the full potential of mRNA.

In 2020, we leveraged our mRNA technology to develop a COVID-19 vaccine which became the **first mRNA drug approved for human use** and the fastest vaccine developed against a new pathogen in the history of medicine.

Relentless scientific rigor driving innovation

With their work, Ugur Sahin and Özlem Türeci solved the basic mRNA-associated problem, namely the issue of low and short-lived protein production. In parallel, Katalin Karikó approached the emerging technology from another angle and found that the immunogenicity of mRNA could be mitigated effectively by modifying the nucleotide uridine. Discovery by discovery, improvement by improvement, the company's scientific teams harnessed the power of mRNA while exploring new and exciting ways to deploy it.

To date, the scientists behind BioNTech have optimized the structural components of mRNA (cap, the poly-A tail and its untranslated regions) to achieve increased intracellular stability of synthetic mRNA and translation, especially in immune cells. The rapid development of our COVID-19 vaccine was only possible because we were able to build on the research, expertise and technology that we have accumulated over decades.

BioNTech was founded on the idea of using mRNA to activate the immune system against a patient's individual tumor – an approach that we believe can also be tailored to target several kinds of diseases. Through our groundbreaking R&D efforts, we have become a pioneer in many ways:

Developed the **first vaccines using non-nucleoside modified RNA for personalized cancer therapies targeting a patient's unique tumor**, with the first patient being dosed in a clinical trial in 2012.

Developed RNA vaccine nanoparticle **delivery strategies that target tissue-derived dendritic cells body-wide** to increase the immune response. We moved from animal studies to clinical trials in humans, **pioneering the first intravenous nanoparticle delivery of mRNA vaccines in humans in 2015.**

- Discovered and identified several fundamental approaches to induce a comprehensive immune response, improving the potency of mRNA technology by 1,000-fold.
- Developed a nanoparticle-based delivery strategy for mRNA vaccines targeting antigen-presenting cells body-wide, allowing intravenous administration.
- Advanced an individualized mRNA-based cancer immunotherapy into clinical trials.
- Established a proprietary, easily scalable manufacturing process for mRNA products.

The basis of the first mRNA vaccine

From the very beginning, our co-founders have been focused on building a fully-integrated immunotherapy leader deeply rooted in science.

Scientific Breakthroughs

2006

Improvements to the non-coding regions increasing the stability and translational efficiency of RNA molecules in dendritic cells

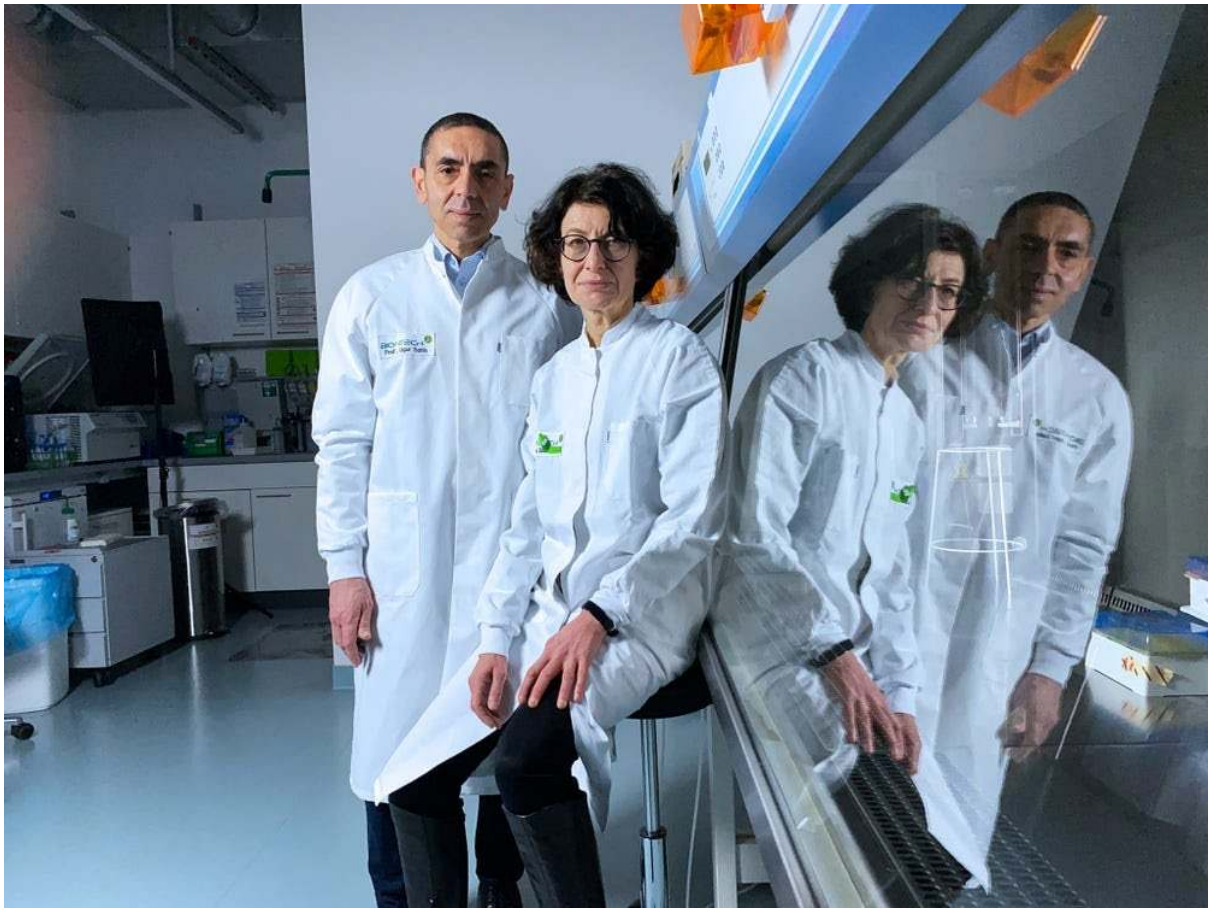
Read the publication

Scientific Breakthroughs

2008

Engineering RNA to route the encoded cargo to specific places within the cell which increases the CD8 and CD4 response significantly

Read the publication



Business Development

2008

BioNTech is founded by Prof. Ugur Sahin, M.D., Prof. Özlem Türeci, M.D., and Prof. Christoph Huber, M.D., to develop and produce treatments for individualized cancer immunotherapy. (Seed round 180m USD)

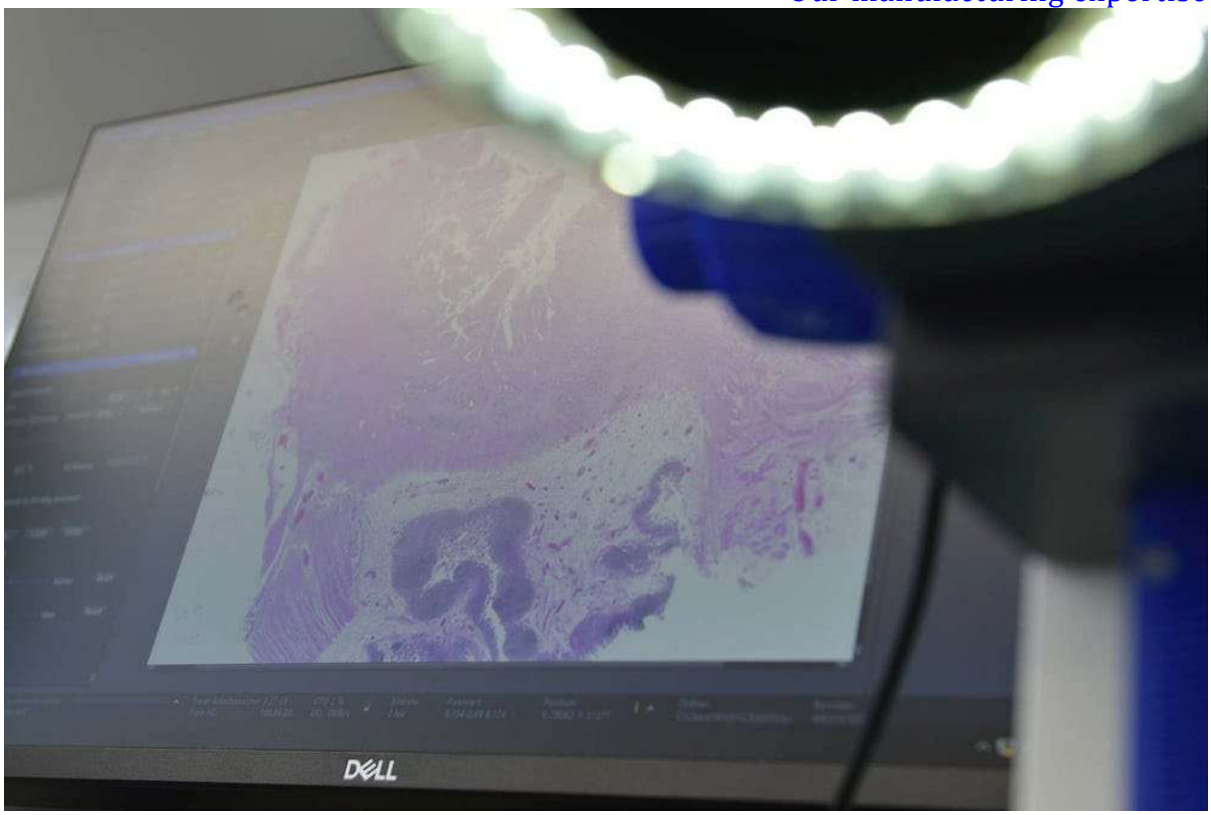
View management

Business Development

2009

BioNTech acquires EUFETS and JPT Peptide Technologies

Our manufacturing expertise

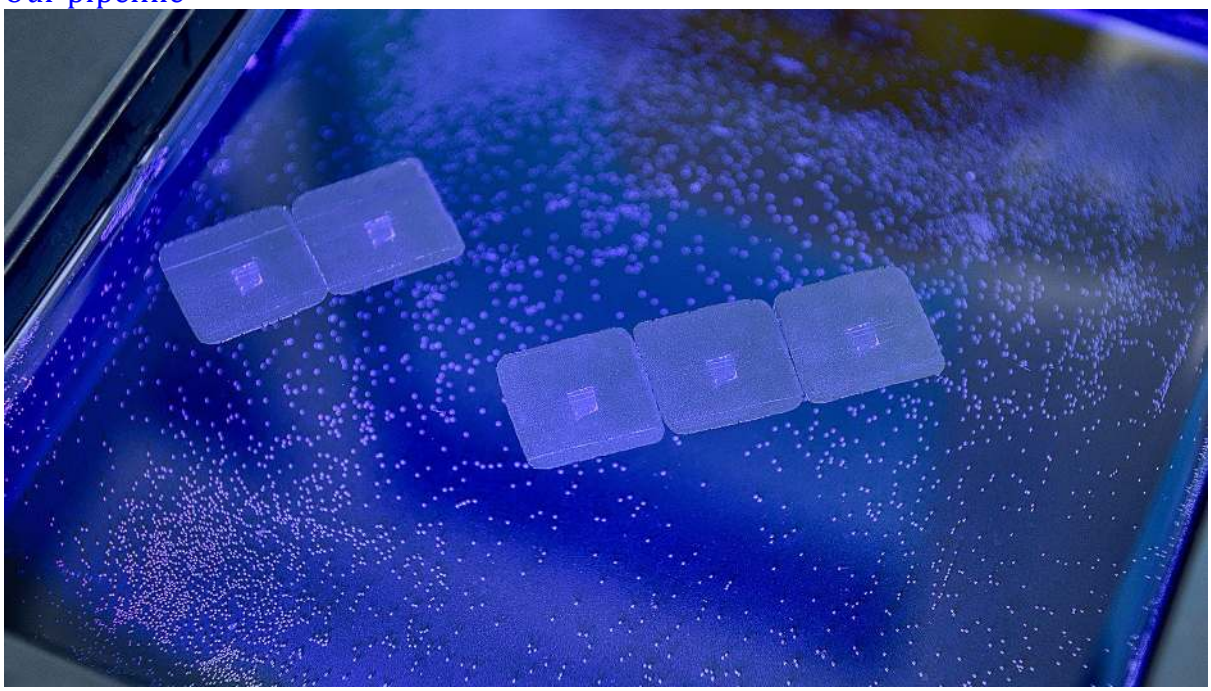


Scientific Breakthroughs

2012

Start of the first Phase 1 clinical trial with RNA immunotherapy in melanoma, today known as our FixVac approach

Our pipeline



Scientific Breakthroughs

2014

Start of the first Phase 1 clinical trial with a fully individualized RNA immunotherapy in melanoma, today known as the iNeST approach

Our pipeline

Business Development

2014-2018

Strategic collaborations across the pipeline (Bayer Animal Health, Genentech, a member of the Roche Group, Genmab, Siemens, Sanofi, Regeneron, Genevant, Pfizer, University of Pennsylvania)

Our collaborators

Scientific Breakthroughs

2015

RNA cancer immunotherapy data published in *Nature.*

In addition, we pioneered the first intravenous nanoparticle delivery of mRNA vaccines in humans

Read more

Scientific Breakthroughs

2016

First results of intravenous administered mRNA clinical trial published in *Nature*

Read more

Scientific Breakthroughs

2017

1. mRNA-encoded bispecific antibodies data published in *Nature Medicine*

2. iNeST clinical results published in *Nature*

More publications

Business Development

2018

Completion of 270 million USD Series A financing round

Read more

Business Development

2019

BioNTech becomes a publicly traded company on the NASDAQ Global Select Market under the ticker symbol BNTX

Read more

Business Development

2020

Beginning of “Project Lightspeed” to quickly develop a safe and effective vaccine to address the emerging SARS-CoV-2 pandemic. The Pfizer-BioNTech COVID-19 vaccine is the first vaccine to receive emergency use authorization following a worldwide Phase 3 trial

Project Lightspeed

Business Development

2020

Acquisition of Neon Therapeutics to bolster our global leadership position in T cell therapies and open US headquarters

Read more

Scientific Breakthrough

2020

Pfizer and BioNTech achieve first authorization in the world for a vaccine to combat COVID-19

Business Development

2020

Establishment of BioNTech Manufacturing Marburg to produce COVID-19 vaccine, which became one of the largest mRNA manufacturing facilities in 2021

Marburg Manufacturing Fact Sheet

Business Development

2021

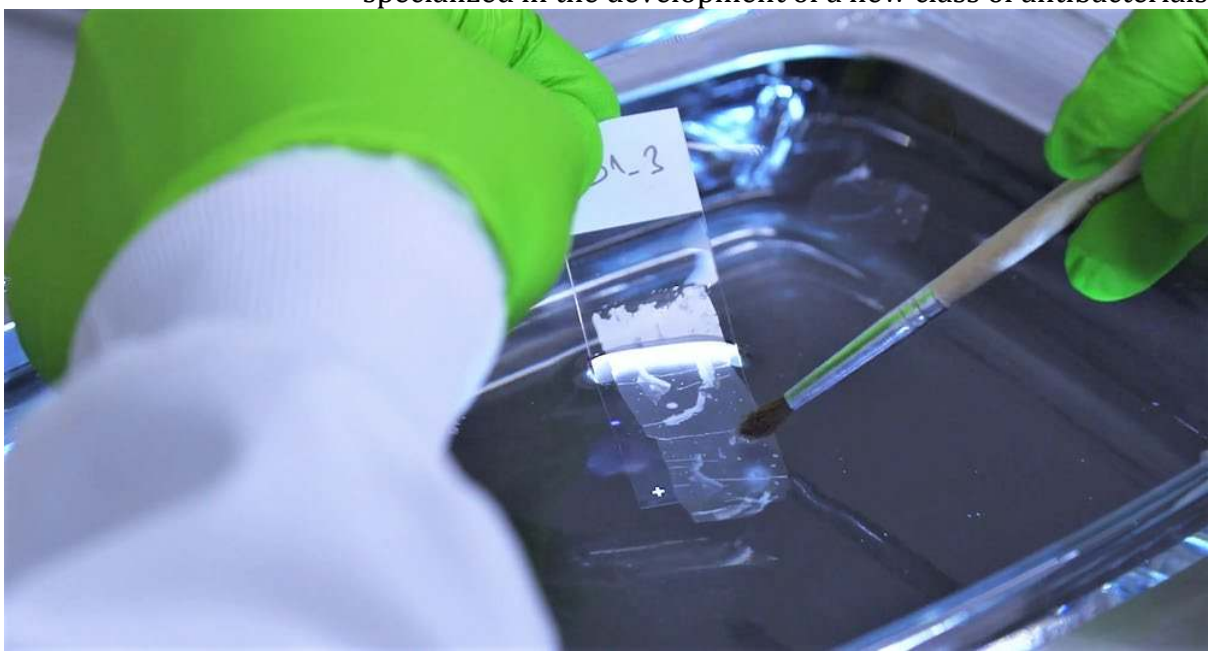
BioNTech acquires Kite’s neoantigen T cell receptor (TCR) R&D platform and clinical manufacturing facility in Gaithersburg, MD

Read more

Business Development

2021

BioNTech acquires PhagoMed BioPharma GmbH, an Austrian biotechnology company specialized in the development of a new class of antibacterials



Scientific Breakthrough

2021

The first colorectal cancer patient was treated with the individualized mRNA cancer vaccine candidate BNT122 in a Phase 2 clinical trial

Business Development

2022

Introduction of first modular mRNA manufacturing facility to promote scalable vaccine production in Africa, called BioNTainer

Read more

Scientific Breakthrough

2022

BioNTech presents positive preliminary Phase 1/2 data for first-in-class CAR-T program BNT211

Business Development

2022

Groundbreaking for BioNTech's first mRNA vaccine manufacturing facility in Africa

Scientific Breakthrough

2022

Phase 1 clinical trial for malaria vaccine program BNT165 initiated

Read also

Our Pipeline

We have built a unique pipeline of investigational immunotherapies and vaccines based on multiple drug classes aiming to achieve medical breakthroughs

Our pipeline

Scientific Publications

We maintain a culture of scientific excellence and drive future innovation by sharing our key findings in a peer reviewed format

Our publications

Our Team

Our team of first-movers and entrepreneurs in the fields of immunology and oncology is dedicated to ushering in a new era of immunotherapies

Our management

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Company

Quick Links

Productie 24

Press release

English
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Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Press release

2023-10-02

The Nobel Assembly at Karolinska Institutet

has today decided to award

the 2023 Nobel Prize in Physiology or Medicine

jointly to

Katalin Karikó and Drew Weissman

for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19

The discoveries by the two Nobel Laureates were critical for developing effective mRNA vaccines against COVID-19 during the pandemic that began in early 2020. Through their groundbreaking findings, which have fundamentally changed our understanding of how mRNA interacts with our immune system, the laureates contributed to the unprecedented rate of vaccine development during one of the greatest threats to human health in modern times.

cines before the pandemic

Vaccination stimulates the formation of an immune response to a particular pathogen. This gives the body a head start in the fight against disease in the event of a later exposure. Vaccines based on killed or weakened viruses have long been available, exemplified by the vaccines against polio, measles, and yellow fever. In 1951, Max Theiler was awarded the Nobel Prize in Physiology or Medicine for developing the yellow fever vaccine.

Thanks to the progress in molecular biology in recent decades, vaccines based on individual viral components, rather than whole viruses, have been developed. Parts of the viral genetic code, usually encoding proteins found on the virus surface, are used to make proteins that stimulate the formation of virus-blocking antibodies. Examples are the vaccines against the hepatitis B virus and human papillomavirus. Alternatively, parts of the viral genetic code can be moved to a harmless carrier virus, a "vector." This method is used in vaccines against the Ebola virus. When vector vaccines are injected, the selected viral protein is produced in our cells, stimulating an immune response against the targeted virus.

Producing whole virus-, protein- and vector-based vaccines requires large-scale cell culture. This resource-intensive process limits the possibilities for rapid vaccine production in response to outbreaks and pandemics. Therefore, researchers have long attempted to develop vaccine technologies independent of cell culture, but this proved challenging.

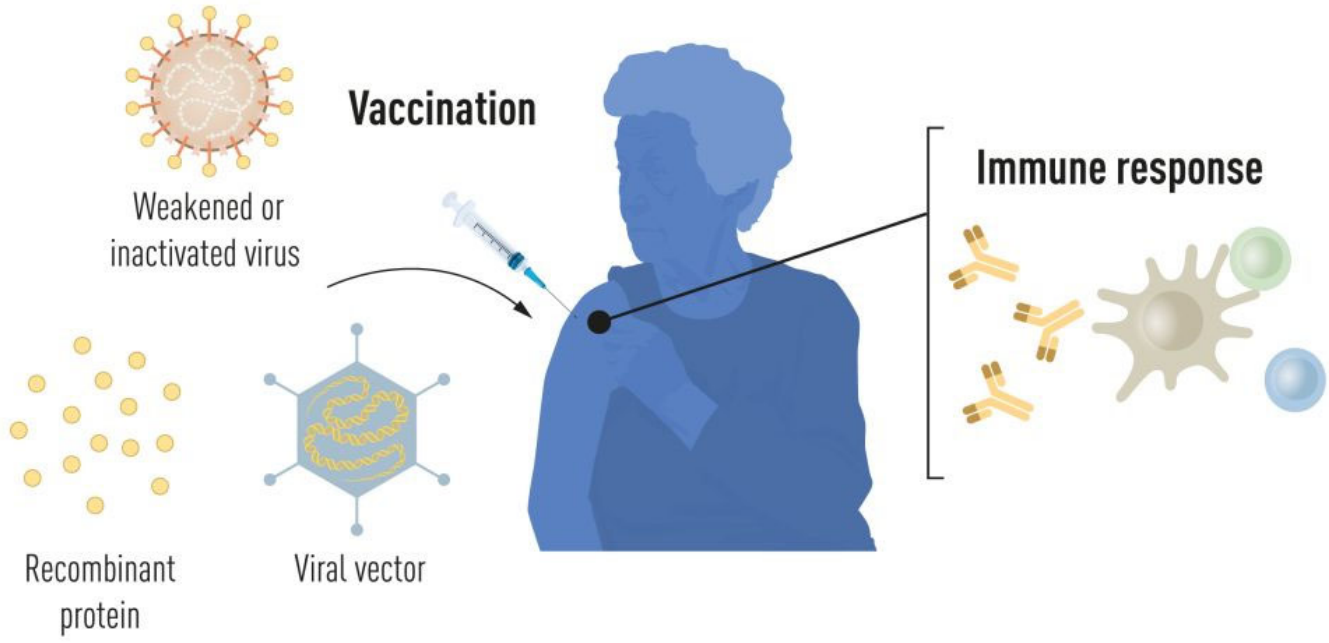

Figure 1. Methods for vaccine production before the COVID-19 pandemic.

© The Nobel Committee for Physiology or Medicine. Ill. Mattias Karlén

mRNA vaccines: A promising idea

In our cells, genetic information encoded in DNA is transferred to messenger RNA (mRNA), which is used as a template for protein production. During the 1980s, efficient methods for producing mRNA without cell [illegible]e were introduced, called *in vitro* transcription. This decisive step accelerated the development of [illegible]ular biology applications in several fields. Ideas of using mRNA technologies for vaccine and

therapeutic purposes also took off, but roadblocks lay ahead. *In vitro* transcribed mRNA was considered unstable and challenging to deliver, requiring the development of sophisticated carrier lipid systems to encapsulate the mRNA. Moreover, *in vitro*-produced mRNA gave rise to inflammatory reactions. Enthusiasm for developing the mRNA technology for clinical purposes was, therefore, initially limited.

These obstacles did not discourage the Hungarian biochemist Katalin Karikó, who was devoted to developing methods to use mRNA for therapy. During the early 1990s, when she was an assistant professor at the University of Pennsylvania, she remained true to her vision of realizing mRNA as a therapeutic despite encountering difficulties in convincing research funders of the significance of her project. A new colleague of Karikó at her university was the immunologist Drew Weissman. He was interested in dendritic cells, which have important functions in immune surveillance and the activation of vaccine-induced immune responses. Spurred by new ideas, a fruitful collaboration between the two soon began, focusing on how different RNA types interact with the immune system.

The breakthrough

Karikó and Weissman noticed that dendritic cells recognize *in vitro* transcribed mRNA as a foreign substance, which leads to their activation and the release of inflammatory signaling molecules. They wondered why the in *vitro* transcribed mRNA was recognized as foreign while mRNA from mammalian cells did not give rise to the same reaction. Karikó and Weissman realized that some critical properties must distinguish the different types of mRNA.

RNA contains four bases, abbreviated A, U, G, and C, corresponding to A, T, G, and C in DNA, the letters of the genetic code. Karikó and Weissman knew that bases in RNA from mammalian cells are frequently chemically modified, while *in vitro* transcribed mRNA is not. They wondered if the absence of altered bases in the *in vitro* transcribed RNA could explain the unwanted inflammatory reaction. To investigate this, they produced different variants of mRNA, each with unique chemical alterations in their bases, which they delivered to dendritic cells. The results were striking: The inflammatory response was almost abolished when base modifications were included in the mRNA. This was a paradigm change in our understanding of how cells recognize and respond to different forms of mRNA. Karikó and Weissman immediately understood that their discovery had profound significance for using mRNA as therapy. These seminal results were published in 2005, fifteen years before the COVID-19 pandemic.

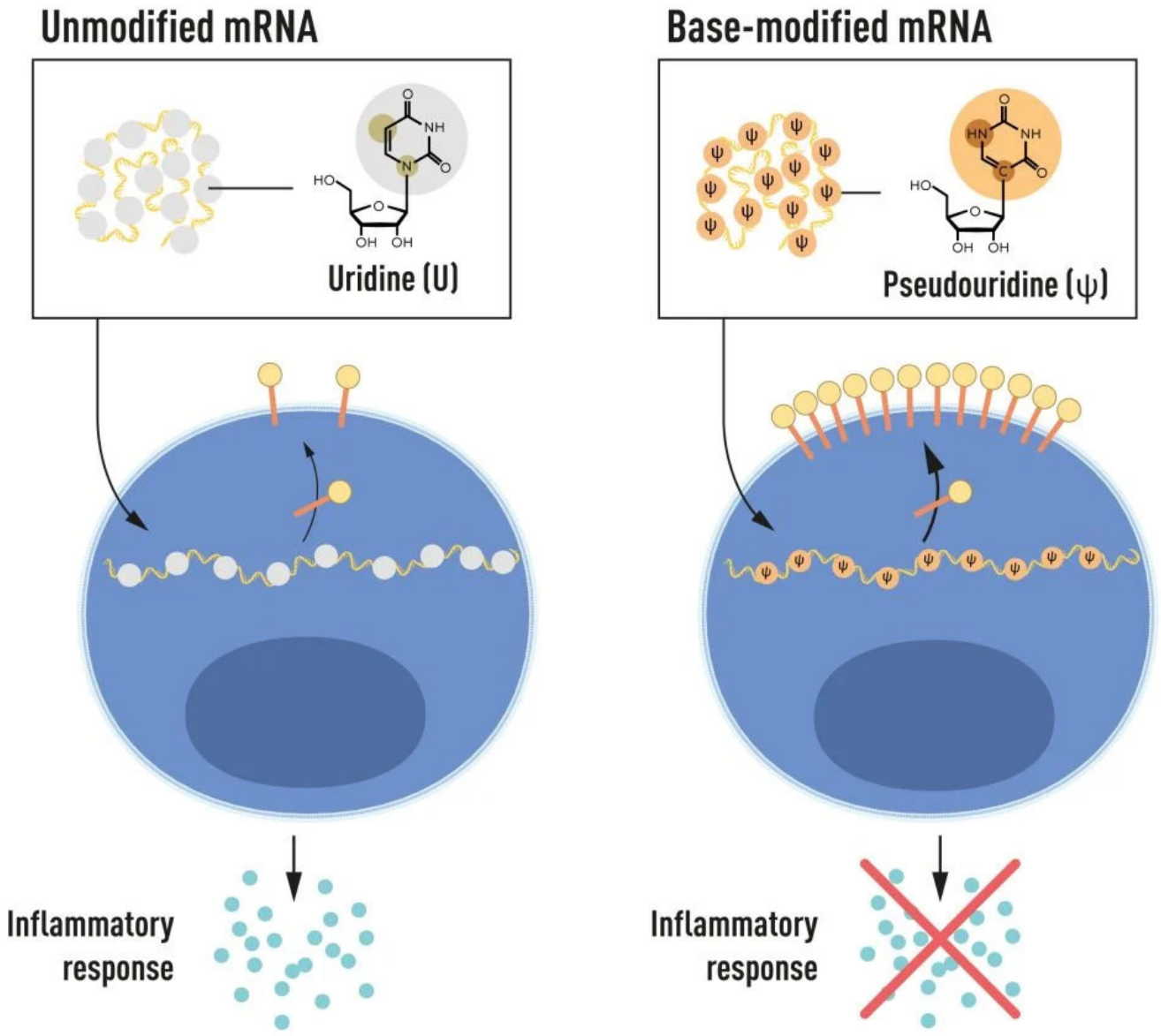

Figure 2. mRNA contains four different bases, abbreviated A, U, G, and C. The Nobel Laureates discovered that base-modified mRNA can be used to block activation of inflammatory reactions (secretion of signaling molecules) and increase protein production when mRNA is delivered to cells.

© The Nobel Committee for Physiology or Medicine. Ill. Mattias Karlén

In further studies published in 2008 and 2010, Karikó and Weissman showed that the delivery of mRNA generated with base modifications markedly increased protein production compared to unmodified mRNA. The effect was due to the reduced activation of an enzyme that regulates protein production. Through their discoveries that base modifications both reduced inflammatory responses and increased protein production, Karikó and Weissman had eliminated critical obstacles on the way to clinical applications of mRNA.

mRNA vaccines realized their potential

st in mRNA technology began to pick up, and in 2010, several companies were working on developing ethod. Vaccines against Zika virus and MERS-CoV were pursued; the latter is closely related to SARS-

CoV-2. After the outbreak of the COVID-19 pandemic, two base-modified mRNA vaccines encoding the SARS-CoV-2 surface protein were developed at record speed. Protective effects of around 95% were reported, and both vaccines were approved as early as December 2020.

The impressive flexibility and speed with which mRNA vaccines can be developed pave the way for using the new platform also for vaccines against other infectious diseases. In the future, the technology may also be used to deliver therapeutic proteins and treat some cancer types.

Several other vaccines against SARS-CoV-2, based on different methodologies, were also rapidly introduced, and together, more than 13 billion COVID-19 vaccine doses have been given globally. The vaccines have saved millions of lives and prevented severe disease in many more, allowing societies to open and return to normal conditions. Through their fundamental discoveries of the importance of base modifications in mRNA, this year's Nobel laureates critically contributed to this transformative development during one of the biggest health crises of our time.

Key publications

Karikó, K., Buckstein, M., Ni, H. and Weissman, D. Suppression of RNA Recognition by Toll-like Receptors: The impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* **23**, 165–175 (2005).

Karikó, K., Muramatsu, H., Welsh, F.A., Ludwig, J., Kato, H., Akira, S. and Weissman, D. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. *Mol Ther* **16**, 1833–1840 (2008).

Anderson, B.R., Muramatsu, H., Nallagatla, S.R., Bevilacqua, P.C., Sansing, L.H., Weissman, D. and Karikó, K. Incorporation of pseudouridine into mRNA enhances translation by diminishing PKR activation. *Nucleic Acids Res.* **38**, 5884–5892 (2010).

Read more about this year's prize

Scientific background: Discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19

Katalin Karikó was born in 1955 in Szolnok, Hungary. She received her PhD from Szeged's University in 1982 and performed postdoctoral research at the Hungarian Academy of Sciences in Szeged until 1985. She then conducted postdoctoral research at Temple University, Philadelphia, and the University of Health Science, Bethesda. In 1989, she was appointed Assistant Professor at the University of Pennsylvania, where she remained until 2013. After that, she became vice president and later senior vice president at BioNTech RNA Pharmaceuticals. Since 2021, she has been a Professor at Szeged University and an Adjunct Professor at Perelman School of Medicine at the University of Pennsylvania.

Drew Weissman was born in 1959 in Lexington, Massachusetts, USA. He received his MD, PhD degrees from Boston University in 1987. He did his clinical training at Beth Israel Deaconess Medical Center at Harvard Medical School and postdoctoral research at the National Institutes of Health. In 1997, Weissman established his research group at the Perelman School of Medicine at the University of Pennsylvania. He is the Roberts Family Professor in Vaccine Research and Director of the Penn Institute for RNA Innovations.

Illustrations: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén

The Nobel Assembly, consisting of 50 professors at Karolinska Institutet, awards the Nobel Prize in Physiology or Medicine. Its Nobel Committee evaluates the nominations. Since 1901 the Nobel Prize has been awarded to scientists who have made the most important discoveries for the benefit of humankind.

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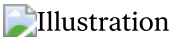
<https://www.nobelprize.org/prizes/medicine/2023/press-release/>

Nobel Prizes 2023

Eleven laureates were awarded a Nobel Prize in 2023, for achievements that have conferred the greatest benefit to humankind. Their work and discoveries range from effective mRNA vaccines and attosecond physics to fighting against the oppression of women.

See them all presented here.



Productie 25

How COVID-19 vaccines were made so quickly without cutting corners

The spread of the virus and the public's attention to science helped to shorten the timeline

Cuts in time spent waiting on experimental results and public interest in science accelerated COVID-19 vaccine development.

Marvin Tolentino/Alamy Stock Photo

Six months after the first COVID-19 shots started going into arms in the United States, the pace of vaccination has slowed. That's prompted White House officials to scale back their goal of getting at least one dose to 70 percent of all U.S. adults by July 4; they're now aiming for 70 percent of those 27 and older.

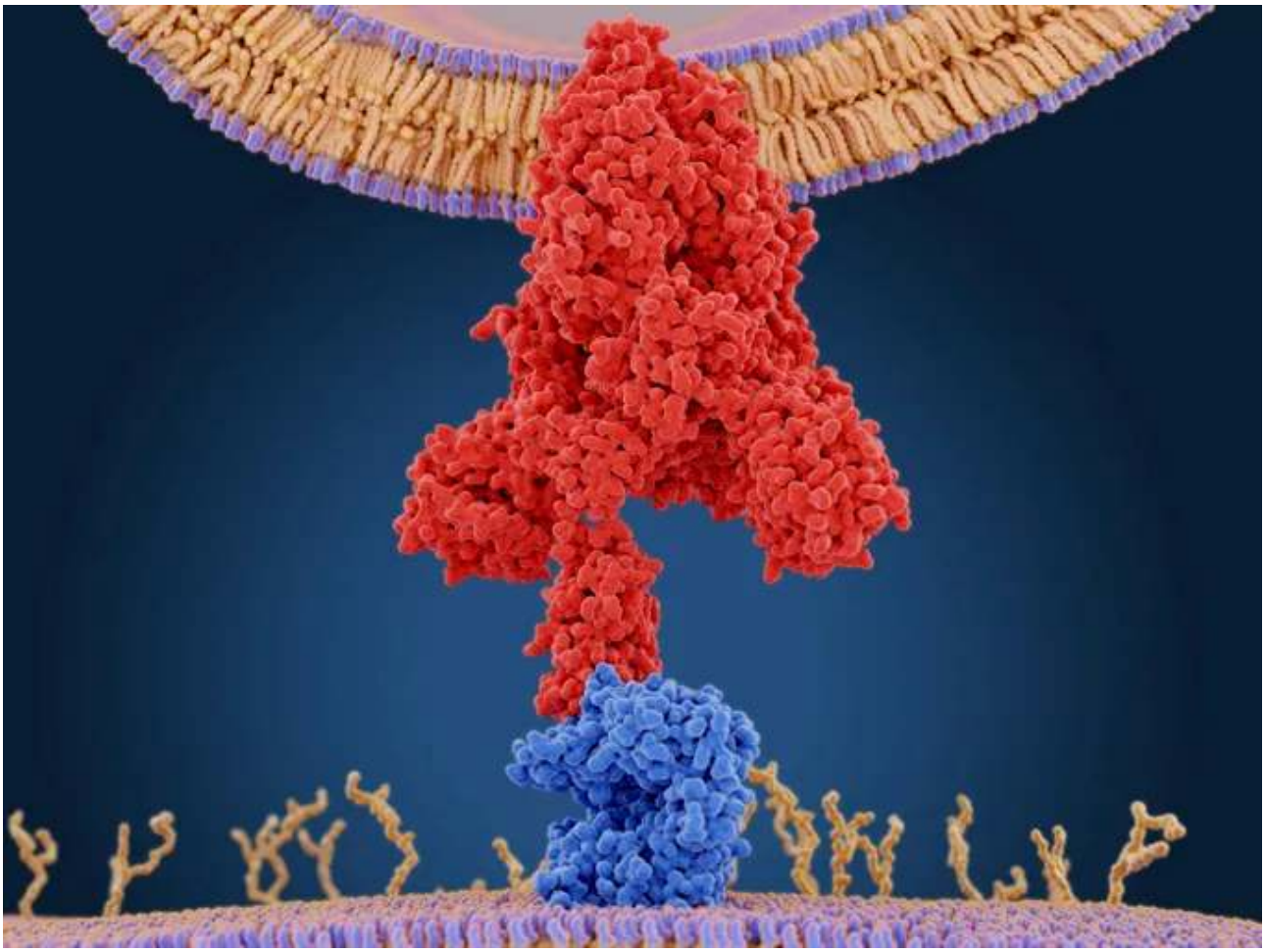
Even so, more than 1 in 5 Americans say they won't get vaccinated, according to a recent poll by the American Psychiatric Association. Among the reasons that often pop up are worries that the vaccines were developed too fast: Normally, drug research takes years or even decades from idea to reality. The first vaccines to combat COVID-19 were developed, tested and given emergency use authorization in 11 months.

Driven by a global urgency and underpinned by decades of prior work on vaccine technology, vaccine developers found a way to chop not just days or months, but years off the timeline (*SN: 2/21/20*). What was jettisoned was not the science, or the safety tests, but rather the wait time baked into the development process — waiting for results and waiting for regulatory approvals (*SN: 7/10/20*).

By comparing the new vaccines with earlier drugs that have used the same tech under more traditional research timelines, it is possible to calculate approximately how much time got chopped off the development process once shots were ready to go into arms: roughly four years. Here's how.

Unlocking the coronavirus' secrets

To back up a bit first, designing the vaccines began far earlier than the jabs-in-arms stage. It began with deciphering the exact genetic makeup of SARS-CoV-2, the virus that causes COVID-19 (*SN: 12/11/20*). By early January 2020, that genetic blueprint was in hand and the first vaccines to test were ready just a few weeks later.



A coronavirus spike protein (red) binds to an angiotensin-converting enzyme 2 receptor (blue) on a human cell in this illustration. The virus uses the ACE2 receptor to break into human cells.JUAN GAERTNER/SCIENCE PHOTO LIBRARY/GETTY IMAGES

For some perspective, researchers first deciphered, or sequenced, the entire human genome over a span of almost 13 years, starting in 1990 and wrapping up in 2003 (*SN: 1/17/03*). Because of advances in computers, the same task now can take only hours.

Most crucially, researchers now had the genetic instructions for making the spike proteins that the virus uses to break into cells — a key ingredient for making the vaccines. Jutting out from the virus' surface, these spike proteins make an easy target for the immune system to recognize. Researchers knew to zero in on those proteins thanks to decades of work studying coronaviruses, including two that have caused other outbreaks of human diseases — SARS and MERS. That work also identified the best form of the protein to use: a stable form just before the virus fuses with a cell it's about to infect.

Finding a delivery system

Those instructions could then be fed directly into pre-made delivery vehicles that carry the genetic code to cells to induce an immune response. Scientists had already built these rapid, genetically based templates largely because of the ongoing battle against HIV, says Tom Denny, Chief Operating Officer of the Duke Human Vaccine Institute in Durham, N.C.

"In the last 10 to 15 years, there've been major teams around the world … trying to understand what needed to occur to make a protective HIV vaccine," Denny says. Those efforts have "helped us in our battle with this current pandemic."

These vehicles are like the Potato Head toys of the vaccine development world: Instead of swapping in different facial features, information specific to each virus gets plugged in.

Denny calls it "plug-and-play" vaccine manufacturing. Decades of trying to attack HIV has created a library of safe weapons to use quickly against any new would-be viral marauders. "We got lucky," Denny says, that the developed platforms have worked so well for this new deadly virus.

One of the templates directly carries a nonfunctional, partial strand of viral mRNA to cells in the body, delivering instructions for those cells to create copies of the protein that the immune system recognizes as foreign. That's what's used in the Pfizer-BioNTech and Moderna shots.

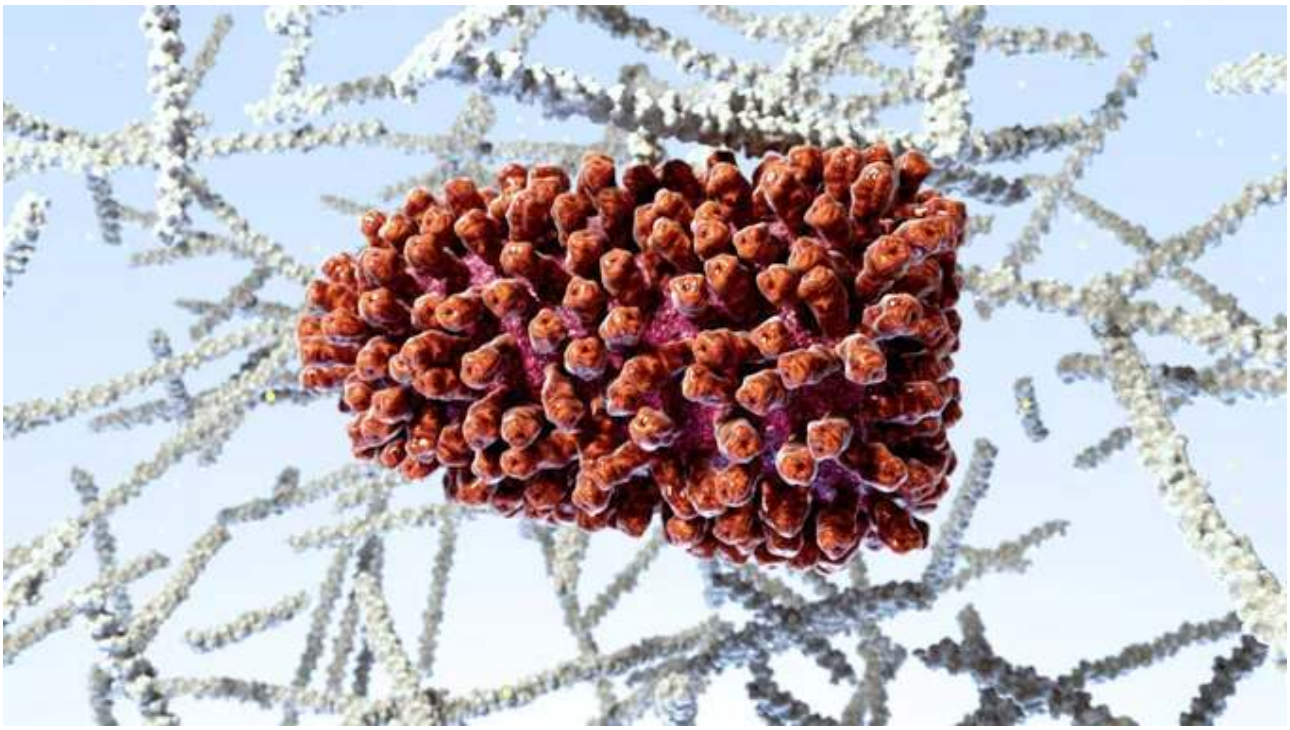
The mRNA for the coronavirus' spike proteins gets packaged inside tiny bubbles of fat called lipid nanoparticles. These tiny fat bubbles have been around for decades and safely used for dozens of other drugs, some approved, others still in the pipeline. So all that needed to be changed to target SARS-CoV-2 were the directions nestled inside.

The contents of the fat bubbles are known as their "payload," says Vicki Stronge (*SN: 11/20/20*). She's the director of product management at Precision NanoSystems in Vancouver, which manufactures equipment and compounds for the development of lipid nanoparticles. She explains why those fat bubbles are so crucial: If the mRNA is injected alone outside a bubble, it breaks down quickly, degrading into harmless biological raw bits and pieces that get recycled by our bodies.

Benefiting from past research

Two key therapies — one still in the works and one approved — paved the way for COVID-19 vaccine developers to hit the ground running with RNA-based templates.

One therapy, made by Germany-based CureVac, is the first vaccine to reach human trials that was developed using mRNA to fight an infectious disease. It targets the rabies virus and was injected into human volunteers starting in 2013. Decades earlier, in 1971, researchers developed the first syringefuls that they thought were safe for humans, which they initially tested by injecting themselves. The first version of the mRNA-based rabies vaccine prompted only a weak immune system response but did show that the technology was safe. A newer version of this rabies vaccine is starting to show promising results in clinical trials. (CureVac is also developing an mRNA COVID-19 vaccine, although early results have been disappointing.)



The rabies virus, illustrated here, was the first targeted by an mRNA-based vaccine.NANOCLUSTERING/SCIENCE PHOTO LIBRARY/GETTY IMAGES

The other therapy is patisiran, an RNA-based drug for a rare but often fatal heredity disease in which amyloid proteins build up in nerves and some organs. It uses the same design based on lipid nanoparticles as the mRNA-based COVID-19 vaccines, just with a different payload inside.

Years of data from monitoring patients who had been injected with these RNA fragments wrapped in lipid nanoparticles shows they're safe, says Sascha Tuchman, a hematologist-oncologist at the University of North Carolina at Chapel Hill who oversaw a site for the Phase III patisiran trials. Patients who receive a dose of patisiran have a lower risk of side effects than those who got injections with placebo saline. And when it comes to long-term negative consequences from RNA and lipid nanoparticles, Tuchman says, "we haven't seen anything additional in terms of the safety that would indicate that there is some reason to be concerned."

Six years after the first shots began being tested, the FDA approved patisiran, a little faster than standard pace for new treatments. That makes it a good comparison to show where the COVID-19 vaccines were able to cut time, not counting the decades of research of development that got us to this point. So let's start the clock.

Recruiting volunteers

After the first syringefuls of prospective COVID-19 vaccine emerged from the "plug-and-play" mRNA labs, years were removed from the timeline by cutting out the long stretches of pure waiting that are built into most human testing. Driven by the urgency of the pandemic, nearly half a million people in America alone had offered up their deltoids for the cause through the COVID-19 Prevention Network in a matter of months, in many cases even before the first public inklings of success, according to the American Medical Association.

For instance, it took just under 16 weeks to recruit and enroll more than 43,000 volunteers for the final phases of testing Pfizer's vaccine. When volunteer recruitment began for clinical trials of the rabies mRNA vaccine in 2013, it took 813 days to get 101 participants enrolled. Based on this comparison, that's roughly 730 days — nearly two years — saved in recruiting alone.

Late last year, Pfizer and Moderna were already manufacturing vaccine doses in anticipation of authorization. Here, workers prepare to ship doses out of Pfizer's Kalamazoo, Mich., plant just two days after the U.S. Food and Drug Administration granted emergency use authorization for that vaccine.Morry Gash/Getty Images

Getting fast results

Another, more dismal factor contributed to the scientific speed: How fast the virus spread.

Scientists can begin to calculate a vaccine's efficacy when a sufficient number of people in the group that got a placebo rather than a vaccine have gotten infected naturally (*SN: 10/4/20*). If an outbreak peters out, it takes longer to reach that threshold. That's true too if a virus naturally spreads more slowly — say a virus like HIV, herpes or human papillomavirus, or HPV, which are transmitted primarily through sex. In contrast, just breathing or talking can spread SARS-CoV-2 — and everybody does that (*SN*: 4/2/20).

Loosely comparing vaccine trials for COVID-19 with HPV vaccine trials offer clues to just how many days may have been lopped off the COVID-19 timeline because of the new virus's astronomical rate of spread. The HPV trials took about 529 days, or 1.4 years, to reach a point at which efficacy could be calculated, when the placebo group got to an infection rate of 3.8 percent.

The Pfizer Phase II/III coronavirus trial, in contrast, got initial efficacy results for the first of its two doses in just 105 days, when it hit a nearly 2.4 percent infection rate in the placebo group. That's 424 days faster than HPV. Why? Because just months into the pandemic, SARS-CoV-2 was infecting hundreds of thousands of people per day globally.

Jumping the line

There was also waiting time recouped from the U.S. Food and Drug Administration's review process. Typically, it takes the FDA 10 months to review a new drug.

However, with the COVID-19 death toll rising, the FDA rushed all coronavirus vaccines to the front of the review lines. The Pfizer vaccine got reviewed and authorized for emergency use only

21 days after submission and the Moderna vaccine in just 19 days (SN: *12/11/20; SN: 12/18/20*). Compared with a more typical 10-month wait time, that's about another 283 days saved.

In total, that's 1,437 days, or 3.9 years, cut off the normal timeline for a new vaccine. And that doesn't include other time savings, such as putting the ethics reviews at the front of the line. Add that saved time to the 11 months it actually took to get the first COVID-19 vaccines and it would add up to nearly five years — remarkably close to the six years needed to test and approve patisiran.

In a final jolt of speed, some pharmaceutical companies, bolstered by big vaccine contracts and research cash from the U.S. government's Operation Warp Speed, were also churning out doses during clinical trials in the hopes that the vaccines would work. Once the companies had emergency use authorization in hand, they were ready to ship doses immediately.

Decades of previous work combined with a fast-moving virus, a public willingness to help and elimination of wait times drove the rapid development of COVID-19 vaccines. No safety steps were skipped, says Stanley Plotkin, emeritus professor of pediatrics at the University of Pennsylvania, who is perhaps best known for his work developing the rubella vaccine.

The rapid creation of the COVID-19 vaccines, Plotkin says, are "a sea change in how to develop vaccines." They are an example of what scientists can do when unfettered from waiting.

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Review

SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond

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Abstract: To successfully protect against pathogen infection, a vaccine must elicit efficient adaptive immunity, including B and T cell responses. While B cell responses are key, as they can mediate antibody-dependent protection, T cells can modulate B cell activity and directly contribute to the elimination of pathogen-infected cells. In the unprecedented race to develop an effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the respiratory disease coronavirus disease 2019 (COVID-19), messenger RNA (mRNA) vaccines have emerged as front runners thanks to their capacity for rapid development and ability to drive potent adaptive immune responses. In this review article, we provide an overview of the results from pre-clinical studies in animal models as well as clinical studies in humans that assessed the efficacy of SARS-CoV-2 mRNA vaccines, with a primary focus on adaptive immune responses post vaccination.

Keywords: SARS-CoV-2; coronavirus; mRNA vaccines; adaptive immunity; antibodies; germinal centers; long-lived plasma cells; memory B cells; T follicular helper cells; Th1 cells

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1. Introduction

In December of 2019, the betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causative agent of the debilitating coronavirus disease 2019 (COVID-19). At the time this review was written (December 2020), this disease had led to over 80 million infections and 1.8 million deaths globally [1], highlighting the crucial need to develop a safe and effective vaccine. Thus far, there are 61 SARS-CoV-2 vaccine candidates already under clinical evaluation and 172 in preclinical development [2]. In this unprecedented effort to generate one or more successful vaccines for SARS-CoV-2, many different vaccine platforms have been deployed. Several of the candidates currently under investigation are based on traditional vaccine approaches, such as inactivated/live-attenuated virus or recombinant proteins (detailed in [3]). Others exploit novel and promising platforms, like the nucleic acid-based messenger RNA (mRNA) vaccines that deliver the genetic information to produce the antigen, rather than the antigen itself. While conventional vaccine approaches have been safely and ubiquitously used for many decades, the unknowns of mRNA vaccination are many, seeing as this is a first-in-class licensure for mRNA vaccines. After briefly discussing some crucial aspects of design strategy for mRNA vaccines, this review will highlight our current knowledge on the adaptive immune responses to SARS-CoV-2 mRNA vaccines based on animal studies from many different groups, as well as clinical data available from the SARS-CoV-2 mRNA vaccines mRNA-1273, co-developed by Moderna (Cambridge, MA, USA) and the National Institutes of Allergy and Infectious Diseases Vaccine Research Center, along with BNT162b1 and BNT162b2, from BioNTech (Mainz, Germany)/Pfizer (New York City, NY, USA). Furthermore, the major strengths and challenges associated with the usage of mRNA vaccines will also be outlined here. We must also note that, although there are promising self-replicating RNA candidates currently in clinical development, this review will only focus on SARS-CoV-2 mRNA vaccine candidates.

2. Design Strategies for SARS-CoV-2 mRNA Vaccines

The conceptualization of mRNA vaccines might seem quite simple at first, due to the straightforward *modus operandi* of mRNA vaccines. Upon delivery of an mRNA vaccine encoding a target antigen, cells will take up the mRNA and translate it into protein in situ. The individual's immune system will then mount a robust adaptive immune response against the target protein. Nevertheless, the actual design process of mRNA vaccines requires important considerations of mRNA modifications to reduce reactogenicity and optimize protein expression; proper selection of the target antigen; and optimal formulation allowing for an efficient delivery [4].

2.1. Modifications to mRNA

The first aspect to consider in the development of mRNA vaccines is that unmodified mRNA itself is not ideal for use in vaccine development [4]. In fact, mRNA is both extremely labile and rapidly degraded in unfavorable environments. Moreover, it is highly immunogenic and able to activate a variety of pathogen-associated molecular pattern sensors. In an effort to improve half-life as well as translatability and safety, Karikó et al. tested a variety of naturally occurring modifications to nucleosides in mRNA molecules, including pseudouridine, 5-methylcytidine, N6-methyladenosine, 5-methyluridine, and 2-thiouridine [5]. Of these variants, they found that the incorporation of N1-methyl-pseudouridine (m1Ψ) in place of uridine led to a 10-fold increase in translation over unmodified mRNA. Furthermore, they were able to show that mRNA molecules possessing this modification did not trigger pathogen-associated molecular pattern sensing mechanisms such as toll-like receptors (TLRs) or retinoic acid-inducible gene I (RIG-I) [4,5]. This is crucial to avoid excessive inflammation, which could result in undesired vaccine side-effects. For these reasons, many candidates, including the two recently licensed mRNA vaccines mRNA-1273 and BNT162b2, adopted this m1Ψ mRNA modification in their vaccine design [6–16]. It is important to note here that, although there are other potential modifications that vaccine manufacturers can apply to mRNA molecules, m1Ψ is the most ubiquitously used modification, and it will be the only mRNA modification discussed in this review.

2.2. Antigen Selection

In selecting the antigen for an mRNA vaccine, it is essential to choose a target that is both immunogenic and capable of eliciting a protective immune response. Of the multiple epitopes on SARS-CoV-2, the spike (S) glycoprotein is the target commonly selected for COVID-19 vaccine development [3], since it is the major SARS-CoV-2 surface protein and mediates viral entry by binding to the angiotensin-converting enzyme 2 (ACE2) receptor in host cells [17–19]. SARS-CoV-2 S is a class I viral fusion glycoprotein, consisting of a receptor binding subunit (S1) and a fusion subunit (S2) that are joined by a furin cleavage site unique to this coronavirus (Figure S1) [18,20]. S is cleaved post-translationally at this furin site. However, the S1 and S2 subunits stay associated until S is bound to the ACE2 receptor via the receptor binding domain (RBD), leading to irreversible conformational changes and membrane fusion. Information gleaned from previous work with similar fusion glycoproteins has shown how important it is to use prefusion stabilized proteins that preserve neutralization-sensitive epitopes for the development of effective vaccines [21,22]. To stabilize the S protein, a few different strategies have been adopted (Figure S1). A mutation where amino acids 986 and 987 are replaced with prolines (S-2P), stabilizing the transmembrane-anchored S glycoprotein in the prefusion conformation but still allowing for cleavage of the S1 and S2 subunits [17,21], is the approach used in the licensed vaccines mRNA-1273 and BNT162b2 [6–12,15,16]. Another approach consisted of designing an mRNA construct where the full-length S protein lacks the furin cleavage site (Δfurin) and cannot be cleaved after translation [23,24].

As an alternative to the full-length S protein, RBD could exclusively be targeted as an antigen by mRNA vaccines (Figure S1), as several studies have shown that the many neutralizing epitopes are included within RBD [25–29]. One of the clinical candidates origi-

nally developed by BioNTech/Pfizer and tested in early clinical studies, BNT162b1 [13–15], encoded a secreted trimerized RBD. The choice of either full-length S or RBD might have different advantages. For instance, while RBD is enriched for epitopes important for SARS-CoV-2 neutralization, the full-length S is a notably bigger protein and contains additional epitopes that might be important to elicit broader adaptive immune responses.

2.3. Delivery of mRNA

Finally, although naked mRNA can be directly injected for immunization, this method of delivery is rather inefficient. Indeed, mRNA molecules must be able to penetrate a cell's lipid membrane in order to reach the machinery required to translate the transcripts into proteins. Thus, delivery methods facilitating the cytosolic localization of mRNA vaccines are important for achieving efficient protein translation. In early studies, standard laboratory lipid encapsulation methods, such as lipofectamine [5], worked well for in vitro applications. These methods, however, had limited efficacy when tested in vivo and were also found to be highly cytotoxic [4]. The advent of lipid nanoparticle (LNP) encapsulation was a turning point in the development of mRNA vaccines, as LNPs are able to efficiently deliver mRNA in vivo [30,31]. When injected intramuscularly, mRNA-LNPs can be internalized and quickly translated by antigen-presenting cells at both the injection site and in draining lymph nodes, thus promoting the initiation of adaptive immune responses [32]. Additionally, LNPs can protect mRNA from degradation by nucleases. Although the precise composition of the LNPs used by many vaccine developers is proprietary information, it is known that LNPs contain a combination of ionizable cationic lipids, cholesterol, phospholipid and PEGs that self-assemble into ~100 nm nanoparticles encapsulating the mRNA [33–35]. Of the vaccine candidates in clinical trials, LNPs are the standard method being used to introduce mRNA vaccines to participants. Additional delivery methods that are not used by any SARS-CoV-2 preclinical or clinical candidates have been thoroughly reviewed elsewhere [4].

3. Immune Responses Elicited by SARS-CoV-2 mRNA Vaccines: Lessons from Animal Studies

A schematic representation of the immune responses elicited by SARS-CoV-2 mRNA vaccines, built on the data from animal studies discussed in this section, is depicted in Figure 1. While mRNA vaccine uptake/biodistribution and the innate immune response to mRNA vaccines are critical for the initiation of adaptive immunity, these processes are thoroughly reviewed elsewhere [36] and will not be covered in this article due to a lack of available data generated in the context of SARS-CoV-2 mRNA vaccines.

3.1. B Cells and Antibody Responses

Most licensed vaccines confer protection from viral infection by eliciting protective antibody (Ab) responses that last over time [37]. Affinity-matured, long-lasting Abs against viruses are generated in microanatomical sites of secondary lymphoid organs named germinal centers (GCs) [38]. In GCs, antigen-activated B cells undergo random mutations and diversify their immunoglobulin genes to generate Abs with high affinity for the pathogen. Next, only the B cells that have acquired higher affinity are positively selected and rescued from apoptosis. This sophisticated Darwinian process ultimately leads to the formation of high-affinity long-lived plasma cells (LLPCs) and memory B cells (MBCs). LLPCs secrete Abs, some of which are neutralizing Abs (nAbs) and can potentially mediate sterilizing immunity [39]. Importantly, LLPCs can survive for years, or even several decades in some cases, continuously secreting Abs without the need for further antigen stimulation [40]. Conversely, MBCs become activated in the event of a subsequent pathogen exposure and give rise to a new burst of high-affinity Ab-secreting cells [39]. Hence, both LLPC and MBCs are desirable cell types to induce by vaccination.

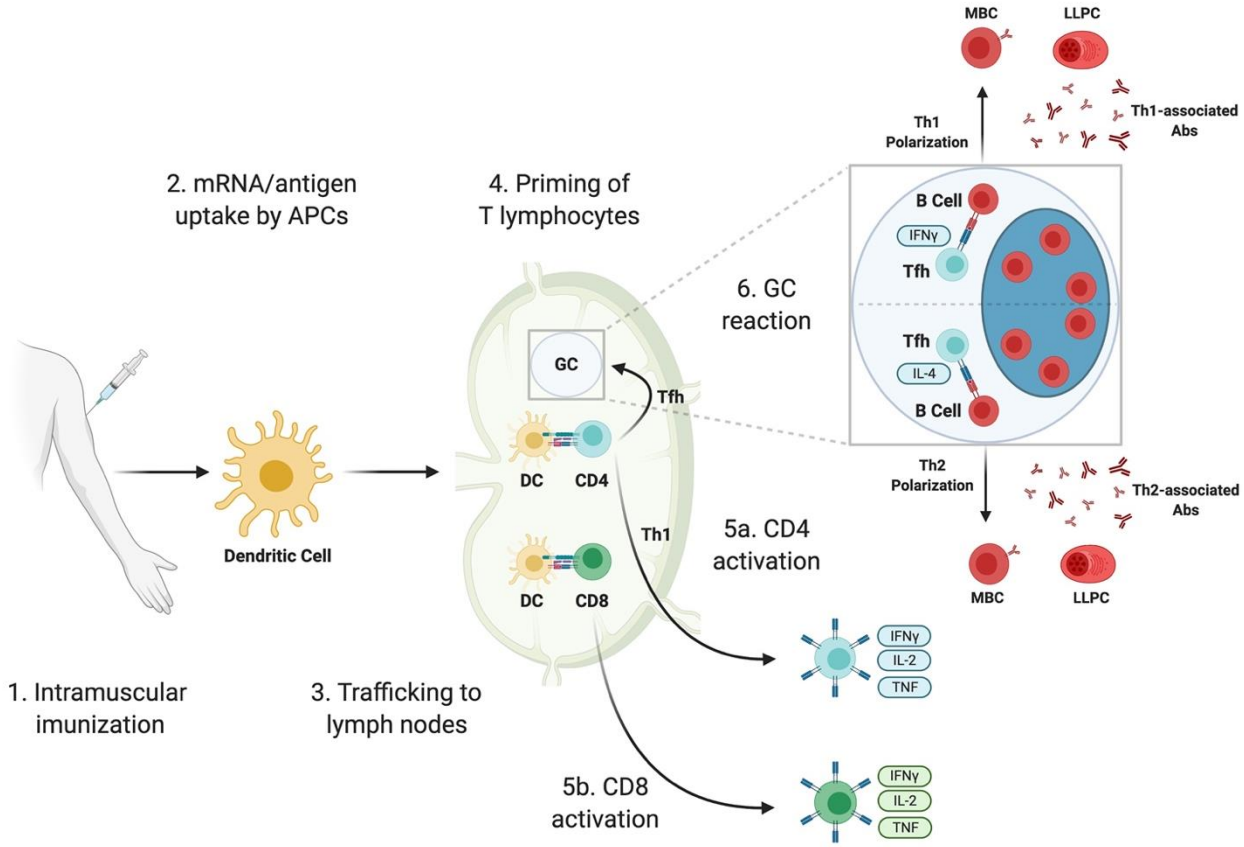

Figure 1. Immune responses elicited by SARS-CoV-2 mRNA vaccines. SARS-CoV-2 mRNA vaccines are administered intramuscularly (1). Either mRNA-LNPs or locally produced antigen are taken up by antigen-presenting cells (APCs) (2), such as dendritic cells (DCs). These APCs then traffic to the lymph nodes (3) where they are able to prime CD4 and CD8 T lymphocytes (4). The events in (2)–(4) are reviewed in detail in [36]. The priming of CD8 T cells can induce the formation of cytotoxic T lymphocytes (5b) which are capable of directly killing infected cells. Antigen-primed CD4 T cells can differentiate into Th1 cells (5a) or T follicular helper (Tfh) cells. Tfh cells help to initiate a germinal center (GC) reaction (6). GC reactions induced by vaccination will result in the formation of affinity-matured memory B cells (MBCs) and the antibody-secreting long-lived plasma cells (LLPCs). Tfh cells can be skewed towards either a Th1 or Th2 phenotype, which will affect the class switching of antibodies (Abs) produced by LLPCs to either Th1- or Th2-associated Abs (6).

3.1.1. Induction of SARS-CoV-2 Binding and Neutralizing Abs

Studies of natural infection in humans have shown that individuals infected with SARS-CoV-2 can produce potent neutralizing Abs (targeting the SARS-CoV-2 S protein) that might inhibit infection by SARS-CoV-2 in vitro and/or in vivo [29,41]. Based on this knowledge, pre-clinical evaluations of SARS-CoV-2 mRNA vaccines have focused on the ability of these vaccines to elicit robust SARS-CoV-2-binding and neutralizing Ab responses in mice, as an initial step in assessing vaccine efficacy. Work done by our group has shown that a single 30μg dose of an mRNA-LNP vaccine, encoding either the full-length Δfurin S or the RBD of SARS-CoV-2 (Figure S1), was able to promote high SARS-CoV-2-binding immunoglobulin G (IgG) titers in mice as early as two weeks post-immunization [23,24]. Despite a high vaccine dose being utilized in our work [23,24], studies of the clinical candidates mRNA-1273 (Moderna), BNT162b2 (BioNTech/Pfizer) and CVnCoV (CureVac (Frankfurt, Germany)), all encoding a full-length, pre-fusion stabilized S protein (Figure S1) [8,12,42] and ARCoV [43], encoding the RBD, reported that the production of SARS-CoV-2-specific Abs was driven by a significantly lower dose (ranging from 0.2 to 10 μg) of these vaccine candidates in mice. Importantly, various groups found that the Ab responses induced by these SARS-CoV-2 mRNA vaccines were able to neutralize the virus in vitro, as measured by both pseudovirus- and SARS-CoV-2-based neutralization assays [8,12,23,24,42–45], and

that nAb levels were sustained for two months, or more, post-immunization [23,24,44,45]. Analyses of the Ab responses elicited by different vaccine doses indicated that mRNA vaccines induced a dose-dependent SARS-CoV-2-specific Ab response upon priming that was enhanced by a booster immunization [8,24,42,43]. While a single immunization with a high vaccine dose (30 μg) appeared sufficient to promote an elevated humoral response in mice [23,24], a booster immunization was necessary for nAb generation at the lower vaccine doses (1 μg or 2 μg) [8,42,43]. Altogether, the data from these different mouse studies suggest that either high doses of mRNA or a booster immunization might be required to reach detectable nAb levels after immunization with SARS-CoV-2 mRNA vaccines. Interestingly, the antigen choice seems to have an impact on a vaccine's capacity to drive Ab responses, as indicated by a study wherein a SARS-CoV-2 S1 mRNA vaccine (Figure S1) was not as effective at inducing SARS-CoV-2-binding Abs and nAbs as the RBD mRNA vaccines [45]. This is different from the potent humoral responses observed by several other groups utilizing mRNA vaccines encoding either the S Δfurin [23,24] or the S-2P constructs [8,12,42], suggesting that a full-length S, where the S1 and S2 subunits are both present, might be a better immunogen than the simple S1 subunit.

Beyond mice, studies in non-human primates (NHPs) are instrumental in determining the efficacy of vaccine candidates for SARS-CoV-2, as the wild-type virus cannot efficiently replicate in common laboratory mouse strains, due to the lack of appropriate receptors to initiate viral infection [46]. In NHPs, the clinical candidates mRNA-1273 (10 or 100 μg) and BNT162b2 (30 or 100 μg) both demonstrated a robust, dose-dependent capacity to elicit SARS-CoV-2 specific Abs after two immunizations [7,12]. A similar trend was also observed for the in vitro neutralizing capacity of these Abs [7,12], with nAb values elicited in NHPs by BNT162b2 that were even higher than those from SARS-CoV-2 convalescent human sera [12]. The candidate CVnCoV was tested at much lower dosages (0.5 or 8 μg), but only the higher dosage elicited significant levels of S- and RBD-binding IgG titers after a single immunization, which increased over time [47]. In all cases, the nAb responses elicited by these candidates were combined with in vivo protection against SARS-CoV-2 challenge after the booster immunization [7,12,47]. Although viral replication was detected in the upper respiratory tract of the infected animals that received any of these vaccines, it was transient and only measurable for a few days. Importantly, the lower respiratory tract of immunized NHPs was fully protected from viral replication, as indicated by the absence of measurable SARS-CoV-2 subgenomic RNA in bronchoalveolar lavage fluid at any time point [7]. These studies also demonstrated that the higher vaccine doses conferred greater protection of the upper respiratory tract, while both dosages were equally effective in protecting the lower respiratory tract [7,12].

For coronavirus vaccine development, there are some noteworthy concerns when it comes to the quality of Ab production. One concern is that SARS-CoV-2 vaccines might favor the development of Ab-dependent enhancement, a phenomenon that could occur when vaccine-induced Abs fail to effectively neutralize viruses because of insufficient concentration/affinity, or the wrong specificity [48]. While no evidence has shown that Ab-dependent enhancement can occur in SARS-CoV-2 infection, the robust levels of SARS-CoV-2 binding Abs and nAbs driven by all SARS-CoV-2 mRNA vaccines discussed above, combined with the in vivo protection data in NHPs, seem favorable in order to avoid any potential for Ab-dependent enhancement.

3.1.2. Germinal Center-Derived B Cell Response

GC reactions are fundamental for the generation of high-quality B cell responses that can confer protection over an extended time. Data from our group demonstrated that a single 30 μg dose of a SARS-CoV-2 mRNA vaccine, encoding either the full-length Δfurin S protein or the RBD, was able to promote robust formation of primary GCs 7 days post-immunization in mice [24]. This was opposed to a minimal GC induction in response to the immunization with the more traditional recombinant RBD (rRBD) protein vaccine, formulated with the MF59-like adjuvant AddaVax (rRBD-AddaVax). In this study, GCs

were evaluated by both flow cytometry and microscopy. Similarly, GC induction by SARS-CoV-2 mRNA vaccines in mice was also described by two additional studies: Vogel et al. showed a significant increase in GC B cells in both the spleen and the draining lymph nodes 12 days after immunization with a single 5 µg dose of BNT162b2 [12], whereas Tai et al. [45] observed the presence of GCs 10 days after a booster immunization with a 30 µg dose of SARS-CoV-2 mRNA vaccines.

In our study, the GC B cells elicited by a single dose of mRNA vaccines were SARS-CoV-2-specific and peaked around day 7, then progressively waned over time and were mostly resolved by day 28 [24]. Such a GC kinetic in response to mRNA vaccines can be considered fast, as primary GC responses to protein antigens in the adjuvant usually peak between days 10 and 14 post-immunization [49]. Interestingly, although there was a deep quantitative reduction in GCs at week 4 post-immunization, the elevated frequency of SARS-CoV-2-specific GC B cells at this time point indicated that some residual low-level GC activity was still present in response to mRNA vaccines. This residual GC activity could contribute to the elevated SARS-CoV-2-specific IgG titers and nAbs found 60 days post-immunization [24]. Additionally, a booster immunization resulted in a second wave of SARS-CoV-2-specifc GC B cell formation measured 10 days post-boost.

As discussed above, the most desirable B cell populations to generate by vaccination are affinity matured LLPCs and MBCs, cell types canonically generated through GC reactions. In two recent studies from our group, we examined GC-derived B cell responses generated in mice by a single immunization with SARS-CoV-2 mRNA vaccines, starting from the analysis of LLPCs [23,24]. Specifically, we observed a high level of SARS-CoV-2-specific Ab-secreting cells in the bone marrow of mice immunized 9 weeks earlier with SARS-CoV-2 mRNA vaccines. Because of the location and time point of analysis, these data were indicative of the successful generation of LLPCs following the GC reactions. In these studies, SARS-CoV-2-specific MBCs were also evaluated post-immunization with mRNA vaccines. Consistent with the detection of memory precursors (CCR6-expressing cells in GC light zones) during the early phase of immune responses [24], we further demonstrated that there was a measurable pool of antigen-specific, class-switched MBC 60 days post-vaccination [23,24].

The data emerging from Lederer et al. further illustrated that vaccination with SARS-CoV-2 mRNA vaccines resulted in more efficient nAb production in comparison to rRBD-AddaVax, as measured by both microneutralization and pseudoneutralization assays [24]. Importantly, we observed a strong correlation between the magnitude of GC responses and the levels of nAbs induced by SARS-CoV-2 vaccination, suggesting that the formation of GCs could be necessary for a neutralizing response to SARS-CoV-2. It is worth noting that our finding linking GC reactions to efficient nAb responses upon immunization is apparently discordant with data from SARS-CoV-2 natural infection in humans. Several studies have indeed described that near-germline nAbs endowed with potent in vitro neutralization activity are elicited during SARS-CoV-2 infection, and are characterized by low-grade mutations [27,50–52]. These data are indicative of a limited GC process involved in the generation of such nAbs. Nevertheless, it is important to remember that GCs do not only harbor the affinity maturation process, but are also important for generating LLPCs that live for extended times and mediate durable Ab production. It is therefore possible that the plasma cells producing the near-germline nAbs might have a limited lifespan. While the majority of the studies on the longevity of Ab responses to SARS-CoV-2 upon infection have shown that SARS-CoV-2-binding IgG are only moderately reduced at 5–8 months post-infection [53,54], there are some conflicting results regarding the longevity of nAbs. Some studies indeed suggested that COVID-19 might generate slowly waning nAbs [53–55]. Conversely, others reported a steeper decline in nAbs over time [56,57], which could indicate that natural SARS-CoV-2 infection might sometimes elicit nAb responses of limited durability. Additionally, in a postmortem evaluation of lymph nodes from severe COVID-19 donors, a profound decrease in/lack of GC formation was recently described by Pillai and colleagues [58]. This study suggests that natural SARS-

CoV-2 infection might not efficiently generate GC-derived long-lasting humoral immunity, at least in the most severe COVID-19 cases. While future studies will be important to assess the actual longevity of Ab responses elicited by SARS-CoV-2 natural infection, with special emphasis on nAb responses, it appears highly desirable that a SARS-CoV-2 mRNA vaccine might induce robust GC responses in order to potentially give rise to long-lasting serological memory and MBCs.

3.2. T Cell Responses

While vaccine-induced protection largely relies on Ab responses [39], effective vaccine candidates for SARS-CoV-2 could greatly benefit from the induction of T cell responses, for multiple reasons. Firstly because, among CD4 T cells, T follicular helper (Tfh) cells are crucial regulators of GC and affinity-matured Ab responses [59,60]. Secondly, other CD4 T cell subsets might serve different important functions [39], including facilitating optimal CD8 T cell responses. Thirdly, cytotoxic CD8 T cells, which are responsible for the direct killing of pathogen-infected cells by the release of molecules such as granzyme and perforin, are an important "safety net" to generate by vaccination, in case protective Abs fail to completely block a productive viral infection [39]. Additionally, in some instances, vaccine-elicited T cell responses can also correlate with a protective response [37]. Finally, studies in patients with the primary immunodeficiency agammaglobulinemia suggest that in the absence of properly functioning B cell and antibody responses, other cell types (including T cells) might be able to clear SARS-CoV-2 infection with minimal/moderate disease [61,62].

3.2.1. T Follicular Helper Cell Response

Tfh cells, a specialized type of CD4 T cells shaping GC reactions, are of particular interest to vaccine developers because of their crucial importance for the development of GC-derived B cell responses. By delivering co-stimulatory molecules and cytokines to B cells, Tfh cells mediate the formation of GCs and the selection of affinity-matured GC B cells, which can further differentiate into LLPCs or MBCs [59,60]. An effective induction of Tfh cells by the mRNA-LNP platform was previously described in the context of influenza vaccination [31,63]. To verify that this observation could be extended to SARS-CoV-2 mRNA vaccines, we evaluated the induction of Tfh cells after the immunization of BALB/c mice with SARS-CoV-2 mRNA vaccines or with rRBD-AddaVax [24]. As anticipated, the mRNA-LNP platform was a potent inducer of Tfh cells also in the context of a SARS-CoV-2 vaccine, whereas rRBD-AddaVax only induced a more modest Tfh cell population in comparison to SARS-CoV-2 mRNA. The generation of Tfh cells post-SARS-CoV-2 mRNA vaccination was also seen by Tai et al., although the induction was only significant with the RBD-encoding mRNA vaccine, and not with the S1-encoding mRNA [45]. Furthermore, Vogel et al. found a significant increase in the amount of Tfh cells after immunization with BNT162b2 in draining lymph nodes, spleen and blood [12].

Interleukin 21 (IL-21) is a canonical cytokine produced by Tfh cells that can mediate the proliferation of GC B cells and plasma cell differentiation [64]. Of note, our study also revealed that the Tfh cell population driven by SARS-CoV-2 mRNA vaccines was antigen-specific, as measured by the detection of IL-21-producing Tfh cells upon in vitro restimulation with a SARS-CoV-2 peptide pool [24]. In line with our data, Corbett et al. showed that mRNA-1273 was able to promote the generation of IL-21-producing circulating Tfh cells in the blood of NHP-immunized animals, another indicator of robust Tfh cell induction by this vaccine platform [7]. Taken together, these data point at the importance of a vaccine platform that can potently induce Tfh and GC B cells, in a coordinated fashion, with the promise of eliciting long-lasting neutralizing immunity to SARS-CoV-2.

3.2.2. Functional Polarization of CD4 T Cells

The cytokine milieu promoted by a vaccine guides the functional polarization of CD4 T cells. A T helper 1 (Th1)-skewed response is important to vaccine developers because it

is the type of immune response required to control intracellular pathogens, such as viruses, as opposed, for instance, to a T helper 2 (Th2) response, which is more critical for the control of helminth infections [39]. In addition, vaccines for respiratory viruses that favor the differentiation of CD4 T cells with a Th2 functional polarization (characterized by the secretion of cytokines such as IL-4 and IL-13) might potentially be detrimental, as they have been linked to vaccine-associated enhanced respiratory disease (VAERD) [48]. In humans, VAERD has only ever been diagnosed in children immunized with inactivated measles and respiratory syncytial virus vaccines, as well as in animal models of respiratory syncytial virus immunization with inactivated virus in alum, a Th2 polarizing adjuvant. The mechanisms involved in VAERD include Th2-biased immune responses. Although no evidence of VAERD has emerged for current SARS-CoV-2 mRNA vaccines, it is important to keep this phenomenon in mind, as the alum-adjuvanted inactivated SARS-CoV vaccine in animals has caused VAERD [48].

In a study by Corbett et al., the authors reported that mice immunized with mRNA-1273 had predominant Th1 response (especially at the highest mRNA vaccine dose), measured by the production of Th1 cytokines IFNγ, TNF, and IL-2 by total CD4 T cells upon in vitro restimulation with SARS-CoV-2 peptide pools [8]. By contrast, mice immunized with the prefusion stabilized recombinant S-2P protein in alum tended to have a Th2-biased response, as indicated by the production of IL-4, IL-5 and IL-13. This finding was confirmed by our group and others, who found that multiple mRNA-LNP vaccine constructs elicited a robust production of Th1 cytokines (including IFNγ, TNF, and IL-2) based on intracellular cytokine staining or ELISpot of total CD4 T cells from lungs and spleen [12,23] or in total splenocytes [42,43]. Similar studies with the vaccines BNT162b2 and mRNA-1273 in rhesus macaques further indicated that total CD4 T cells are heavily Th1-skewed after immunization with both constructs, as indicated by their ability to secrete Th1 but not Th2 cytokines upon stimulation ex vivo [7,12].

Tfh cells are a functionally heterogeneous population. Since different pathogens or vaccine platforms might differentially shape their functional profile, an interesting question is what Tfh cell functional properties are modulated by mRNA-LNP vaccines. In our recently published study [24], we further assessed the quality of the Tfh cell response in SARS-CoV-2 mRNA-immunized mice. To this aim, we measured the polarization of Tfh cells towards either a Th1 or Th2 phenotype, characterized by the production of IFNγ or IL-4, respectively, after in vitro restimulation with a SARS-CoV-2 peptide pool. We demonstrated that mRNA-LNP vaccines skewed Tfh cells towards a Th1 phenotype when using full-length S Δ furin as immunogen, or towards a mixed Th1/Th2 phenotype when RBD was the immunogen. By contrast, rRBD-AddaVax induced Th2-biased Tfh cells. Of note, the functional polarization of Tfh cells was associated with differential ratios of SARS-CoV-2-binding IgG1 to IgG2a or IgG2b Abs, with rRBD-AddaVax favoring higher IgG1/IgG2a or IgG1/IgG2b ratios than mRNA vaccines [24]. This was an anticipated outcome, as in mice Th2-biased responses are associated with IgG1 production. Conversely, Th1 polarized responses are linked to IgG2 Ab production [65–67]. Although Tfh cell responses were not evaluated in this study, similar IgG1 to IgG2a relative ratios were also reported when the IgG responses induced by mRNA-1273 were compared to those driven by S-2P protein formulated in alum [8]. Since a skewing toward vaccine-induced IgG1 production was found in mice developing VAERD in a SARS-CoV model [68], a more balanced IgG1/IgG2a ratio could be a favorable outcome for mRNA vaccines.

Based on these data, it appears that SARS-CoV-2 mRNA-LNP vaccines favor the functional polarization of total CD4 T cells toward Th1, while Tfh cells are characterized by the production of both Th1 (IFNγ) and Th2 (IL-4) cytokines. In keeping with the notion that IL-4 is also an important cytokine produced by Tfh cells, as it mediates an anti-apoptotic helper function on B cells [64], it appears a desirable feature that the mRNA vaccine-induced Tfh cells are capable of retaining some IL-4 production even in a Th1 polarizing cytokine milieu. In line with this idea, in recovered patients with COVID-19, the highest plasma-neutralizing activity was associated with increased frequencies of Th1-

and Th2-biased circulating Tfh cells [69]. This finding strengthens the idea that Th1- and Th2-biased Tfh cells are both relevant in shaping a neutralizing response to SARS-CoV-2, and that the simultaneous generation of these two different functional types of Tfh cells could be a favorable feature of SARS-CoV-2 mRNA vaccines.

3.2.3. Cytotoxic T Cell Response

On the whole, mRNA vaccines seem to have a mixed ability to activate CD8 T cell responses. We previously described that a single dose of SARS-CoV-2 mRNA in mice is able to elicit, in both the spleen and the lungs, polyfunctional antigen-specific CD8 T cell responses characterized by the production of IFNγ, IL-2 and/or TNF [23]. Furthermore, the CD8 T cells activated by SARS-CoV-2 mRNA vaccines possessed the typical markers of cytotoxic T cells (Granzyme B and CD107a). In an independent study, Lu et al. found a significant increase in SARS-CoV-2-specific CD8 T cells post-vaccination with SARS-CoV-2 mRNA, measured by IFNγ production on CD8 T cells upon restimulation with vaccine antigens [44].

Preclinical studies of the mRNA clinical candidates also investigated the induction of cytotoxic T cells post-immunization in small and large animal models, with some controversial results. BNT162b2 administration in mice resulted in increased amounts of IFNγ- and IL-2-secreting CD8 T cells in the spleen 12 days after immunization, a result that was mirrored in rhesus macaques [12]. A similar finding was reported in $CD8^+$ splenocytes by Rauch et al. with CVnCoV [42]. Additionally, Zhang et al. were able to measure, after vaccination of mice with the clinical candidate ARCoV, a significant expansion of CD8 T effector memory cells, which were likely enriched for SARS-CoV-2-specific cells [43]. On the other hand, Moderna's mRNA-1273, which elicited a CD8 T cell response in mice [8], failed to induce detectable CD8 T cell responses in preclinical trials in macaques, even with doses as high as 100 µg [7]. A lack of CD8 T cell response to vaccines in which SARS-CoV-2 S is used as the immunogen is not too dissimilar to natural infection in humans, where the S protein has been shown to elicit relatively modest CD8 T cell response only in some, but not all, COVID-19 cases [70]. While potentially beneficial, there is no indication that the induction of cytotoxic CD8 T cells is required for successful protection against SARS-CoV-2 via vaccination.

4. Results from Human Clinical Trial with SARS-CoV-2 mRNA Vaccines

The efficacy of a vaccine is often measured by the proportional disease reduction in a population that is vaccinated versus one that has not been vaccinated [71]. Given the strong correlation between vaccine efficacy and the production of protective Abs that has emerged from several decades of human vaccine studies [37], early phase 1/2 research initially relied on this metric to define the efficacy of vaccine candidates. As more data from phase 2 and 3 clinical trials become available, a clear correlation between SARS-CoV-2 mRNA vaccines and protection from COVID-19 is starting to be established.

4.1. Phase 1/2

At the time of writing this article, only two vaccine developers, Moderna and BioNTech/Pfizer, have published peer-reviewed phase 1/2 studies on SARS-CoV-2 mRNA vaccines. For this reason, although other mRNA-based vaccine candidates are currently under development, we will focus only on clinical phase 1/2 reports from these two vaccine manufacturers.

4.1.1. Efficacy Profiles: Humoral Responses

In a phase 1 study of mRNA-1273, the vaccine co-developed by the National Institute of Allergy and Infectious Diseases and Moderna, 45 participants received two immunizations (prime and boost) with 25, 100, or 250 µg of this SARS-CoV-2 mRNA vaccine, 28 days apart [6]. Sera from all participants were tested by enzyme-linked immunosorbent assay (ELISA) for full S- and RBD-specific IgG binding titers. Participants in all dosage groups

developed anti-SARS-CoV-2 Ab responses, with S-2P- and RBD-specific IgG titers from the 100 and 250 μg vaccine dose groups within the median range of convalescent sera 15 days after initial immunization. Antigen-specific IgG titers continued to increase after the boost, with median post-boost titers from all vaccine dosage groups in the upper range of SARS-CoV-2 convalescent sera controls. Viral neutralization was measured by in vitro neutralization assays with a pseudotyped lentivirus and wild-type SARS-CoV-2. While a dose effect was observed, nAbs reached levels in the range of convalescent serum only after the second immunization in all vaccine groups, indicating the importance of a prime-boost immunization regimen to prompt robust neutralizing responses. Of note, participants from the 100 μg dosage group were followed up to 119 days after the initial vaccination (90 post-boost) and, despite a slight decrease, nAb levels remained significantly elevated in all participants [11]. These data suggest that mRNA-1273 has the potential to induce a durable Ab response. The vaccine candidates BNT162b1 and BNT162b2 were co-developed by BioNTech in collaboration with Pfizer. BNT162b1 encodes a secreted trimerized version of the SARS-CoV-2RBD protein, while BNT162b2 encodes the full-length S protein with the S-2P mutation described earlier. BioNTech and Pfizer concurrently began two phase 1/2 umbrella trials: one with the candidate BNT162b1 in Germany [13] and another one with candidates BNT162b1 and BNT162b2 in the US [14,15]. In the US trial, participants were vaccinated with 10, 30, or 100 μg of BNT162b1 and BNT162b2, while in the German trial doses of 1, 10, 30, 50, or 60 μg of BNT162b1 were tested. All doses of BNT162b1, were able to elicit an RBD-specific IgG response in the range of SARS-CoV-2 convalescent plasma within 21-days of initial vaccination, with an increase in titer after boost [13,14]. Moreover, S-binding IgG Abs were induced by both BNT162b1 and BNT162b2 at relatively comparable levels after the second immunization [15]. Similar to Moderna's results, both BioNTech's vaccines elicited nAbs values well above the baseline, measured via an in vitro neutralization assay with a modified SARS-CoV-2 reporter virus, only after the second immunization [13–15]. Taken together, these data indicate that SARS-CoV-2 mRNA vaccines are effective at inducing SARS-CoV-2 IgG responses, even at very low dosages. However, a second dose of either mRNA vaccine formulation seems to be required to reach significant levels of nAbs. It is also important to note that only SARS-CoV-2-binding IgG titers and nAb titers were measured in these human trials, and that a deeper analysis of B cell responses post-vaccination will have to be conducted in humans to connect the clinical data with those generated in animal studies.

The elderly population (≥65 years) poses a unique challenge for vaccine developers due to age-associated immunosenescence [72]. Impaired immune responses can potentially reduce vaccine efficacy in elderly subjects and make this population more likely to become critically ill upon infection with SARS-CoV-2. Indeed, the severity of disease and mortality due to COVID-19 are particularly high in the elder population [73]. For these reasons, individuals 65 years of age and older have been studied as a group of special interest. In a small phase 1 dose-escalation trial of mRNA-1273, 40 older adults were stratified according to age (56 to 70 years or ≥71 years) and immunized twice with either 25 or 100 μg of mRNA-1273. The authors found a good reactogenicity profile in both older cohorts, with robust binding and neutralizing Ab responses after two immunizations [9]. The data from this study also suggest that time- and dose-dependent trends were similar to those previously observed in a younger cohort [6], and that individuals over 56 years of age developed higher nAb responses after a second immunization and in response to the higher vaccine dose (100 μg). BioNTech/Pfizer's candidates were also reviewed in elderly individuals, with both BNT162b1 and BNT162b2 eliciting antigen-specific IgG titers after the first vaccination in elderly individuals that were enhanced by a second immunization [15]. Similar to the younger group, a booster immunization was required in the elderly group to elicit nAbs production, even though nAb titers were overall lower in elder participants in comparison to younger individuals. It is important to note here that since data from both of these companies were from phase 1 trials, the small numbers of participants in each group precluded the authors from performing meaningful statistical analyses.

4.1.2. Efficacy Profiles: Cellular Responses

As discussed earlier, it appears desirable for a SARS-CoV-2 mRNA vaccine to elicit Th1 CD4 T cell responses. Moreover, the induction of SARS-CoV-2-specific cytotoxic CD8 T cells can also be considered favorable, as this could provide an extra layer of immune-mediated protection. In phase 1 trials, Moderna's vaccine mRNA-1273 displayed measurable SARS-CoV-2-specific total CD4 T cell responses that were strongly biased towards the production of Th1 cytokines, with minimal Th2 cytokine production [6,9]. In both the younger and the elderly study groups, these responses appeared to be higher in individuals receiving 100 μg of mRNA-1273 in comparison to the 25 μg dose group. On the other hand, SARS-CoV-2-specific CD8 T cell responses were almost undetectable in most vaccinated individuals for this vaccine formulation, even after the boost dose. This outcome is not surprising, given that no antigen-specific CD8 T cell responses were found after immunization with mRNA-1273 in rhesus macaques during preclinical trials, even with doses as high as 100 μg [7]. BioNTech/Pfizer's BNT162b1 vaccine was also able to drive SARS-CoV-2-specific CD4 T cell responses [13]. The SARS-CoV-2-specific total CD4 T cells promoted by BNT162b1 were polarized toward a Th1 functional profile, as measured by the frequency of SARS-CoV-2-specific CD4 T cells producing IFNγ and IL-2 but not IL-4, upon stimulation with SARS-CoV-2 peptides. Differently from mRNA-1273, BNT162b1 was able to drive a SARS-CoV-2-specific CD8 T cell response in the majority of the trial subjects [13]. The phase 1/2 data are in line with all the animal studies on different mRNA vaccines described in 3.2.3, thus confirming that mRNA-1273 seems to be unique in its inability to trigger SARS-CoV-2-specific CD8 T cell response, while other mRNA vaccines are capable of inducing detectable virus-specific CD8 T cells. It is unclear why mRNA-1273 is unable to promote effective CD8 T cell response in larger animal models and humans. Possible contributors might be the SARS-CoV-2 mRNA design or the formulation of the LNPs.

4.1.3. Safety Profiles

These mRNA vaccine candidates have relatively favorable safety profiles. mRNA-1273 had no serious adverse events reported during the phase 1 trial that met the criteria for halting the trial. Among the reported adverse events, local pain at the injection site was common, whereas systemic events including fever, chills and headache were registered with increased incidence and severity after the booster immunization and with the higher vaccine doses [6]. The same safety profile was also observed in the elderly population [9].

The safety profiles of BNT162b1 and BNT162b2 are very similar to that of mRNA-1273 [13–15]. All vaccine groups reported pain and tenderness at the injection site as the most common adverse event. Fever, fatigue and chills were the most frequently reported systemic adverse events. Reactogenicity was dose-dependent and was more pronounced after the boost dose. On the basis of the higher reactogenicity reported at higher doses upon one immunization and after the boost at the lower vaccine doses, participants who received an initial 100 μg [14] or 60 μg [13] dose did not receive a second vaccine injection. Importantly, BNT162b2 induced less adverse events, including fever and chills, than BNT162b1, particularly in participants aged 65–85 years. The lower reactogenicity of BNT162b2, along with a comparable immunogenicity of the two candidates, supported the advancement of BNT162b2 to subsequent phase 3 studies [15].

4.2. Phase 3 Trials

As of 30 December 2020, the mRNA vaccine candidates BNT162b2 from BioNTech/Pfizer and mRNA-1273 from Moderna have both been approved for emergency use authorization in the United States. As such, mRNA vaccine administration to the public has commenced. Although necessary to halt the SARS-CoV-2 pandemic, with this decision also comes the issue of confounding the continuation of phase 3 studies. The individuals originally in the placebo control groups will also be vaccinated, making the long-term double-blinded study of SARS-CoV-2 vaccine-induced immunity impossible.

BioNTech/Pfizer have recently published data from the ongoing phase 2/3 clinical trial that is testing their vaccine, BNT162b2, for both safety and efficacy [16]. About 44,000 participants are enrolled in the trial, with ages ranging from 16 to 85 years of age. The participants were split randomly, at a 1:1 ratio, into two groups to receive either BNT162b2 or a placebo. The injections were given as a two-dose series, whereby the BNT162b2 group received two 30 µg doses, 21 days apart, and the placebo group received two saline injections instead. This two-dose immunization regimen conferred a remarkable 95% protection against COVID-19, citing that of those who received BNT162b2, only eight developed COVID-19, whereas 162 cases were reported in the placebo group. BNT162b2 displayed a very favorable safety profile, with only 27% of the BNT162b2 group and 12% of the placebo group reporting adverse events. These events were mostly short-term mild-to-moderate local reactions, such as pain at the injection site, and short-term systemic reactions such as fatigue, headache, and fever.

The Moderna vaccine mRNA-1273 is also currently undergoing a phase 3 clinical trial, data from which has recently been published [10]. This trial consists of around 30,000 participants with ages ranging from 18 to 85 years of age who were split randomly, at a 1:1 ratio, into two groups to receive either mRNA-1273 or a placebo. All participants received a two-dose injection series of either 100 µg of mRNA-1273 or a saline placebo, separated by 28 days. Moderna reported a 94.1% efficacy rate for mRNA-1273. Only 11 COVID-19 cases were reported in the mRNA-1273 vaccine group, versus 185 cases in the placebo group. The safety profile of this vaccine was also very favorable, with no specific safety concerns identified.

While both BNT162b2 and mRNA-1273 are currently approved for emergency use authorization, it is important to remember that the phase 3 trials are not complete. Participants will continue to be monitored over the coming months, and potentially years, to fully assess the vaccine safety and efficacy.

5. Strengths and Limitations of SARS-CoV-2 mRNA Vaccine Candidates

5.1. Strengths

mRNA-based vaccines have become an increasingly attractive platform to fight the ongoing SARS-CoV-2 pandemic for a multitude of reasons. Firstly, the need for only a DNA template of the desired antigen to produce a vaccine candidate, resulting in an exceedingly fast manufacturing timeline [4]. Clinical testing of the first mRNA vaccine candidate (mRNA-1273) began on March 2020 [74], just 66 days after the SARS-CoV-2 sequence was publicly released on January 2020 [75], with the second candidates (BNT162b1 and BN162b2) entering into phase 1/2 clinical trials only a month later [76,77]. By contrast, the development of vaccine candidates utilizing traditional vaccine platforms has been lengthy because of the inherently slow nature of developing cell lines, generating virus, and/or producing clinical-grade protein subunits, as demonstrated by the fact that the only vaccines that have been granted emergency authorization by the FDA thus far are mRNA vaccines.

Secondly, mRNA vaccines elicited a very potent immune response in both animal studies and human clinical trials, as extensively discussed in Sections 3 and 4. Importantly, these potent immune responses are substantiated by an impressive protection from COVID-19 in phase 2/3 studies [10,16]. While the FDA has initially stated that SARS-CoV-2 vaccines will require a minimum of 50% efficacy to qualify for approval [78], both of the current mRNA vaccines currently approved for emergency use authorization (mRNA-1273 and BNT162b2) reported a greater than 94% efficacy [10,16]. This level of efficacy sets a very high standard for SARS-CoV-2 vaccines, considering that the next most-advanced vaccine candidate in clinical trials (ChAdOx1 nCoV-19), an adenoviral vector vaccine from AstraZeneca/University of Oxford, is only about 70% effective [79].

mRNA vaccines also possess additional desirable features. Compared to other vaccine platforms, mRNA vaccines are appealing because of their minimalist nature. mRNA vaccines do not need a vector for their delivery/expression, thus removing the possible

complication of pre-existing and/or de novo anti-vector immunity [80]. Differently from inactivated or attenuated vaccines, less important antigenic targets that do not lead to nAb generation are not included. Since there is no need for the involvement of any viral growth, the possibility of other contaminating viruses from the cell lines is removed. mRNA vaccines that are encapsulated in LNPs also do not require complex delivery methods involving electroporation, as required by DNA vaccines, nor do they need the addition of an adjuvant, which is required with protein vaccines. Moreover, as described earlier, all available data suggest that the mRNA-LNP platform polarizes T cells towards a Th1 bias, suggesting that the likelihood of these vaccines causing adverse events, such as VAERD (discussed in Section 3.2.2), seems quite remote.

Finally, mRNA vaccines can be readily modified based on need. Target immunogenic epitopes can be easily switched in and out of candidates, as all that is needed is the DNA sequence of the antigen to serve as a template. A SARS-CoV-2 vaccine construct can be quickly adjusted to target a newly emerged coronavirus strain [8].

5.2. Challenges and Limitations

Although all the clinical data generated thus far indicate that mRNA vaccines are safe to use in humans, this is the first time that a vaccine of this type has been licensed. With that comes some potential unknowns. For example, there have been rare, recent reports of individuals experiencing anaphylaxis following immunization with a COVID-19 mRNA vaccine [81]. As with all vaccines, some people can have allergic reactions to one or more of the components that make up the vaccine. As it stands, it is unclear what the offending component(s) of this mRNA vaccine is (are), but anaphylaxis represents a major concern for people with a history of severe allergies.

Another uncertainty is the length of the immunity conferred by SARS-CoV-2 mRNA vaccines in humans. All preclinical data indicate that there might be long-term immunity elicited by this platform in animal models, but extended studies to address this point have not been published yet. In experiments utilizing an influenza hemagglutinin (HA)-based mRNA-LNP vaccine, it was shown that HA inhibition titers only slightly decrease in mice up to 400 days post-immunization [31], indicating that this vaccine platform is capable of generating durable Ab responses. To date, the persistence of mRNA vaccine-induced Abs in humans has only been reported up to 119 days post-initial immunization [11]. These data do, however, indicate that SARS-CoV-2-specific Ab titers only slightly wane in this time period, indicating the potential for long-lasting vaccine-induced immunity with this platform.

The need for ultracold storage required by mRNA vaccines is also a concern. Some research has suggested, however, that these vaccines are fairly stable at 4 °C for a week [43]. As it stands, the current recommendations for storage of the mRNA vaccine BNT162b2 are −80 °C to −60 °C for up to 6 months, or 2 °C to 8 °C for up to 5 days, to preserve potency [82]. Recommendations for the storage of the Moderna vaccine, mRNA-1273, are slightly different, with the FDA recommending long-term storage at −25 °C to −15 °C and storage at 2 °C to 8 °C for up to 30 days [83]. While the transportation and storage in many countries will not be an insurmountable issue, a wide distribution in remote locations and in developing countries appears quite challenging for mRNA vaccines.

6. Conclusions

Moving from the release of the SARS-CoV-2 genome sequence to SARS-CoV-2 mRNA vaccine phase 1/2 clinical trials within a couple of months has been an unprecedented endeavor for vaccine developers. Usually, the development of vaccines using standard approaches requires multiple years before an effective vaccine is licensed for human use. With the expedited development of SARS-CoV-2 mRNA vaccines comes public concern over cutting corners, and a fear of releasing a vaccine to the public before safety and efficacy are deeply assessed. Herein, we have provided a synopsis of SARS-CoV-2 mRNA vaccines, with emphasis on the adaptive immune responses elicited by the vaccine in preclinical and

clinical studies. Additionally, we have laid out the pros and cons of the mRNA vaccine platform. Published data from the current clinical candidates demonstrate a high degree of both efficacy and safety for this vaccine modality. Based on the available data, the mRNA vaccine platform offers a paradigm shift for both the development of vaccines as well as the preparedness for future pandemics.

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Abbreviations

Ab	Antibody
ACE2	Angiotensin-converting enzyme 2
APC	Antigen-presenting cell
COVID-19	Coronavirus Disease 2019
Δfurin	Full-length S lacking the furin cleavage site
DC	Dendritic cell
ELISA	Enzyme-linked immunosorbent assay
GC	Germinal center
HA	Hemagglutinin
Ig	Immunoglobulin
IL	Interleukin
LLPC	Long-lived plasma cell
LNP	Lipid nanoparticle
m1Ψ	N1-methyl-pseudouridine
MBC	Memory B cell
mRNA	Messenger RNA
nAb	Neutralizing antibody
RBD	Receptor binding domain (of SARS-CoV-2 S)
RIG-I	Retinoic acid inducible gene I
rRBD	Recombinant RBD
rRBD-AddaVax	rRBD given with the adjuvant AddaVax
S	Spike protein (of SARS-CoV-2)
S-2P	Spike 2-proline (SARS-CoV-2 S with proline substitutions at amino acids 986 and 987; stabilized in a prefusion conformation)
S1	Subunit 1 (of SARS-CoV-2 S)
S2	Subunit 2 (of SARS-CoV-2 S)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
Tfh	T follicular helper cells
Th1	T helper 1
Th2	T helper 2
TLR	Toll-like receptor

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Review

Opportunities and Challenges in the Delivery of mRNA-Based Vaccines

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Abstract: In the past few years, there has been increasing focus on the use of messenger RNA (mRNA) as a new therapeutic modality. Current clinical efforts encompassing mRNA-based drugs are directed toward infectious disease vaccines, cancer immunotherapies, therapeutic protein replacement therapies, and treatment of genetic diseases. However, challenges that impede the successful translation of these molecules into drugs are that (i) mRNA is a very large molecule, (ii) it is intrinsically unstable and prone to degradation by nucleases, and (iii) it activates the immune system. Although some of these challenges have been partially solved by means of chemical modification of the mRNA, intracellular delivery of mRNA still represents a major hurdle. The clinical translation of mRNA-based therapeutics requires delivery technologies that can ensure stabilization of mRNA under physiological conditions. Here, we (i) review opportunities and challenges in the delivery of mRNA-based therapeutics with a focus on non-viral delivery systems, (ii) present the clinical status of mRNA vaccines, and (iii) highlight perspectives on the future of this promising new type of medicine.

Keywords: mRNA; vaccines; therapeutic; prophylactic; drug delivery systems; lipids; polymers; nanoparticles; nanomedicine

1. Introduction

Vaccination has had a tremendous impact on global health and the quality of human life by reducing the mortality and morbidity caused by infectious diseases. The development of vaccines is predicated on the classical 3I's paradigm of "isolating, inactivating and injecting" the causative microorganism, coined by Louis Pasteur [1]. Vaccines can be prophylactic or therapeutic and can broadly be classified as live attenuated vaccines (weakened microorganisms), inactivated vaccines (killed microorganisms), subunit vaccines (purified antigens), or toxoid vaccines (inactivated bacterial toxins). As opposed to the conventional concept of injecting live-attenuated or inactivated pathogens, modern vaccine approaches, i.e., subunit vaccines, focus on exhibiting efficacy similar to conventional vaccines while obviating the safety risks associated with whole-cell vaccines. However, subunit antigens often display lower immunogenicity, which can be rectified by employing delivery systems and/or immunopotentiating compounds as adjuvants to boost immunogenicity. The modern genome-based rational vaccine design offers tremendous potential over conventional whole-organism-based vaccine approaches.

Nucleic acid-based vaccines, i.e., DNA (as plasmids) and RNA (as messenger RNA (mRNA)) vaccines, pave the way for safe and efficacious biologics to mimic inoculation with live organism-based vaccines, particularly for stimulation of cell-mediated immunity [2]. This technology exhibits promising potential for the development of novel vaccines against a wide variety of indications and diseases, extending from prophylactics to therapeutics for infectious diseases, cancer, autoimmune diseases, and hypersensitivities. While nucleic-acid-based vaccines demonstrate significant advantages over traditional vaccines [3] in terms of safety, efficacy, induction of both B- and T-cell responses and specificity, it is noteworthy to mention that mRNA vaccines have advantages when compared to vaccines based on other types of nucleic acids. A technical challenge associated with DNA vaccines is to ensure delivery into the cell nucleus, where antigen transcription takes place prior to nuclear export and translation into protein in the cytoplasm. In addition, DNA vaccines carry a potential risk of integration into the host genome, which may result in insertional mutagenesis. In contrast, mRNA vaccines are only targeted for cytoplasmic delivery, circumventing the risk of genomic integration [4]. The relatively short half-life results in transient and more controlled expression of the encoded antigen. Moreover, mRNA can be produced in a cell-free environment by in vitro transcription (IVT), thereby eschewing the use of microbes or cultured cells for production, and avoiding the associated quality and safety issues in the production. This permits simple downstream purification and rapid and cost-effective manufacturing [5]. However, mRNA is often promulgated on the grounds of the popular opinion that when using mRNA, unlike DNA, the stringent gene-therapy regulations are bypassed because mRNA does not integrate into the host genome. However, in reality, this only holds true in the US since in Europe, any active pharmaceutical ingredient, which contains or consists of a recombinant nucleic acid, used in or administered to human beings, falls under the scope of the regulation for advanced therapy medicinal products [6]. Therefore, mRNA-based therapeutics are categorized as gene therapy. The burgeoning field of mRNA vaccines is very exciting [3,7] and considerable amounts of relevant preclinical data have been generated, and several clinical trials have been initiated during the last decade. This gives rise to the vision of translating the mRNA vaccines into human application for prophylaxis and therapy. In this review, we discuss the current trends in mRNA vaccine approaches and various strategies and systems for delivering mRNA vaccines.

2. mRNA as Vaccines

The central dogma of molecular biology states that DNA is transcribed into mRNA, which is subsequently translated into protein [8]. The flow of genetic information in time and space is orchestrated by complex regulatory mechanisms. Gene therapy represents the introduction of genetic material into an individual's cells and biological tissues. Techniques like insertion, alteration, or removal of genes are employed for correcting defective genes responsible for disease development, which then cures a disease or ameliorates the clinical status of a patient [9]. Several vectors have been utilized for gene therapy and they are generally classified as non-viral and viral vectors. Non-viral vectors possess several advantages compared to the viral vectors, including low host immunogenicity and potential for scale-up [10]. However, the success of non-viral gene therapy has been very limited in the past, primarily due to the barriers existing for plasmid DNA (pDNA) delivery, e.g., the necessity to cross the nuclear membrane before translation, the presence of antibiotic resistance genes in pDNA, and most importantly, the difficulty in controlling and regulating long-term expression. The lack of control of long-term expression of pDNA poses a huge disadvantage in terms of the duration of treatment and possible side effects, which is in contrast to conventional drugs, where the treatment can be stopped instantaneously. These disadvantages of pDNA can possibly be overcome by using mRNA [11]. The mRNA carries genetic information from the DNA in the nucleus to the cytosol, where it is used by the ribosomes as a template for protein synthesis. As opposed to pDNA, the mRNA is efficacious in both mitotic and non-mitotic cells because mRNA exerts its function in the cytoplasm, hence its function is not dependent on active cell division. Furthermore, unlike pDNA or viral vectors, mRNA does not contain additional foreign genes, which makes mRNA a safer vector. The challenge of long-term

expression posed by pDNA can also be overcome by using mRNA, since mRNA mediates a rapid, transient expression of the encoded protein and the duration of the production is well-defined (usually a few days or weeks, depending on the specific mRNA platform). This makes mRNA expression easier to control than the gene expression from pDNA and viral vectors [11]. In addition, the manufacturing of mRNA is cell-free, which strongly reduces the chance of mRNA contamination with bacterial components. This makes it easier to produce mRNA than pDNA under good manufacturing practice conditions [12]. Finally, vector-induced immunogenicity can be avoided for mRNA therapeutics, unlike for viral vectors or virus-like particles, which may elicit a specific immune response against the exposed viral proteins [13]. Specific therapeutic applications of mRNA, which are currently being explored include (i) vaccination against cancer and infectious diseases, (ii) protein-replacement therapy, and (iii) gene editing. Table 1 summarizes examples of ongoing clinical trials of mRNA-based therapeutic and prophylactic vaccine candidates.

Two classes of mRNAs, i.e., non-replicating and self-amplifying mRNA, are commonly used as vaccine vectors. Non-replicating mRNA encodes only the protein antigen(s) of interest, while self-amplifying mRNA also encodes proteins enabling RNA replication [14]. Vaccines based on self-amplifying mRNA encode the RNA genome of a single-stranded RNA virus, e.g., an alphavirus, a flavivirus [15], or a picornavirus [7]. They are engineered to increase the duration and level of expression, as well as the subsequent immune response induced by the encoded antigen(s). They efficiently amplify the production of sub-genomic mRNA encoding antigen(s) of interest subsequent to a single round of replication. While both self-amplifying mRNA and non-replicating mRNA find application in prophylactic vaccines for infectious diseases, non-replicating mRNA is used for cancer vaccines.

3. Fundamental Pharmacology of mRNA Vaccines

In vitro transcribed (IVT) mRNA is employed therapeutically as it mimics fully mature native mRNA present in the eukaryotic cytosol [16]. This may be achieved either by ex vivo transfection of cells with mRNA that are then adoptively transferred or by direct in vivo delivery of the IVT mRNA to the cytosol [17]. These approaches are explored for genome engineering, genetic reprogramming, adoptive T cell and dendritic cell (DC) based cancer and infectious disease immunotherapies, tolerization regimens to treat allergies, and protein replacement therapies. Both ex vivo transfection and direct in vivo transfection enable the target cells to synthesize the encoded protein(s) in situ, where mRNA is used as a template and the protein(s) represents the active product. The open reading frame (ORF) of mature mRNA encoding the protein(s) of interest (the active product) marked by start and stop codons, respectively, is flanked by untranslated regions (UTRs), and ideally consists of a 5′ cap and a poly(A) tail [3].

The pharmacodynamic activity of both native and IVT mRNA takes place in the cytosol (Figure 1). However, in contrast to endogenous mRNA, which is transcribed from DNA in the nucleus and enters the cytosol through nuclear export, IVT mRNA enters the cytosol from an extracellular source [18]. Once the IVT mRNA is delivered to the cytosol, its pharmacology is governed by the same complex cellular mechanisms that regulate the stability and translation of endogenous mRNA. The engineered IVT mRNA resembles the endogenous mRNA so closely that the cellular translation machinery is seamlessly utilized to synthesize a protein that may undergo post-translational modifications, eventually resulting in mature protein product(s). In the case of vaccines, this mature protein product(s) represents the antigen(s), which may elicit potent pathogen-specific humoral and cell-mediated immune responses. However, the final intracellular destination is determined by the natural or engineered sequence(s) of the signal peptide or the transmembrane domain [7]. Therefore, mRNA vaccines can be designed for the delivery of the encoded protein(s) to the desired cellular compartment for proper presentation and/or function [19].

Table 1. Examples of ongoing clinical trials of mRNA-based vaccines.

mRNA	Mechanism of Action	Disease/Condition	Administration Route	Study Phase	Sponsor/Collaborator	National Clinical Trial Identifier
Therapeutic mRNA						
W_ova1 vaccine	Induction of an anti-tumor immune response	Ovarian cancer	Intravenous	Phase I	University Medical Center Groningen/BioNTech	NCT04163094
CT7, MAGE-A3, and WT1 mRNA-electroporated Langerhans cells (LCs)	Electroporation of dendritic cells with antigen mRNA	Multiple Myeloma	Subcutaneous	Phase I	Memorial Sloan Kettering Cancer Center	NCT01995708
Personalized Cellular mRNA	Immunization with DCs pulsed with mRNA encoded tumor antigens	Brain cancer/Neoplasm Metastases	Not specified	Phase I	Guangdong 999 Brain Hospital/Beijing, Tricision, Trinomab, Jinan University Guangzhou	NCT02808416
Personalized mRNA	Immunization with DCs pulsed with personalized mRNA	Glioblastoma	Not specified	Phase I	Guangdong 999 Brain Hospital/Beijing Tricision, Trinomab, Jinan University Guangzhou	NCT02808364
MiHA mRNA	Immunization with DCs loaded with MiHA mRNA	Hematological malignancies	Intravenous	Phase I Phase II	Radboud University/ZonMw: The Netherlands Organization for Health Research and Development Dutch Cancer Society	NCT02528682
WT1-mRNA	Immunization with DCs electroporated with WT1-mRNA	Acute myeloid leukemia	Not Specified	Phase II	Zwi Berneman/Kom Op Tegen Kanker stichting tegen kanker Research Foundation - Flanders (FWO: Fonds Wetenschappelijk Onderzoek)	NCT01686334

Table 1. *Cont.*

mRNA	Mechanism of Action	Disease/Condition	Administration Route	Study Phase	Sponsor/Collaborator	National Clinical Trial Identifier
Therapeutic mRNA						
Human CMV pp65-LAMP mRNA	Immunization with DCs pulsed with CMV pp65-LAMP mRNA	Glioblastoma	Intradermal	Phase II	Gary Archer Ph.D./Duke University	NCT03927222
Personalized mRNA	Personalized mRNA tumor vaccine encoding neoantigen	Advanced esophageal squamous carcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma	Subcutaneous	Enrolling	Changhai Hospital/Stemirna Therapeutics	NCT03468244
mRNA[BI 1361849 (formerly CV9202)]	Not specified	Metastatic non-small cell lung cancer	Not specified	Phase I Phase II	Ludwig Institute for Cancer Research/Cancer Research Institute, New York City, Boehringer Ingelheim MedImmune, CureVac, PharmaJet	NCT03164772
mRNA-5671/V941	Not specified	Neoplasms, carcinoma, non-small-cell lung, pancreatic neoplasms, colorectal neoplasms	Intramuscular	Phase I	Merck Sharp & Dohme	NCT03948763
mRNA-4157	Immunostimulants	Solid tumors	Not specified	Phase I	Moderna/Merck Sharp & Dohme	NCT03313778

Table 1. *Cont.*

mRNA	Mechanism of Action	Disease/Condition	Administration Route	Study Phase	Sponsor/Collaborator	National Clinical Trial Identifier
Therapeutic mRNA						
mRNA-4157	Immunotherapy with the personalized cancer vaccine	Cutaneous melanoma	Not specified	Phase II	Moderna/Merck Sharp & Dohme	NCT03897881
Personalized mRNA	Encoding neoantigen	Esophageal cancer Non-small cell lung cancer	Subcutaneous	Enrolling	Stemirna Therapeutics/The First Affiliated Hospital of Zhengzhou University	NCT03908671
mRNA-3704	Alpha-galactosidase stimulants; Methylmalonyl CoA mutase stimulants; Protein synthesis stimulants	Methylmalonic acidemia, metabolism, inborn errors	Intravenous	Phase I Phase II	Moderna	NCT03810690
mRNA-2416	OX40 ligand modulators	Relapsed/Refractory solid tumor malignancies or lymphoma	Intratumoral	Phase I	Moderna	NCT03323398
mRNA-2752	IL36G protein stimulants; Interleukin 23 stimulants; OX40 ligand modulators	Relapsed/Refractory solid tumor malignancies or lymphoma	Intratumoral	Phase I	Moderna/AstraZeneca	NCT03739931

Table 1. *Cont.*

mRNA	Mechanism of Action	Disease/Condition	Administration Route	Study Phase	Sponsor/Collaborator	National Clinical Trial Identifier
Prophylactic mRNA						
mRNA-1647, mRNA-1443	Not specified	Cytomegalovirus	Not specified	Phase I	Moderna	NCT03382405
mRNA-1893	Not specified	Zika virus	Not specified	Phase I	Moderna/Biomedical Advanced Research and Development Authority	NCT04064905
mRNA-1653	A combined human metapneumovirus and human parainfluenza virus type 3 vaccine	Human metapneumovirus and Human Parainfluenzavirus	Not specified	Phase I	Moderna.	NCT03392389 NCT04144348
mRNA-1944	Encoding for an anti-Chikungunya virus monoclonal antibody	Chikungunya virus	Parenteral	Phase I	Moderna	NCT03829384
mRNA-1653	Immunostimulants	Metapneumovirus and Parainfluenza virus	Parenteral	Phase I	Moderna	NCT03392389
CV7202	Immunostimulants	Rabies	Intramuscular	Phase I	CureVac	NCT03713086

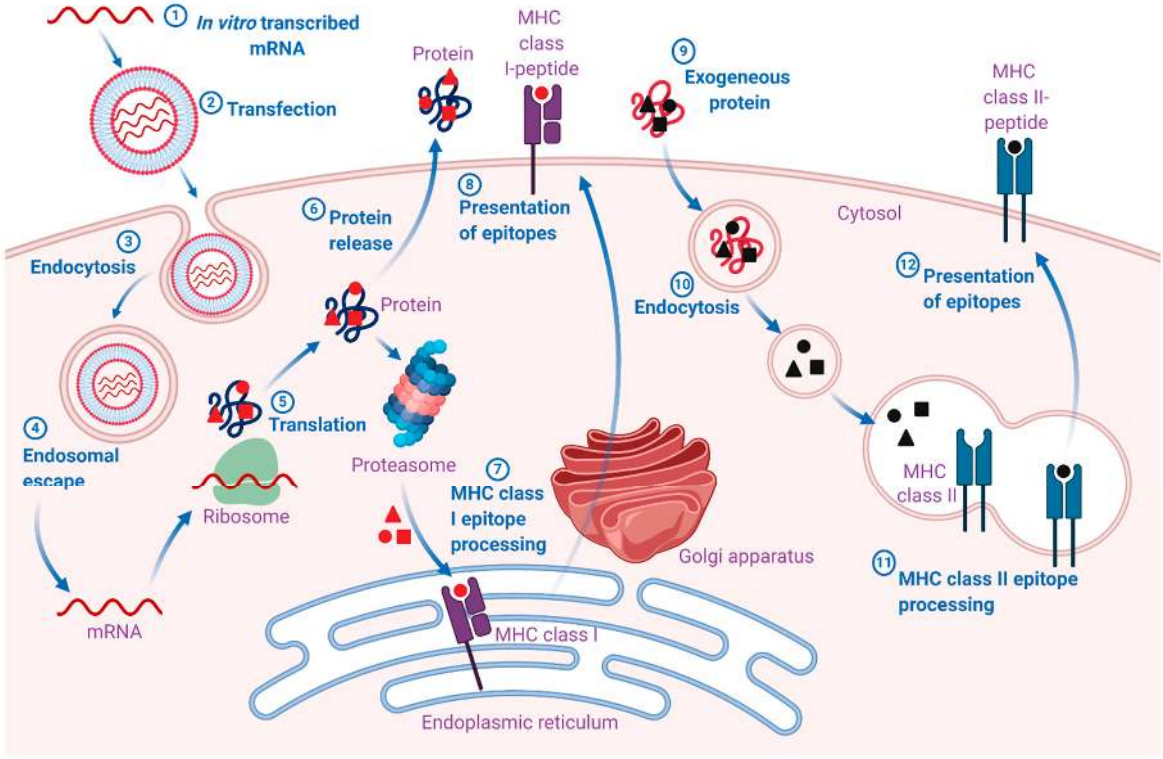

Figure 1. Mechanism of action of mRNA vaccines. 1. The mRNA is in vitro transcribed (IVT) from a DNA template in a cell-free system. 2. IVT mRNA is subsequently transfected into dendritic cells (DCs) via (3) endocytosis. 4. Entrapped mRNA undergoes endosomal escape and is released into the cytosol. 5. Using the translational machinery of host cells (ribosomes), the mRNA is translated into antigenic proteins. The translated antigenic protein undergoes post-translational modification and can act in the cell where it is generated. 6. Alternatively, the protein is secreted from the host cell. 7. Antigen protein is degraded by the proteasome in the cytoplasm. The generated antigenic peptide epitopes are transported into the endoplasmic reticulum and loaded onto major histocompatibility complex (MHC) class I molecules (MHC I). 8. The loaded MHC I-peptide epitope complexes are presented on the surface of cells, eventually leading to the induction of antigen-specific $CD8^+$ T cell responses after T-cell receptor recognition and appropriate co-stimulation. 9. Exogenous proteins are taken up DCs. 10. They are degraded in endosomes and presented via the MHC II pathway. Moreover, to obtain cognate T-cell help in antigen-presenting cells, the protein should be routed through the MHC II pathway. 11. The generated antigenic peptide epitopes are subsequently loaded onto MHC II molecules. 12. The loaded MHC II-peptide epitope complexes are presented on the surface of cells, leading to the induction of the antigen-specific $CD4^+$ T cell responses. Exogenous antigens can also be processed and loaded onto MHC class I molecules via a mechanism known as cross-presentation (not shown in the figure). The figure was created with BioRender.com.

The pharmacokinetics of IVT mRNA is determined by the half-life of the mRNA and the resulting mature protein after post-translational modification. The two major factors influencing the bioavailability of exogenous mRNA in the cytosol are (i) rapid RNase-mediated degradation and (ii) lack of passive diffusion across the plasma membrane owing to high molecular weight and electrostatic repulsion between the negative charges of the proteoglycan-coated cell membrane and the negatively-charged mRNA molecules [20]. Naked mRNA is rapidly degraded by extracellular

RNases, thus hindering its efficient delivery and efficacy. A wide range of in vitro and in vivo transfection reagents have been shown to protect the mRNA against degradation and facilitate the cellular uptake and endosomal escape of mRNA. Major efforts have been dedicated to improving the enzymatic RNA stability, as discussed further below [3]. Ultimately, the IVT mRNA composed of natural nucleotides is metabolized by inherent physiological mechanisms, hence reducing the risk of metabolite-induced toxicity. Therefore, the delivery issues can be overcome by approaches including encapsulation of mRNA in drug delivery systems consisting of cationic molecules, lipids, polymers, and nanoparticles [21] as well as targeting DCs [22]. In addition, physical transfection methods like electroporation have been shown to enhance the delivery efficiency of large, self-amplifying mRNA in vivo, upon measuring reporter gene expression and immunogenicity of genes encoding HIV envelope proteins [23].

4. Approaches for Enhancing mRNA Stability

The development of mRNA-based drugs dates back to 1990 with the successful expression of a number of different proteins upon injecting mRNA encoding these proteins directly into the muscles of mice [24]. This led to (i) the testing of the first mRNA-based vaccine in 1993, which was shown to induce an anti-influenza cytotoxic T-lymphocyte response in mice [25], and (ii) the first vaccination with mRNA-encoding cancer antigens in 1995 [26]. These inceptive demonstrations ratified the potential of mRNA for (i) in situ expression of specific proteins and (ii) for induction of protective antigen-specific cellular and humoral immunity. However, the field was neglected for almost ten years until the potential of in vivo application of mRNA, i.e., induction of specific cytotoxic T lymphocytes and antibodies, was discovered [27]. Advances in the mRNA field were slow due to the labile nature of mRNA, which makes experiments employing unmodified mRNA very challenging unless precautions to handle mRNA are strictly adhered to [28]. Instead, the focus was directed towards DNA-based drugs, since DNA is more stable than RNA.

In a cell-free system, mRNA can be synthesized by IVT of a DNA template (e.g., a linearized plasmid or a PCR product), which encodes all the structural elements of a functional mRNA. To perform an IVT reaction, all the elements of the natural transcription process are required, i.e., a DNA template, an RNA polymerase, and nucleotide building blocks. During the subsequent purification of the mRNA, the DNA template is often degraded by the addition of DNases, followed by purification by means of other conventional methods for isolating mRNA, e.g., precipitation and chromatography. This process results in highly pure mRNA products ready for use [29–31]. Several strategies have been pursued to cope with mRNA's inherent lack of stability and potential immunogenicity, which are discussed further below.

4.1. Molecular Stabilization

Strategies including engineering of sequences and/or structure to enhance mRNA stability (extend the half-life) and translation are often instrumental in increasing the protein expression levels. Techniques employed to achieve this includes elongation of the poly(A) tail, modification of the 5′ cap, engineering of the UTRs and the sequence patterns in the ORF, and/or incorporation of modified nucleotides (Figure 2).

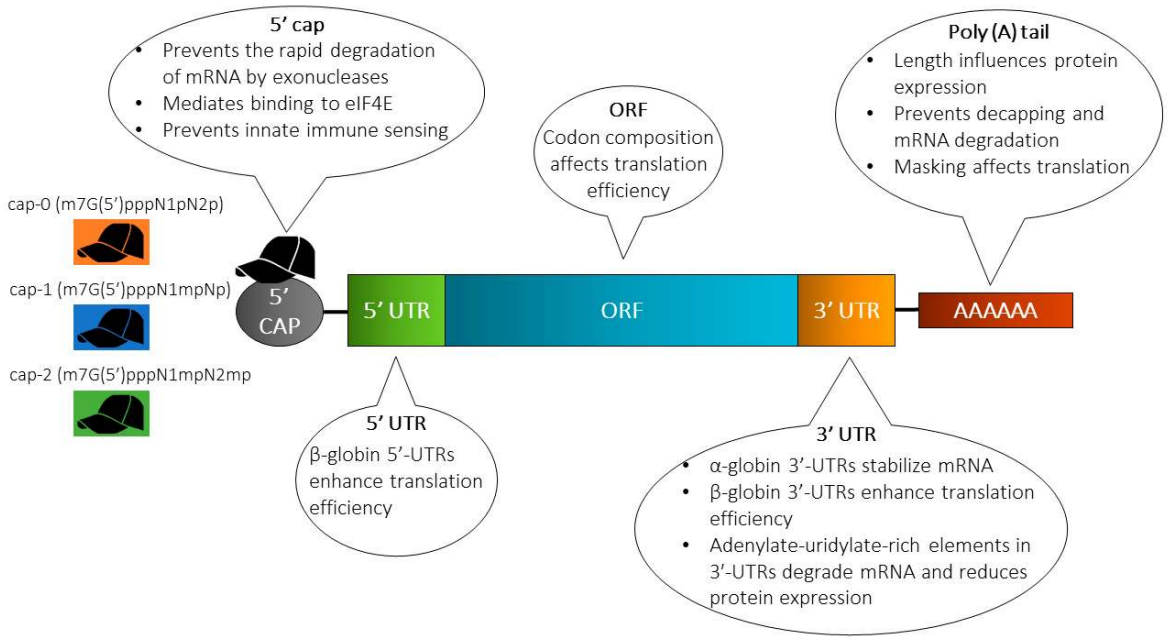

Figure 2. Structure of in vitro transcribed (IVT) mRNA and commonly used modification strategies. The design of IVT mRNA is based on the blueprint of eukaryotic mRNA, and it consists of a 5′ cap, 5′ and 3′ untranslated regions (UTRs), an open reading frame (ORF) encoding antigen(s), and a 3′ poly(A) tail. The IVT mRNA can be modified in one or multiple sites, e.g., by modification of the caps, the UTRs and/or the poly(A) tail, to modulate the duration and kinetic profile of protein expression. eIF4E, eukaryotic translation initiation factor 4E.

4.1.1. Cap Analog

A synthetic cap analogue can readily be added to the mRNA because the 5′ end cap is not encoded by the DNA template. Natural eukaryotic mRNA has a 7-methylguanosine (m7G) cap coupled to the mRNA during the transcription process via a 5′-5′-triphosphate bridge (ppp) [32]. The m7GpppN structure at the 5′ end of the mRNA cap serves several functions [33]. First, it protects the mRNA from rapid degradation by exonucleases. Second, it plays an indispensable role during translation because the eukaryotic initiation factor (eIF) 4E recognizes and binds to the cap of the mRNA. It further plays a role in preventing innate immune sensors from recognizing the mRNA [34]. The mRNA may contain one of three distinct caps, i.e., cap-0 [m7G(5′)pppN1pN2p], cap-1 [m7G(5′)pppN1mpNp] and cap-2 [m7G(5′)pppN1mpN2mp], respectively [11]. Capping of IVT mRNA can be performed using two different approaches: The first approach includes the addition of a second step with recombinant vaccinia virus-derived capping enzymes after the transcription, resulting in a cap identical to the most frequent endogenous eukaryotic cap structure i.e., 7-methylguanosine (m^7G) cap [30]. Alternatively, a synthetic cap analogue may be added during the in vitro transcription reaction, hence capping and in vitro transcription is performed in a single step. This approach is referred to as co-transcriptional capping [35]. A major drawback of this approach is the competition between the cap analog and the GTP nucleotide required for in vitro transcription, which ultimately results in a fraction of uncapped and translationally inactive mRNA [36]. The fraction of uncapped mRNA containing 5′ ppp groups is more immune-stimulating, which can be rectified by treatment with phosphatase to remove the ppp group at the 5′ end of uncapped mRNA [37].

Three different classes of m7GpppG cap analogs are used [38]: (i) anti-reverse cap analogs (ARCAs) [39], (ii) 3′-O-Me-m7GpppG [40], and (iii) modified ARCAs [41]. Initial mRNA research was performed using mRNA containing the m7 cap analog (GpppG) [42], and it is currently the most commonly used mRNA cap in clinical trials. Unfortunately, a fraction of the m7GpppG cap analog used during in vitro transcription becomes incorporated in the opposite orientation and is therefore not recognized by the ribosomes, eventually resulting in lower translational activity. To avoid this, the so-called ARCA with only one 3′-OH group instead of two 3′-OH groups (ARCAs; $m_2^{7,3'-O}$GpppG) has been introduced to prevent incorporation in the opposite orientation [43]. ARCAs juxtaposing the traditional cap analogues have been shown to exhibit more than four times RNA transcription efficiency [44]. In addition, the duration and the levels of protein expression have been found to be enhanced in cells transfected with ARCA-capped IVT RNA [41]. Recently, new types of chemically-modified cap analogues have been introduced, e.g., of phosphorothioate, phosphorothiolate [35], imidiphosphate [45], locked nucleic acid [46], boranophosphate bonds [47] and other types of modifications, which provide the mRNA with resistance to decapping by the mRNA-decapping enzyme 2, eventually resulting in a longer half-life of the mRNA [48].

Conventionally, the synthetic 5′-Cap 0-capped RNA is transcribed by performing an in vitro transcription, where more than 80% of the GTP added to the reaction is substituted with a dinucleotide cap analog (i.e., m7G[5′]ppp[5′]G), resulting in initiation of transcription with the cap analog [49]. However, this approach has been shown to exhibit a number of efficiency-related drawbacks, which have been overcome by the introduction of ScriptCap™. ScriptCap™ involves the addition of enzymatically built cap-0 structures onto the RNA transcripts by employing a capping enzyme with 100% reaction efficiency [50]. Native eukaryotic mRNA may contain a cap-1 or cap-2 but never a cap-0 [11]. Therefore, IVT mRNA should contain a cap-1 or a cap-2 in order to be less immune-stimulating [51]. A hallmark of these cap structures is the methylation status of the 2′ position of the 5′ second last and third last nucleoside. Prior to the advent of the novel technology of CleanCap™ introduced by TriLink, synthetic mRNA with a cap-1 could only be prepared by enzymatic capping [52,53]. However, cap-1 or cap-2 can now be incorporated during co-transcriptional capping at a capping efficiency of approximately 94% [52]. Notably, the capping efficiency has been shown to be significantly higher than the efficiency achieved by traditional co-transcriptional capping with cap-0 or ARCA [54].

4.1.2. 5′ and 3′ Untranslated Regions (UTRs)

The importance of incorporation of 5′- and 3′-UTRs has been noted during in vitro post-transcriptional regulation of gene expression [55]. The numerous roles that UTRs play include (i) regulation of mRNA export from the nucleus, (ii) regulation of translation efficiency [56], (iii) orchestration of subcellular localization [57], and (iv) mRNA stability [58]. Introduction of α-globin 3′ end UTRs results in stabilization of mRNA, while the incorporation of beta-globin 5′ end and 3′ end UTRs leads to enhanced translational efficiency [59]. The optimal outcome is achieved by using two β-globin 3′-UTRs aligned in a head-to-tail configuration. α-globin and β-globin UTRs have been incorporated for tweaking the RNA for optimized in vitro transcription followed by mRNA electroporation of autologous T cells [60] and intranodal injection of naked antigen-encoding RNA [61]. Moreover, DCs transfected with antigen-encoding UTR-optimized mRNA have been used in a study involving immunization of cytomegalovirus-seropositive individuals and cancer patients [62]. In some situations, destabilizing the mRNA might be a viable approach to reduce the duration of protein synthesis. This may be accomplished by introducing adenylate-uridylate-rich elements in the 3′-UTRs of the mRNA, eventually resulting in faster mRNA degradation and shortening of the duration of protein expression [63].

4.1.3. Poly(A) Tail

The poly(A) tail plays a significant role in mRNA translation as well as for the enzymatic stability of mRNA. The poly(A) tail binds to several polyadenosyl binding proteins (PABPs) while working synergistically with 5′m7Gcap sequences to regulate translational efficiency [64]. Eukaryotic translation initiation factor eIF4E binds to the 5′m7G cap, which in turn complexes with eIF4G and eIF4A. PABP then interacts with the N-terminus of the eukaryotic translation initiation factor eIF4G, which forms an mRNP (messenger ribonucleoprotein) or a polysome complex [65]. The former depicts the mRNA-protein complex not yet involved in protein synthesis, while the latter is one that is already being translated. An adequately long poly(A) tail is required to circularize the mRNA via binding of PABPs to the poly(A) tail and the cap [55,66]. It has been observed that increasing the poly(A) tail length improves the efficiency of polysome generation and consequently influences the protein expression levels [67].

It has been shown that a gradual increase in the poly(A) tail length of IVT mRNA to 120 bases commensurately increases the protein expression level, while an increase in the number of bases beyond 120 does not further enhance protein expression [68]. Poly(A) tails can be added to mRNA by encoding the poly(A) tail in the DNA template, or by extension of the IVT RNA after transcription using recombinant poly(A) polymerase. However, polyadenylation with recombinant poly(A) polymerase results in variable poly(A) tail length, thereby yielding polyadenylated mRNA with varying lengths. Therefore, the preferred approach is the generation of poly(A) tails with well-defined length from the mRNAs transcribed from poly(A) tail-encoding DNA templates [69]. The physical interactions between the 5′ and 3′ ends of mRNA take place between the cap and the poly(A) tail [70]. The poly(A) tail also plays a role in preventing decapping and mRNA degradation because removal or shortening of the poly(A) tail to less than 12 residues results in degradation of the mRNA through cleavage of the 5′ cap structure and 5′ to 3′ exonucleolytic digestion or 3′ to 5′ degradation [71].

4.2. Formulation Strategies

Despite the promising potential of mRNA-based vaccines, efficient intracellular delivery of mRNA to the cytosol continues to pose a major hurdle, especially for mRNA administered systemically. The large molecular weight (10^5–10^6 Da) [21] and high negative charge density of mRNA impair the permeation of mRNA across cellular membranes. It is well known that the absorption of mRNA in the absence of a delivery system is extremely low, and the half-life of mRNA is approximately 7 h [72]. Moreover, mRNA is an inherently unstable molecule, which is highly prone to degradation by 5′ exonucleases, 3′ exonucleases, and endonucleases [73]. Consequently, delivery systems are imperative for intracellular delivery of mRNA to the therapeutic site of action in vitro as well as in vivo [8,74]. Different strategies have been investigated to improve RNA delivery, including improved injection strategies such as microinjections [75], RNA patches [76], gene gun-based administration [77], protamine condensation [78], RNA adjuvants [79], and encapsulation of RNA in nanoparticles consisting of lipids and/or polymers [80]. Generally, IVT mRNA for cytosolic delivery is formulated with a delivery system by mixing with a complexing agent [81], which can protect the mRNA against rapid degradation and facilitate cellular uptake. Although the general dogma in the field is that efficient carriers are needed for substantially enhancing the in vivo transfection of mRNA, naked mRNA have been applied in many in vivo studies. Hence, the following section discusses the delivery of naked mRNA, followed by sections discussing vector-based mRNA delivery [82–85].

4.2.1. Naked RNA

The simplest administration strategy comprises intramuscular (i.m.) injection of naked mRNA, and proof of concept was originally demonstrated by in vivo reporter gene expression in mice [24]. Since then, the effectiveness of naked mRNA has been confirmed upon i.m. [86], subcutaneous (s.c.) [87] or intradermal (i.d.) [88] injections. I.d. and s.c. administration of mRNA has been shown to mediate healing of various skin diseases and to ameliorate wound healing by in situ expression of specific proteins in the skin [75,89]. Adopting this approach circumvents several obstacles otherwise associated with systemic administration of mRNA, e.g., clearance from the bloodstream via the liver, the kidneys, and the spleen [75]. Very efficient translation of the encoded protein has been shown for mRNA administered s.c. [90–92]. Interestingly, more efficient translation has at times been measured when compared to mRNA-loaded nanoparticle-based delivery systems [90,93]. Hence, it circumvents the need to employ carriers, eventually contributing to reduced cost and potential risk. Another advantage of administering mRNA-based vaccines via the s.c. route is that both cellular and humoral immune responses are induced [94] because the mRNA is expressed by both skin-resident DCs [95] and non-immune cells [96]. However, the outermost stratum corneum layer of the epidermis serves as a tight barrier to the absorption of topically administered drugs [97]. Heretofore, various approaches have been adopted to overcome this barrier, including physical (e.g., microporation [98], microneedles [99], and jet injection [100,101]), active (e.g., electroporation [102], iontophoresis [103], and sonophoresis [104]), and passive methods (e.g., nanoparticles [105] and liposomes [106]). Electroporation and sonoporation can transiently permeabilize the skin by means of electric pulses and low-frequency ultrasound, respectively, for efficient delivery of genes into the skin [107]. Modified mRNA-encoding vascular endothelial growth factor-A was formulated in citrate-buffered saline without the use of a delivery system and was used for i.d. vaccination of patients with type 2 diabetes [108]. However, in spite of pronounced, sustained, dose-dependent and cargo-specific vasodilation, blood flow increase, oxygen-metabolic upregulation, angiogenesis and neovessel formation in animal models, the vasodilatory and angiogenic activity did not translate into humans [108,109]. Microneedle-based delivery is also an efficient technique where micron-sized needle patch/arrays composed of water-soluble polymeric or sugar excipients are employed, into which the mRNA is incorporated [76]. The patches/arrays provide mechanical strength needed for the needle to permeate the stratum corneum and penetrate into the viable skin layers. Following injection, depending upon the type of microneedles, the patches/arrays degrade/dissolve and the encapsulated drug is released in the interstitial fluid of the skin [75]. Administration of mRNA by using dissolvable microneedles provides an important advantage, i.e., delivery in a solid dosage form circumvents the necessity of dealing with mRNA in a liquid dosage form [110], which therefore eliminates the menace emanating from RNase contamination, along with increasing mRNA stability, and shelf life [76]. Scavenger receptor-mediated endocytosis and micropinocytosis have been shown to be the active uptake mechanisms for naked mRNA in immature DCs [16]. However, naked mRNA displays a short plasma half-life, is prone to ribonuclease degradation, and faces difficulties in entering the cell. Therefore, delivery systems have been propounded to protect the mRNA and shield its negative charge.

4.2.2. Viral Vectors

Delivery of mRNA can be mediated by viral and non-viral vectors. Non-viral vectors can further be categorized into lipid-based delivery systems, polymer-based delivery systems, and lipid-polymer hybrid systems [111]. For viral RNA delivery, there has been a great deal of interest in the engineering of adeno-associated viruses to carry nucleic acid cargoes [112]. Genetically-modified viruses are usually employed for mRNA/gene delivery. The genes of these viruses are partially or fully substituted with model or therapeutic genes. A benefit of RNA viruses is that they are replicated and expressed locally in the cytoplasm. Positive strand RNA viruses are distinguished by a genomic sequence that can be translated directly into proteins of interest by host ribosomes. Notably, alphaviruses (e.g., Sindbis and Semliki Forest virus) [113], picornaviruses [114], and flavivirus [115] (e.g., Kunjin virus) have

been employed for mRNA delivery. Various alphavirus vectors can be used to express high levels of exogenous protein in a wide spectrum of hosts [116]. Commonly used approaches include the direct substitution of structural genes with heterologous expression or placing the nonstructural genes downstream of the RNA sub-genomic promoter [117]. However, alphaviruses induce severe cytopathogenic effects, which restrict their application in gene therapy, although different strategies can be employed to surmount this challenge [118]. Some of these strategies include engineering of mutant vectors with mitigated cytotoxicity and temperature-inducibility, and self-inactivating vectors with point mutations in the nsP2 gene (especially at position 726, 259 and 650) [119]. Sendai virus (SeV) (murine parainfluenza virus type 1 or hemagglutinating virus of Japan) that belongs to the Paramyxoviridae family is worth mentioning owing to its popular application as a vector. It is favored for its high but transient gene expression levels, wide host cell specificity, low pathogenicity, and strong immunogenicity [120]. As a vaccine platform, the Venezuelan encephalitis virus is of particular interest [121]. These vaccines encompass the live-attenuated viral vaccine TC-83 and a formalin-inactivated variety of it is referred to as C-84, which boosts the efficacy and increases the duration of immunity upon administering the TC-83 vaccine via different administration routes, intranasal being the most widely used [122]. However, using viral vectors embodies crucial drawbacks associated with genome integration, and possible host rejection (immunogenicity and cytotoxicity) among others [123], hence provoking the need for non-viral vectors for mRNA delivery [10].

4.2.3. Polymer-Based Vectors

Diethylaminoethyl (DEAE) dextran was the first polymer to be tested as a delivery reagent for IVT mRNA [124]. Later, it was shown that lipid-mediated mRNA transfection is 100 to 1000 times more efficient than DEAE-dextran [125]. This discovery stalled the progress of polymeric carriers and paved the way for lipid-based transfection reagents for nucleic acids, including mRNA. A comprehensive study compared the polymers poly-beta-amino-esters (PBAE) and polyethylenimine (PEI) with commercial transfection reagent Lipofectamine™ 2000 and 1,2-dioleoyl-3-trimethylammonium propane (DOTAP)/1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) for functional, antigen-specific T-cell responses after mRNA delivery [126]. All carriers were complexed with mRNA encoding the HIV-1 antigen *gag*. Gag-specific, IFN-γ secreting T cells were measured in the spleen and lymph nodes of mice immunized with gag mRNA complexed with cationic lipids but not in mice immunized with naked and polymer-complexed mRNA. PEI and its derivatives are among the most commonly employed cationic polymers [127]. They are water-soluble, display a high density of positive charge associated with the amino groups, and are proven mRNA carriers for in vitro transfection [128]. However, PEI displays toxicity issues owing to the high molecular weight (>25 kDa), which may arise from the adsorption of anionic serum proteins onto the polyplex surface between cationic polymers and anionic serum plasma proteins. However, the resultant increase in size is only transient as the proteins adsorbed on the surface of polyplexes prevent particle–particle aggregation in the long run [129]. Various efforts have been made to mitigate these challenges. The first proof of concept for safe and efficacious mRNA vaccine transfection employing cationic polymer was obtained by intranasal administration of 2 kDa PEI conjugated to cyclodextrin. Cyclodextrin conjugated to PEI enabled delocalization of the charge density on the polyamine backbone, hence reducing cytotoxicity and at the same time maintaining protonatable groups, resulting in improved transfection [130]. Polymeric nanoparticles composed of biodegradable polymers, e.g., poly(lactic-*co*-glycolic acid) (PLGA), are well suited for incorporation of hydrophobic and positively-charged molecules. They provide good colloidal stability, low toxicity, and the possibility of sustained release. However, due to the anionic nature of PLGA at physiological pH [131], the mRNA encapsulation efficiency is very low. Polymer-based carriers exhibit considerable potential for gene therapy owing to the substantial transfection efficiency and tolerable toxicity [132]. A series of multifunctional block copolymers, i.e., dimethylaminoethyl methacrylate (DEAMA), poly(ethylene glycol) methacrylate, and DEAEMA-co-n-butyl methacrylate, demonstrated a transfection efficiency of 77% and 50% in RAW 264.7 macrophages and DC2.4 dendritic

cells, respectively, thereby exhibiting potential as a carrier for mRNA-based intracellular vaccine delivery [133]. While different types of polymers and copolymers have been tested, the correlation between the structure of polymers and their biological response, e.g., transfection and toxicity, was found to be poor and thus, design of various polymer-based delivery systems relies on empirical, rather than rational approaches [134]. Despite the advantages mentioned above, polymer-based delivery systems are not as clinically advanced as lipid-based delivery systems owing to their polydispersity and challenges pertaining to metabolism of large molecular weight polymers [21].

4.2.4. Lipid-Based Vectors

Vectors based on lipids or lipid-like compounds (lipidoids) represent the most commonly used non-viral gene carriers [21]. Various synthetic and naturally-derived lipids have been employed to form liposomes (complexes of liposomes and nucleic acids are referred to as lipoplexes) or lipid nanoparticles (LNPs), both of which have been reported to efficiently deliver mRNA-based vaccines (Table 2). LNPs are often formulated by using cationic lipids displaying tertiary or quaternary amines to encapsulate the polyanionic mRNA. Cationic lipids spontaneously encapsulate negatively-charged mRNA, mediated by a combination of attractive electrostatic interactions with RNA and hydrophobic interactions, and thus have been used alone or in combination for lipofection of mRNA. The first reported use of LNPs as delivery system for mRNA came in 2015, with the delivery system consisting of ionizable cationic lipid/phosphatidylcholine/cholesterol/PEG-lipid in the ratio of (50:10:38.5:1.5 mol/mol) [86]. Examples of cationic lipids include e.g., 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) [135], DOTAP [136], and zwitterionic DOPE [137,138]. They are structurally denoted by a cationic headgroup, a hydrophobic tail group, and a linking group in between [139]. However, cationic lipids have been observed to exhibit pro-inflammatory reactions and undesirable side effects [140]. Therefore, neutral lipids are also incorporated into cationic liposomes to decrease toxicity and attain high transfection levels in vivo [106]. The mechanism of LNP-mediated delivery of mRNA is not fully understood, but LNPs are suggested to be internalized by endocytosis and are attached electrostatically and fused with the cell membrane via inverted non-bilayer lipid phases [21].

Liposomes are closed membrane structures, which are formed by self-assembly when phospholipids are dispersed in aqueous systems [141]. They consist of at least one phospholipid bilayer, which mimics the cell membrane structure enclosing an aqueous core [8]. DOTAP/DOPE at a 1:1 molar ratio has been reported as an effective transfection agent for mRNA encoding the HIV-1 antigen Gag, which successfully induced an antigen-specific immune response in vivo in mice [126]. Additionally, 3β-[N-(N′,N′-dimethylaminoethane) carbamoyl](DC)-Cholesterol)/DOPE-based liposomes in a [1:2] ratio achieved high encapsulation efficiency of enhanced green fluorescent protein (eGFP) mRNA, along with high eGFP expression in vitro [106]. Furthermore, an additional multi-component LNP displayed a tumor-suppressant effect when loaded with herpes simplex virus I (HSV I) thymidine kinase encoding mRNA. The LNPs were composed of DOTAP/Cholesterol [1:1] liposomes along with 1,2-distearoyl-phosphatidylethanolamine (DSPE)-polyethylene glycol (PEG) and DSPE-PEG-anisamide (AA) [142]. The principle behind their effectiveness may be summarized as a combination of its electrostatic interactions attributable to opposite charges and hydrophobic interactions with mRNA. Additionally, the endosomal escape capabilities and self-assembling properties resulting in uniform layers enclosing polymeric cores also contribute to the wide application of cationic lipids [143]. However, in vivo studies are more challenging due to the fast elimination of cationic lipids by the mononuclear phagocytic system [144]. Cationic lipids consisting of only one quaternary ammonium headgroup pose safety issues such as toxicity and immunogenicity in vitro [145] and in vivo [146]. For instance, cationic liposomes when administered via the intravenous route may induce hepatotoxicity [147] and can trigger a strong IFN-γ response in mice resulting in inflammation [148,149]. Furthermore, positively-charged lipids, e.g., DOTAP and DOTMA, can be neutralized by anionic serum proteins, leading to toxicity and reduced efficacy [150]. Moreover, challenges like unrestricted protein binding, colloidal instability, and drug leakage may arise [151].

Alternatively, new gene delivery vectors containing ionizable lipids [152] and lipid-like materials termed lipidoids [153] have been introduced to overcome challenges posed by conventional cationic lipids while retaining their advantageous transfection properties. Ionizable lipids for mRNA transfection are positively-charged at low pH (which aids in mRNA complexation when it is carried out in acidic buffer) but are neutral at physiological pH (for reduced toxicity post-injection) [154]. Unlike conventional cationic lipids, these lipidoids display a series of secondary and tertiary amines allowing for more efficient interactions with mRNA without remarkably increasing the overall charge of the delivery system [155]. Encapsulation of mRNA in nanoparticles serves to physically protect nucleic acids from degradation and depending on the specific chemistry can aid in cellular uptake and endosomal escape [156]. The combination of the ionizable lipid C12-200, cholesterol, DOPE and C14-PEG2000 at a 3.5:4.65:1.6:0.25 molar ratio, respectively, encapsulating erythropoietin mRNA (EPO-mRNA) displayed high efficacy in vivo when injected into mice, measured as the cellular expression of EPO [157]. The emphasis on the nanoparticle platform for mRNA delivery is in part due to the application of established DNA and siRNA delivery systems.

4.2.5. Lipid-Polymer Hybrid Nanoparticles

Lipid-polymer hybrid nanoparticles (LPNs) have been demonstrated previously to exhibit effective functional delivery of siRNA in vitro [158] and therapeutic delivery of siRNA in vitro and in vivo [159]. This hybrid delivery system has also shown promising results for delivery of mRNA, with the mRNA being encapsulated in a hybrid nanoparticle composed of the lipid-like material N1, N3, N5-tris(2-aminoethyl)benzene-1,3,5-tricarboxamide (TT) in TT3:DOPE:Cholesterol:DMG-PEG2000 (1,2-dimyristoyl-sn-glycerol, methoxypolyethylene glycol) with a polymeric PLGA core [160]. In addition, optimized LPNs consisting of the degradable polymer PBAE, formulated with PEG-Lipid C14-2000, showed successful delivery of mRNA to the lungs [161]. This, along with reported co-delivery of siRNA and mRNA with lipidoid polymer hybrid nanoparticles [162], shows that LPNs are an emerging nucleic acid delivery system. The hybrid formulation is thermodynamically favorable, with respect to hydrophobic, van der Waal, and electrostatic interactions [80]. Several lipids and polymers have been investigated to formulate stable nucleic acid lipid particles using this delivery system. Most common polymers employed are PLGA, polycaprolactone, polylactic acid, or their combinations, whereas the lipids used include DOTAP, 1,2-dilauroyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphocholine, lecithin, DSPE, and PEG, among others. Structurally, based on small-angle X-ray scattering and cryogenic transmission electron microscopy, these nanoparticles are suggested to entail a polymeric matrix core with lamellar lipid structures with the nucleic acid localized in the core and in the corona [163].

4.2.6. Peptide-Based Vectors

Peptide-based systems for mRNA delivery are gaining momentum due to the versatility peptides can offer. Peptide-based delivery systems, both alone and in combination with other materials such as polymers, have been reported in the literature. In a study concerning ovarian cancer therapy, the commercially available cell-penetrating peptide (CPP) PepFect14 was complexed with eGFP mRNA via attractive electrostatic interactions [164]. This nanoparticulate formulation was more efficient in transfecting eGFP mRNA into cells associated with ovarian cancer than commercially available lipofectamine MessengerMAX. Similarly, the CPP RALA has been used to effectively deliver both eGFP and OVA mRNA and has been demonstrated to outperform the cationic lipid DOTAP and the fusogenic lipid DOPE [165]. However, current limitations include targeted cell delivery [164] and short circulation half-life due to the low stability in serum-containing medium [166].

Recently, a novel polymer-peptide hybrid mRNA delivery nanoplatform was introduced [167] combining both polymer (PLA) based micelles and a cationic fusogenic peptide (RALA) to achieve appropriate degradability, mRNA stability, and endosomolytic properties for translation. It was reported to protect eGFP as well as FLuc mRNA against serum nuclease degradation and achieve DC transfection. Indeed, peptide-based vectors and hybrids are promising and interesting additions to the various existing non-viral carriers for the delivery of mRNA.

Table 2. Examples of nanoparticulate drug delivery systems for mRNA delivery.

Drug Delivery Systems	Composition	RNA	Disease/Condition	References
Polymers	Poly(glycoamidoamine)	Erythropoietin (EPO) mRNA	Anemia and myelodysplasia	[168]
	Polyethyleneimine	HIV-1 gag mRNA	HIV	[169]
	Poly(β-amino ester) (PBAE)	eGFP mRNA	N/A	[170]
	Triblock copolymer (comprising DMAEMA, PEGMA, DEAEMA and BMA)	eGFP and ovalbumin	N/A	[171]
	DEAE-Dextran	Luciferase-encoding mRNA	N/A	[172]
Lipids	DOTAP/DOPE	HxB-2 HIV-1 Gag antigen mRNA	HIV	[126]
	DOPE/DC-Cholesterol [2:1]	eGFP mRNA	N/A	[106]
	DOTAP/Cholesterol [1:1] liposome with DSPE-PEG and DSPE-PEG-AA	HSV I Thymidine kinase mRNA	Cancer	[142]
	C12-200:Cholesterol: DOPE:C14-PEG2000	EPO mRNA	N/A	[157]
	A18	Ovalbumin mRNA	Melanoma	[173]
	cKK-E12	HER2 antibody mRNA	Cancer	[174]
	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), DSPC, cholesterol, and 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol (PEG2000-DMG)	Human erythropoietin		[175]
	DOTAP/DOPE [1:1]	HIV-1 antigen Gag mRNA	HIV	[126]
	3β-[N-(N′,N′-dimethylaminoethane) carbamoyl](DC-Cholesterol)/DOPE (1:2)	eGFP mRNA	N/A	[106]
Lipid polymer hybrid NPs	TT3:DOPE:Cholesterol:DMG-PEG2000 with PLGA core	Firefly luciferase (FLuc) mRNA and eGFP mRNA	N/A	[160]
	PBAE:C14-PEG2000	FLuc mRNA	N/A	[161]
	PBAE:EDOPC/DOPE/DSPE-PEG	Ovalbumin mRNA	N/A	[176]
	PBAE: DOPC, DOTAP, and DSPE-PEG	eGFP mRNA	N/A	[105]
Peptides and peptide-polymer hybrids	PepFect14	eGFP mRNA	Ovarian cancer	[164]
	RALA	eGFP mRNA OVA mRNA	N/A	[165]
	RALA-PLA	eGFPmRNA FLuc mRNA	N/A	[167]

BMA: butyl methacrylate; DEAE: diethylaminoethyl; DEAEMA: diethylaminoethyl Methacrylate; DMAEMA: dimethylaminoethyl acrylate; DOPE: dioleoylphosphatidylethanolamine; DOTAP: dioleoyl-3-trimethylammonium propane; DSPC: dipalmitoylphosphatidylcholine; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol); DSPE-PEG-AA: DSPE-PEG-anisamide; eGFP: enhanced green fluorescent protein; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; HSV: herpes simplex virus; N/A: not applicable; PEGMA: poly(ethylene glycol) methacrylate; PLGA: poly(lactic-co-glycolic acid); TT: N1,N3,N5-tris(2-aminoethyl)benzene-1,3,5-tricarboxamide; PLA: polylactic acid.

4.3. Cell-Specific mRNA Delivery

Cell-specific delivery of mRNA would be beneficial for the development of mRNA-based therapeutics. This can enhance the delivery of mRNA molecules to the targeted cells and hence reduce the required mRNA dose, as well as reducing potential off-target effects. It has been reported that lymphoid organs can be targeted by adjusting the net charge of the formulation [177]. This is based on the principle of APCs being in the vicinity of T cells in these organs, thus providing optimal conditions for efficient priming and amplification of T-cell responses. Site-specific delivery of mRNA-loaded nanoparticles via active targeting has been shown to result in induction of strong effector and memory T-cell responses, and mediation of potent IFN-α-dependent rejection of progressive tumors, as observed with RNAs. In another study, cell-specific delivery of FLuc and IL-10 mRNA to leukocytes (Ly6c+) was achieved by coating the formulated mRNA-containing LNPs with anti-L6c+ monoclonal antibodies [178]. Alternatively, DCs and macrophages express receptors with the ability to present antigens, e.g., C-type lectin receptors [179], which recognize sugar groups such as mannose- and fucose-terminated glycans [180] and mediate the endocytosis of mannose-modified nanoparticles. This has been exploited for transfection of GFP mRNA into DCs by self-assembly of mannose-cholesterol conjugates with varying PEG units as linkers [181].

5. Conclusions and Future Perspectives

The field of mRNA-based therapeutics spans from protein replacement therapy and gene editing to vaccination. With the dozens of mRNA-based vaccine candidates currently in pre-clinical and clinical phases of development, it is evident that the mRNA-based vaccine technology is a promising tool for the development of novel therapeutic and prophylactic vaccines against infectious diseases and cancer. However, the multifarious obstacles associated with mRNA's extremely large size, charge, intrinsic instability, and high susceptibility to enzymatic degradation hamper the translation of mRNA-based therapeutics from the bench to the bedside. Therefore, the wider application of mRNA-based therapeutics is still limited by the need for improved vectors or drug delivery systems. Advanced delivery systems can be applied to overcome the poor stability, cell targeting, and translational efficiency of naked mRNA. However, many clinically tested mRNA vaccine candidates are formulated without any delivery system, which suggests a need for further improvement of delivery systems for mRNA vaccines. Presently, lipoplexes and lipid-based nanoparticles are mostly used for delivering mRNA. Additionally, polymers and lipid-polymer hybrid nanoparticles offer great promise in terms of safety, stability, high transfection efficiency, and low price. Continued advancement in mRNA formulation and delivery using different nanomaterials can improve the wider use of mRNA for the treatment and prevention of infectious diseases and cancers.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 May 2020
EMA/231636/2020
Media and Public Relations

Press release

COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines

As researchers race to develop vaccines and therapeutics against COVID-19, EMA has published an overview of how the Agency will accelerate its regulatory procedures so that marketing authorisations of safe, effective and high-quality COVID-19 related medicines can be granted as soon as possible. The rapid procedures described in the inventory can accelerate every step of a medicine's regulatory pathway and the Agency is fully mobilised to deliver these fast-track assessments in the shortest possible timeframes while ensuring robust scientific opinions are reached.

"Supporting the development and marketing authorisation of safe, effective and high-quality therapeutics and vaccines as soon as possible is one of EMA's top priorities in the COVID-19 public health emergency. Together with our scientific committees and working parties, we have adapted our procedures in order to significantly shorten our own regulatory timelines for the review of new medicines and vaccines against COVID-19," said Executive Director Guido Rasi. "However, the rapid approval of therapeutics and vaccines will only be possible if applications are supported by robust and sound scientific evidence that allows EMA to conclude on a positive benefit-risk balance for these products."

These 'rapid' procedures stem from EMA's emerging health threats plan. The flexible and fast review of medicines is supported by **EMA's pandemic Task Force (COVID-ETF)**, which brings together in one group the best scientific experts from the EU regulatory network. It will work closely with EMA's human medicines committee (CHMP) for optimal and fast coordination of activities related to the development, authorisation and safety monitoring of medicines and vaccines against COVID-19.

Accelerated support during research and development

For products under development, in early stages and/or before the submission of a marketing authorisation application, mechanisms put in place by EMA include:

- **Rapid scientific advice**, through which developers can receive prompt guidance and direction on the best methods and study designs to generate robust data on how well a medicine or vaccine works, how safe it is, as well as on the manufacturing and control process to establish

its quality. In the context of COVID-19, fees for scientific advice are waived and the procedure is reduced to a maximum of **20 days**, compared to normally 40-70 days.

- **Rapid agreement of paediatric investigation plans (PIPs) and rapid compliance check**. The total review time for a PIP for COVID-19 products will be reduced to **20 days**, compared to normally up to 120 days active review time. In case needed, EMA also carries out a check to ensure companies comply with the agreed measures listed in each PIP before a marketing authorisation can be submitted, which will now also be reduced to **4 days**.

All these accelerated mechanisms will require developers to submit well-prepared dossiers to EMA. The Agency therefore continues to encourage developers of vaccines or therapeutics against COVID-19 to make contact as soon as possible, to discuss their strategy for evidence-generation, by emailing 2019-ncov@ema.europa.eu. Depending on the maturity of the development, initial discussions on the various mechanisms to fast-track development and approval will take place, with priority given to the most relevant proposals.

Accelerated evaluation in authorisation and post-authorisation procedures

According to the EU pharmaceutical legislation, the standard timeline for the evaluation of a medicine is a maximum of 210 active days. However applications for marketing authorisation for COVID-19 products will be treated in an expedited manner:

- **Rolling review**. This procedure, used in a public health emergency, allows EMA to assess data for a promising medicine as they become available on a rolling basis. Under normal circumstances, all data supporting a marketing authorisation application must be submitted at the start of the evaluation procedure. In the case of a rolling review, CHMP rapporteurs are appointed whilst development is still ongoing and the Agency reviews data as they become available. Several rolling review cycles can be carried out during the evaluation of one product as data continue to emerge, with each cycle requiring around **two weeks**, depending on the amount of data to be assessed. Once the data package is considered complete, a developer submits a formal marketing authorisation application to EMA which is then processed under a shortened timetable.
- **Accelerated assessment**. This procedure can reduce the review time of products of major interest for public health from 210 days to less than 150 days. In practice, where there is an urgent public health need, assessment timelines will be reduced to the absolute minimum.
- EMA is ready to apply further flexibility, where it is established that shortening of any other procedural step could have an important public health impact in dealing with the COVID-19 pandemic.

The various rapid procedures are also available in the context of extensions of indications for already approved medicines, which are being repurposed in the fight against COVID-19.

The inventory also describes the support EMA can provide in the context of **compassionate use** programmes. Such programmes are set up at the level of individual EU Member States, to give patients access to treatments that are still under development and that have not yet received a marketing authorisation. EMA can provide scientific recommendations as to how these medicines should be used in this context, to support a harmonised EU-wide approach.

Notes

1. This press release, together with all related documents, is available on the Agency's website.
2. Information on EMA's contribution in the COVID-19 pandemic is available here.

3. More information on the work of the European Medicines Agency can be found on its website: www.ema.europa.eu

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Bourla-29

How are COVID-19 vaccines developed?

Dr. Marco Cavaleri
Head of Biological Health Threats and Vaccines Strategy, EMA

An agency of the European Union

Outline

1. Overview
2. Pharmaceutical quality studies
3. Laboratory studies
4. Clinical studies - efficacy and safety
5. COVID-19 vaccines compared with standard vaccines
6. COVID-19 vaccines under assessment for approval by EMA

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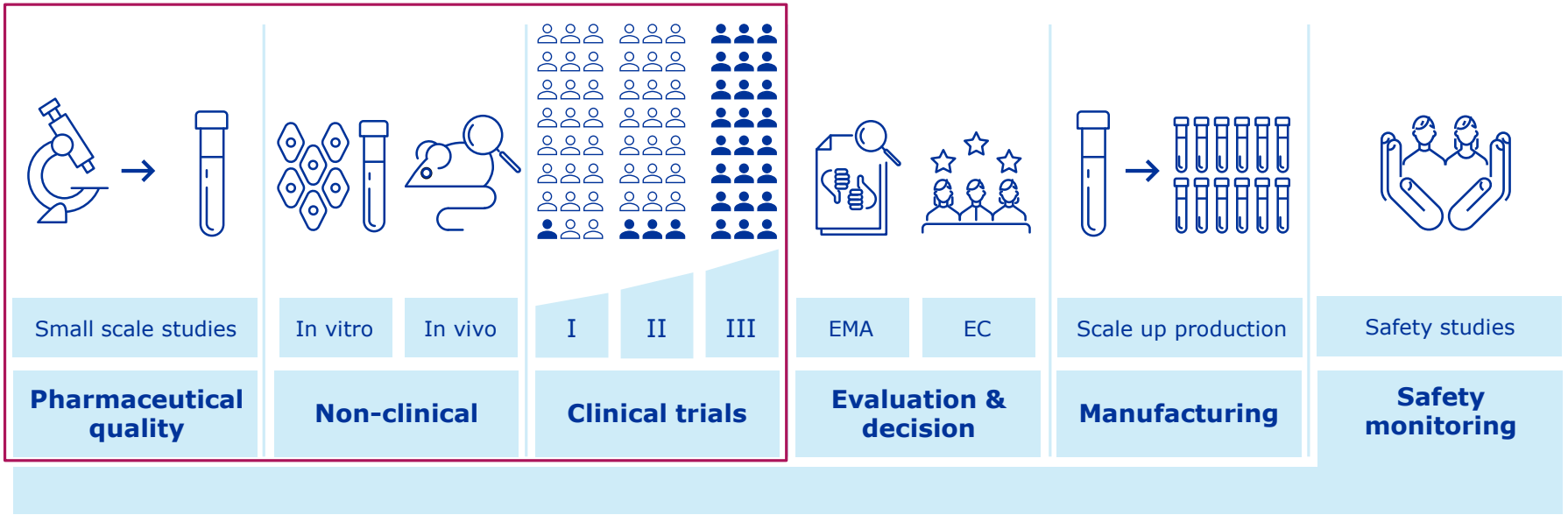
Overview

COVID-19 VACCINE DEVELOPMENT, EVALUATION, APPROVAL AND MONITORING

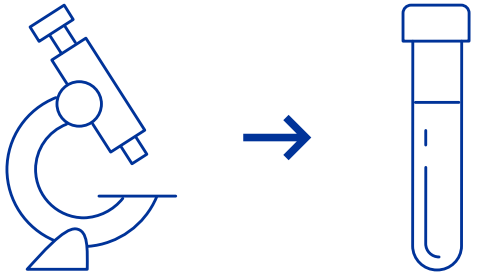


Pharmaceutical quality studies

Pharmaceutical quality | Non-clinical | Clinical trials | Evaluation & decision | Manufacturing | Safety monitoring

Studies to generate data on:

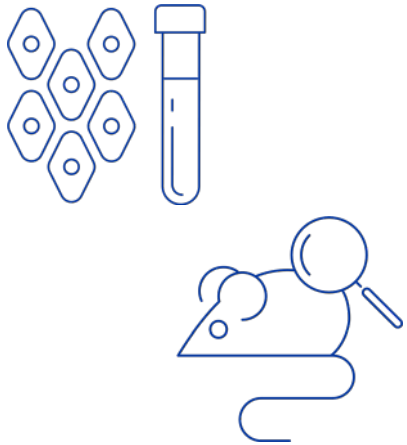
- Vaccine **components** and their **purity**
- Vaccine's biological activity
- Data on each step of **manufacturing**
- Data on the **controls** used to ensure that each batch of vaccine is consistently of good quality
- Conditions for **storing** the vaccine



Laboratory studies

Pharmaceutical quality | **Non-clinical** | Clinical trials | Evaluation & decision | Manufacturing | Safety monitoring

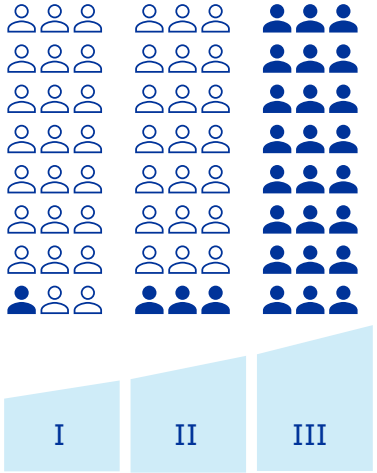
- Studies in the **laboratory before** testing in **humans** for **all vaccines**
- **Types of immune responses** the vaccine causes.
- Can **identify potential safety problems**
- Make sure the vaccine does not cause **fertility problems** nor affect **babies' development** before birth
- **Challenge studies check** if animals given COVID-19 vaccine are protected from disease when exposed to the virus and not worsening the disease
- Sometimes studies on **how the vaccine reaches** body **organs**



Clinical studies – efficacy and safety

Pharmaceutical quality | Non-clinical | **Clinical trials** | Evaluation & decision | Manufacturing | Safety monitoring

- Clinical trials are studies in humans which show:
  - **how safe the vaccine is** (safety)
  - **how well the vaccine works** (efficacy)
  - **immune responses** (immunogenicity)
- Three study phases:
  - Phase I: **early studies**
  - Phase II: **larger exploratory studies**
  - Phase III: **efficacy and safety studies**



Clinical trials follow strict scientific and ethical rules

Clinical studies – efficacy and safety

Pharmaceutical quality | Non-clinical | **Clinical trials** | Evaluation & decision | Manufacturing | Safety monitoring

Phase I trials

- **20 - 100** healthy volunteers
- Expected **immune response**?
- **Safe** to move into **larger studies**?
- Which **doses**?

Phase II trials

- **Several hundred** volunteers
- Best **doses** to use?
- Most common **side effects**?
- Immune response in more people?

Phase III trials

- **Thousands** of volunteers
- How the vaccine **protects against disease** compared with placebo (dummy) or with a non-COVID vaccine
- Less common **side effects**?

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Clinical studies – efficacy and safety

MEASURING COVID-19 VACCINES' BENEFIT

- **Prevention of symptomatic disease as** main measure of benefit
  - **Less disease with symptoms** in people given vaccine *compared to placebo*
- Other benefits likely **uncertain at approval** and only clearer after the vaccine is used:
  - **Long term protection**
  - Prevention of infection (**asymptomatic** cases)
  - Prevention of virus **transmission in the community** - needs specific studies post-approval

Efficacy levels

Studies designed to show efficacy of 50% or more

50% efficacy means the vaccine prevents half of the cases of symptomatic COVID-19 compared with placebo

90% efficacy means the vaccine prevents nine out of 10 cases of symptomatic COVID-19 compared with placebo

Clinical studies – efficacy and safety

- **Large number** of **adults** expected (above 30,000)
- Ideally **one quarter** of all participants **above 65 years** of age
- **Some people** with **underlying diseases** at risk of severe COVID-19
- Some studies include **adolescents above 16** years of age
  - Younger children to be studied after analysing data in adults and adolescents
- Some **minorities** represented
- Follow-up data for **at least** the **6 weeks** after last dose of vaccine
  - Most side effects occur within 4-6 weeks of having a dose
- Trials to last **for at least 1 year:** longer-term protection & side effects

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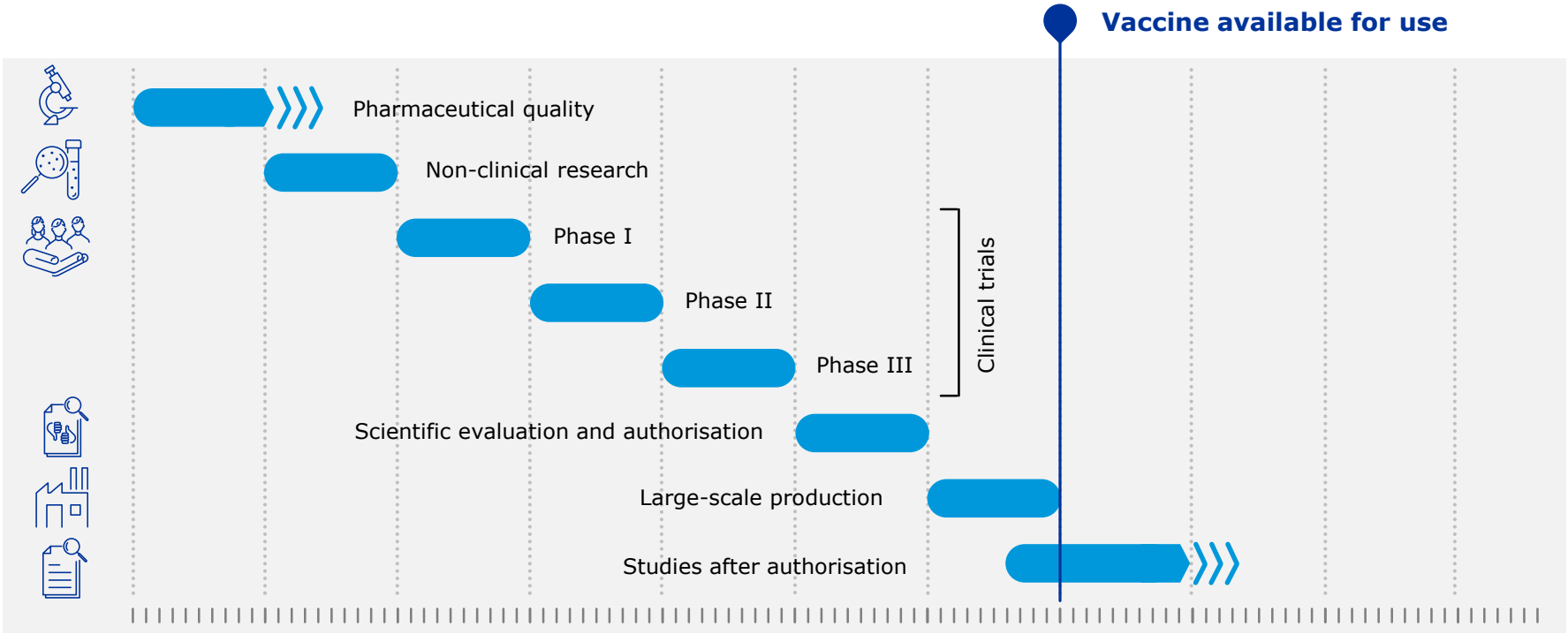
STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Indicative timeline



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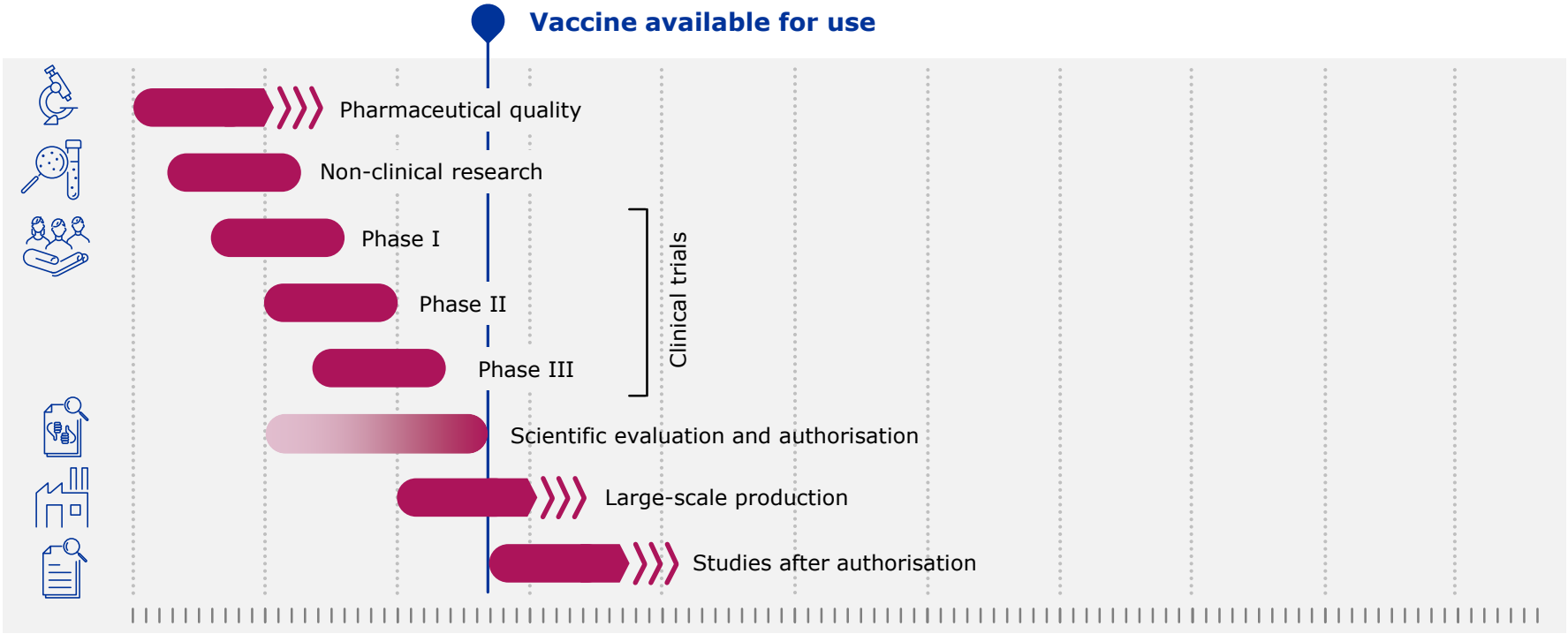
STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Indicative timeline



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Regulatory standards

COVID-19 vaccines must be approved according to the **same standards** that apply to all medicines in the EU

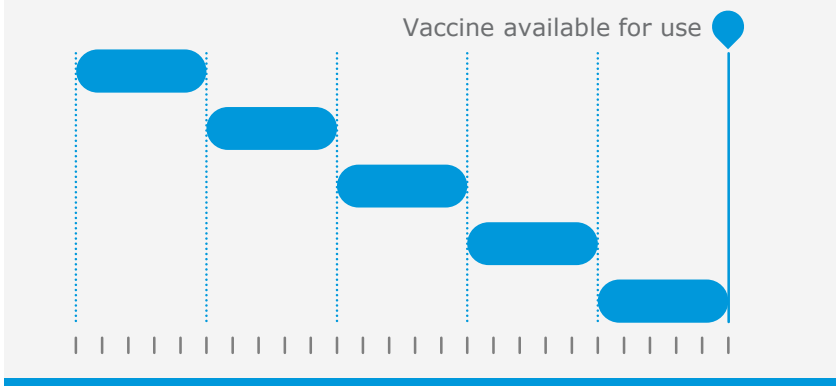
STANDARD

COVID-19

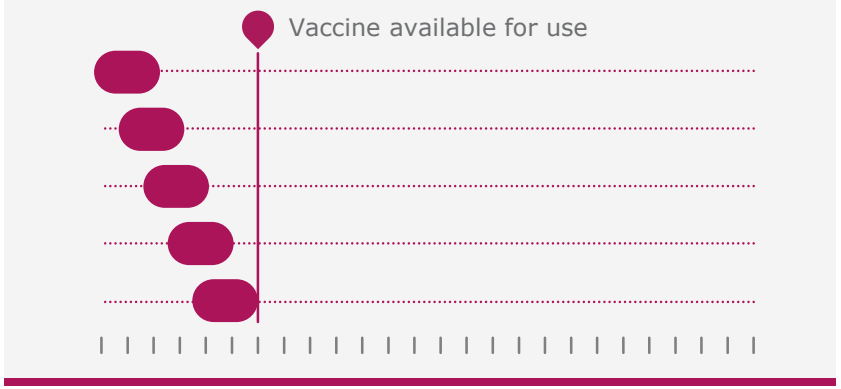
Timelines

COVID-19 vaccine development is **compressed in time**, applying the extensive **current knowledge** on vaccine development

STANDARD



COVID-19

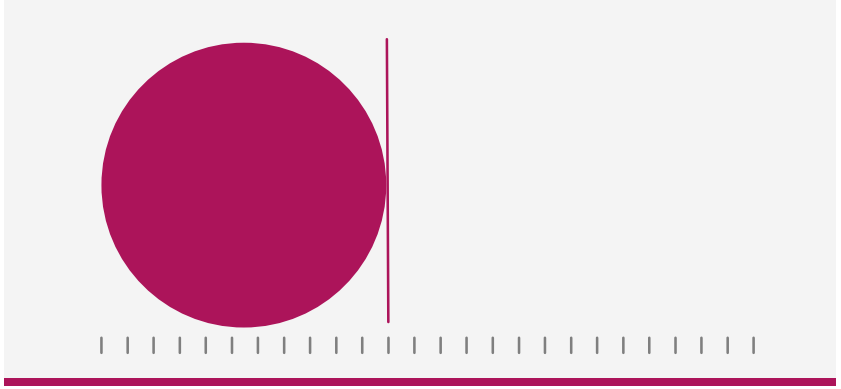


Resources

COVID-19 vaccine development **mobilises more resources simultaneously**

STANDARD

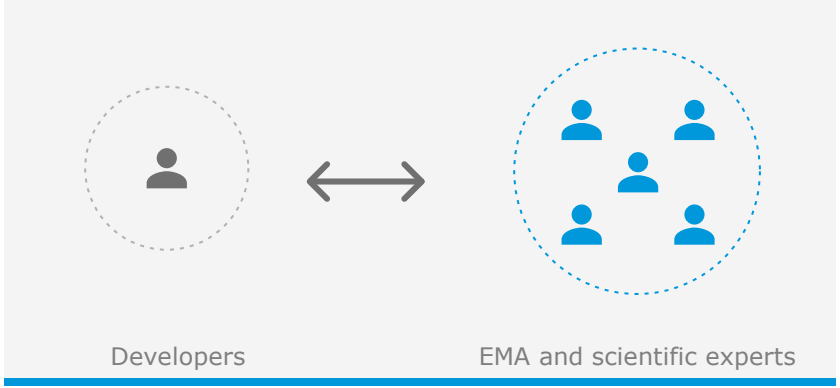
COVID-19



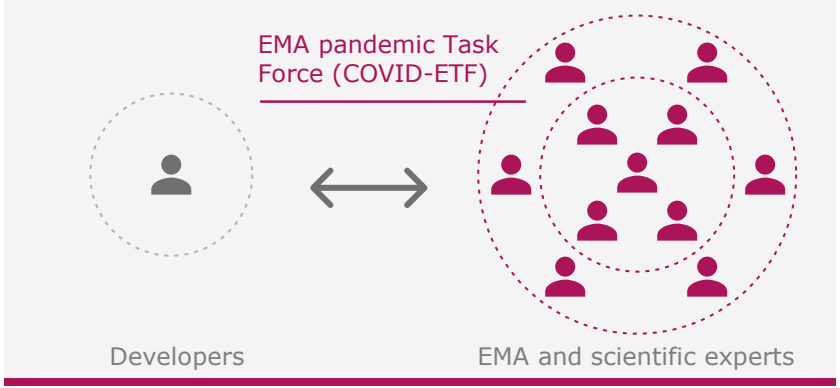
Expert Task Force & continuous dialogue

COVID-19 vaccine development is supported by early, continuous dialogue between developers and a dedicated group of regulatory experts **EMA COVID-19 Task Force**

STANDARD



COVID-19



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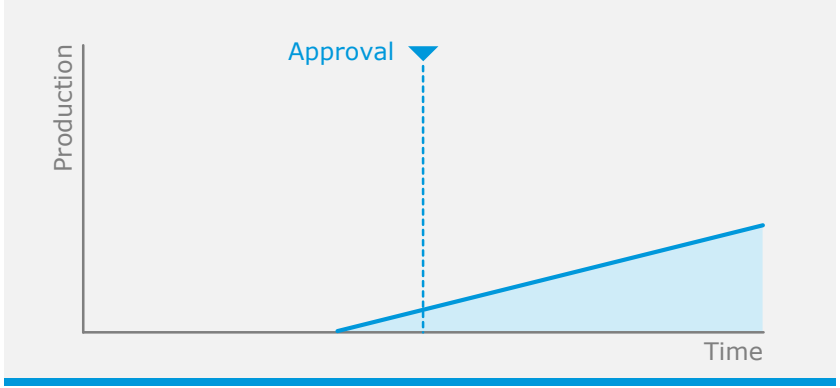
STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

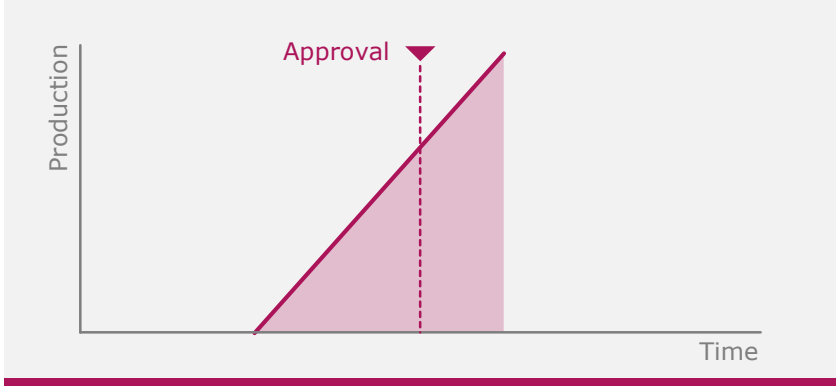
Manufacturing

Companies are **expanding** manufacturing and production **capacity** to ensure efficient vaccine deployment

STANDARD



COVID-19



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COVID-19 vaccines under assessment for approval by EMA

mRNA vaccines contain genetic instructions (mRNA) for making an immune response against coronavirus

- Pfizer-BioNTech (BNT162b2)
- Moderna (mRNA-1273)

Viral vectors use modified harmless adenovirus to carry genetic instructions for making an immune response against coronavirus

- Astra Zeneca/Oxford (ChAdOx1-SARS-CoV-2)
- Janssen (Ad26.COV2.S)

New systems

- Faster development and manufacture of key ingredients
- Based on experience and knowledge with other vaccines and medicines

More vaccines

- With other viral vectors or specific proteins are under development

Conclusions

- **Same types of studies** as for other medicines
- Timelines **shortened** - **Pooling** expertise
- Studies in **large numbers of people**
- Expected benefits at time of initial approval:
  - Demonstrated **reduction in** COVID-19 **disease**
  - Some **uncertainties: long term protection** and **community transmission**
  - Use of facemask, hand hygiene, physical distance **remain important**
- **High** regulatory **standards** for Quality, Safety and Efficacy

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Whither COVID-19 vaccines?

Nature Biotechnology convenes a group of experts to provide their insights into SARS-CoV-2 vaccines in development.

Galit Alter is at Harvard Medical School and the Ragon Institute, Boston, MA, USA.
Kate Bingham is at SV Health Managers, London, UK, and chairs the UK Vaccines Taskforce.
Larry Corey is at the Fred Hutchinson Cancer Research Center, Seattle, WA, USA.
James Dahlman is at Georgia Institute of Technology and Emory University, Atlanta, GA, USA.
Nick Jackson is at Coalition for Epidemic Preparedness Innovations, Shanghai, China.
John Moore is at Weill Cornell Medical School, New York, NY, USA.
Rino Rappuoli is at GlaxoSmithKline, Siena, Italy.

Questions swirl around trailblazing COVID-19 vaccines as they enter late-stage clinical testing (Tables 1 and 2), with anticipation building for an Emergency Use Authorization in the United States. How is broadening knowledge of immune responses to SARS-CoV-2 informing vaccine research? What are the pros and cons of the different vaccine modalities in discovery and clinical development? What are the key challenges associated with clinical testing, and what are their implications for safety and efficacy of immunization programs in the broader global population? And what issues related to regulatory oversight, manufacturing and distribution are likely to be important in the rollout of a COVID-19 vaccine?

How has research on the cellular and humoral immunity to SARS-CoV-2 and other coronaviruses informed vaccine development?

Galit Alter, Harvard Medical School and Ragon Institute.

Galit Alter: Correlates of protection do not need to mimic correlates of resolution of disease. Immune mechanisms that govern clearance of an existing infection need not even include antibodies. However, one can learn about the specific footprints of the most potent neutralizing antibodies, about viral evolution/evasion, about additional 'backup' immune mechanisms that may be critical for eradication of an infection, and about the role of additional intrinsic immune phenomena that may govern asymptomatic infection or long-lived shedding from viral pathogenesis studies. Vaccine studies show that neutralizing antibodies alone do seem to be protective against SARS-CoV-2 infection, although emerging data point to additional antibody effector functions and cellular immune responses that may support the complete elimination of the virus.

Kate Bingham: No vaccine has ever been developed against any human coronavirus, but there are good coronavirus vaccines for chickens and pigs. Although it is clear that both SARS-CoV-1 and SARS-CoV-2 trigger a strong immune response in most people, several studies have shown that antibody titers in those recovering from the virus decline within a few months of infection. This observation may not be surprising — if a person has successfully fought off the infection, you would expect their antibodies to drop to a lower, baseline level. So it is essential to run phase 3 safety and efficacy studies of vaccines to gain a deeper understanding of the immune responses generated to assess which vaccines confer protection against COVID-19, both to avoid infection (namely, via induction of strong mucosal immunity) and to prevent shedding. It is likely that memory T cells and B cells contribute to long-term immunity and protection. Happily, we are in an era of unprecedented capacity to assess the immune response.

The UK government's Vaccine Taskforce [VTF] is investing in building standardized, accredited assays, including quantitative high-throughput spike [S] protein ELISAs [enzyme-linked immunosorbent assays], live viral neutralization assays and T-cell assays to quantify antibody and cellular immune responses to gain a better understanding of which elements of the immune response are necessary for protection and to help define immune correlates of protection. Virus variation may prove challenging to the interpretation of these immune responses, and these responses may vary by different age groups. We are also seeking second-generation vaccines that may elicit a greater breadth of immune response, including mucosal immunity and induction of T-cell responses against a broader set of viral antigens beyond SARS-CoV-2 S protein.

Larry Corey, Fred Hutchinson Cancer Research Center.

Larry Corey: Only vaccine trials themselves with assessment of some threshold of immune protection will define what type and levels of vaccine-induced immunity are needed to achieve protection from either SARS-CoV-2 infection or disease. Natural infection cohorts can give potential targets to consider to achieve immunity, but all the initial vaccine candidates at the moment are designed to induce immune responses to the S protein and not to the panoply of antigens associated with natural infection. Persons with severe disease tend to develop antibodies sooner and at a higher magnitude than those with mild disease — an observation made with both SARS-CoV-1 and SARS-CoV-2.

John Moore: Immunity to the common cold coronaviruses definitely wanes with time, such that people become reinfected after about a year (both naturally and in long-ago virus-challenge experiments). Antibody titers to SARS [severe acute respiratory syndrome] and MERS [Middle East respiratory syndrome] also decrease significantly over time, but very little was ever learned about immune memory to those viruses, and T-cell responses were rarely studied[1].

It's going to be very important to monitor convalescent COVID-19 patients, particularly those with mild disease and low-level antibody titers, to see if and when reinfections do become more common. At the moment, we're hearing only rare and sometimes controversial anecdotes. What's the duration and extent of immune memory? What antibody and T-cell measurements are associated with any reinfections that are well documented?

There is an increasing amount of data on T-cell responses to the OWS [Operation Warp Speed] vaccines, although the balance of evidence is strongly toward neutralizing antibodies being more important for protection. I would like to see much more data on mucosal responses, particularly IgA [immunoglobulin A]. It's pretty surprising there's so little known so far.

My assumption is that vaccine immunity to SARS-CoV-2 may not be long-lasting (a year or two?) and that booster immunizations might be needed if the virus is still circulating. This, of course, remains to be proven.

Rino Rappuoli, GlaxoSmithKline.

Rino Rappuoli: The work on SARS and MERS vaccines showing good protection in animal models increases our confidence that vaccines for SARS-CoV-2 will be possible. The data suggest that serum neutralizing antibodies are sufficient to protect from infection. The importance of serum neutralizing antibodies is also confirmed by the experience of treating COVID-19 patients with plasma from convalescent patients, showing impact on clinical disease and on viral load. Several studies on human monoclonal antibodies derived from memory B cells from COVID-19 convalescent patients also confirm in animal models that neutralizing antibodies protect from infection and improve the disease outcome.

What types of preclinical studies are needed to fill gaps in our knowledge of SARS-CoV-2 immunity and galvanize progress in vaccine design, safety and efficacy?

G.A.: Unquestionably, each vaccine should be tested in non-human primate [NHP] models, where the virus shows different levels of pathogenicity. Thus, rhesus macaques show some lung pathology, but largely experience asymptomatic infection, whereas other monkey species appear to experience more severe disease. Given that the outcome in most vaccine studies will be severity of disease, it is essential to perform deep immunological investigations across animal species with different degrees of disease severity to preempt any potential harm caused by vaccines. Moreover, the identification of mechanistic correlates of immunity that can be defined in passive transfer studies in primates or other animal models would point to specific endpoint immunological assays that could be incorporated into phase 3 testing and help with vaccine licensure.

Kate Bingham., SV Health Managers and UK Vaccines Taskforce. Credit: Tom Kates

K.B.: Non-human primate models are primarily used to assess safety. It is not possible to compare efficacy seen in different NHP models since different challenges and different assays are used that are not standardized. It is too early to define good animal models [for COVID-19]; rhesus macaques appear quite promising as do Syrian hamsters and ferrets. The typical rhesus macaque models used in SARS-CoV-2 studies involve young animals that recover from infection on their own, mirroring that seen in infections of (young) humans. NHP models have been used to show antibody-dependent enhancement (ADE) pathology using the adjuvant alum, and so data from NHP models can form part of the preclinical safety package for regulators.

Given the wealth of immunological, and ultimately efficacy, data that are being generated in clinical trials, preclinical models will be far less relevant than human efficacy clinical data. The problem with lab animals is that they have had no external exposure to disease. NHP data are not likely to have substantial impact on the efficacy decisions of which vaccines to use. The best thing to do is to study the immune response in patients who have been infected with the virus and recovered and try to mimic this with a vaccine. This means deep study of the T- and B-cell responses in humans, in response to both vaccine and the natural infection.

L.C.: Mice and NHP animal models show that high antibody titers are more likely to lead to increased vaccine-induced protection. Passive transfer studies suggest neutralizing antibodies can protect the lung and perhaps, in high titers, the upper airway (likely partially). The human efficacy studies for SARS-CoV-2 in the United States are large (30,000 persons) and hence make it difficult to assay cell-mediated correlates of protection, but are designed to evaluate correlates of protection for neutralizing and binding antibody assays. Hopefully, functional antibody responses to the S protein will be associated with clinical effectiveness.

James Dahlman, Georgia Institute of Technology.

James Dahlman: One key study would be to further optimize mRNA vaccines in non-human primate models by varying the immunogen and the lipid nanoparticle (LNP) carrying the mRNA. It is encouraging that the first-generation mRNA vaccines both demonstrated safety in early clinical trials. Using these first vaccines as a starting point, next-generation SARS-CoV-2 vaccines, which may be needed if the virus persists over the coming years, could be improved.

J.M.: I would like to see animal, particularly macaque, challenge studies [in which viral inoculation is] delayed for substantial periods of time after the peak of the vaccine-induced antibody response. There is a single preprint showing protection (viremia reductions) after a delayed challenge (77 days) in DNA-vaccine-immunized macaques. That kind of study needs to be more widely performed and extended in time, to provide us with a feel for the duration of protective immunity. Ideally, we would have a disease model, and not just the existing mild infection-then-clearance models (macaques, various small animals, transgenic hACE2 [human angiotensin-converting enzyme 2] mice).

R.R.: Although we do not have perfect animal models, rhesus macaques, hamsters and mice expressing the hACE2 receptor are available and provide good information to make decisions before going to humans. Clearly, humans remain the best model. In vitro studies on mucosal IgGs and IgAs may also be important, especially to understand protection in the upper respiratory tract and impact of vaccines on transmission. Finally, studies on T-cell immunity will be important, especially as some of the vaccine platforms, such as RNA and viral vectors, induce $CD8^+$ T cells in addition to neutralizing antibodies.

What have we learned from previous vaccines, and how well have results from non-human primate studies translated to humans?

R.R.: The beautiful work done by Jason McLellan to stabilize the S protein of MERS coronavirus in the prefusion conformation[2] provided the knowledge to up-front engineer SARS-CoV-2 S protein in the prefusion-stabilized form. This information has been the basis for most of the COVID-19

Table 1 | SARS-CoV-2 vaccines in late-stage clinical development

Sponsor	Vaccine type (product)	Clinical stage	Trial ID
Beijing Institute of Biological Products, Sinopharm	Inactivated virus	Phase 3	ChiCTR2000032459, ChiCTR2000034780
Wuhan Institute of Biological Products, Sinopharm	Inactivated virus	Phase 3	ChiCTR2000031809, ChiCTR2000034780
Sinovac Biotech, Instituto Butantan, Bio Farma	Inactivated virus (inactivated SARS-CoV-2 plus alum; CoronaVac; formerly PiCoVacc)	Phase 3	NCT04456595, NCT04352608, NCT04383574, 669/UN6.KEP/EC/2020
University of Oxford, Oxford Biomedica, Vaccines Manufacturing and Innovation Centre, Pall Life Sciences, Cobra Biologics, Halix, Advent, Merck, Serum Institute of India, Vaccitech, Catalent, AstraZeneca, IQVIA	Non-replicating viral vector (chimpanzee adenoviral vector encoding S protein; AZD 1222; formerly ChAdOx1)	Phase 3	NCT04324606, EudraCT 2020-001072-15, EudraCT 2020-001228-32, NCT04400838, ISRCTN89951424, PACTR202006922165132
Moderna, NIAID, Lonza, Rovi, Medidata, Bioqual	RNA-based (nucleoside-modified mRNA vaccine encoding codon-modified S protein encapsulated in ionizable LNPs, containing distearoyl phosphatidylcholine, cholesterol and polyethylene glycol lipid)	Phase 3	NCT04283461, NCT04405076, NCT04470427
Gamaleya Research Institute of Epidemiology and Microbiology	Ad5 and Ad26 with a coronavirus gene, administered separately	Phase 3	NCT04530396
CanSino Biologics, Beijing Institute of Biotechnology, National Research Council of Canada	Non-replicating viral vector (Ad5 vector encoding S protein)	Phase 3	NCT04313127, ChiCTR2000030906, ChiCTR2000031781, NCT04398147, NCT04341389, NCT04456595
BioNTech, Fosun Pharma, Pfizer	RNA-based (mRNA vaccine expressing codon-optimized, nucleoside-modified mRNA that encodes trimerized RBD in ionizable cationic LNPs containing phosphatidylcholine, cholesterol, polyethylene glycol lipid)	Phase 2/3	EudraCT 2020-001038-36, NCT04368728, ChiCTR2000034825
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated virus	Phase 2	NCT04412538, NCT04470609
Anhui Zhifei Longcom Biopharmaceutical; Institute of Microbiology, Chinese Academy of Sciences	Protein subunit (adjuvanted recombinant protein RBD dimer)	Phase 2	NCT04445194, NCT04466085
CureVac	Protamine-complexed mRNA vaccine expressing undisclosed SARS-CoV-2 protein	Phase 2	NCT04515147
Zydus Cadila	Electroporated DNA vaccine encoding undisclosed SARS-CoV-2 protein	Phase 2	CTRI/2020/07/026352

vaccines in development. In theory, the RBD is also sufficient to induce good titers of neutralizing antibodies, but it requires engineering of the protein in dimers or nanoparticles to be an efficient immunogen.

G.A.: The translation of NHP studies to humans has only emerged recently, as our understanding of the genetic and immunologic parallels and differences have begun to emerge. It is essential that these studies be performed. In HIV vaccine design, emerging data have shown similar correlates of protection in NHP and humans, demonstrating the power of the NHP model for the iterative improvement of vaccine strategies, as well as a model in which mechanistic correlates of immunity can be defined. But given the differences in antibody immunology across antibody subclasses/isotypes and in Fc receptors, precise mechanistic correlates of humoral immunity may not be fully defined in the animal model.

K.B. Human challenge models in flu revealed critical information and data about the infectivity of subjects before their showing symptoms, and this was only discovered through tightly controlled human challenge studies. It will be important to explore the ethics and practicalities of human challenge studies for the controlled testing of new COVID-19 vaccines, where subjects receive the vaccine before being [deliberately] infected by the virus. This will require close working with MHRA [the UK's Medicines and Healthcare Products Regulatory Agency] and ethicists to secure regulatory approval, which will include robust protocols to rescue subjects exposed to virus.

J.M.: There's always a concern [about translation] …. In my field of HIV vaccines, there has been a strong tendency over the years to emphasize 'good results' in macaques when it comes to pushing on to human trials, but to dismiss 'bad results' on the grounds that "it's just an animal model."

We also know from the HIV/simian immunodeficiency virus/simian human immunodeficiency virus (and no doubt other) vaccines that it's easier to protect

against minimally replicative/pathogenic viruses than it is against their more virulent counterparts. Hence, there is a nagging concern that we could be seeing protection against SARS-CoV-2 replication and disease in macaques that won't translate to protecting humans. Time will tell ….

There's also no universal standard for how macaque studies are carried out or analyzed. For example, it looks like the Johnson & Johnson vaccine experiment[3] used a rhesus macaque challenge virus dose that's ~10-fold lower than what was done in the [US National Institute of Allergy and Infectious Disease (NIAID)] Vaccine Research Center/Moderna study[4]. And variation in the challenge stock/dose/route is generally true across the macaque challenge studies. How do those differences affect the outcome? It's also very difficult, and sometimes impossible, to cross-compare the antibody and T-cell responses in the various studies because the assays and data presentation methods are too different. There sometimes seems to be an emphasis on finding ways to report 'big numbers'.

Considering the diverse range of vaccines under development, which are most likely to induce protective antibodies with an acceptable safety profile?

G.A.: This is a loaded and difficult question. I do not think it is challenging to induce neutralizing RBD [receptor binding domain]-specific antibodies against SARS-CoV-2. These antibodies seem to be sufficient to provide protection against viremia in the lung. Moreover, there are many vaccine platforms that appear to make antibody responses that last for several years. It is therefore likely that many types of vaccine are feasible against SARS-CoV-2. However, whether distinct platforms will drive similarly long-lived immune responses remains unclear, but will emerge from the multitude of phase 3 trials that will take place in the race against this virus. These data will not only be informative for SARS-CoV-2 vaccine development, but will have a tremendous impact on how we think of vaccines for the future.

K.B.: SARS-CoV-2 vaccines in development (including viral vectors, nucleic acid, protein and inactivated whole-virus vaccines) have generally been selected on strong preclinical data in a variety of species that show good immune responses (including antibody and T-cell responses) and in most cases protective immunity in preclinical models. Protein antigens as vaccines often have insufficient immunostimulatory capabilities on their own so are usually coadministered with adjuvants, such as GlaxoSmithKline's ASO3 or Dynavax's CpG 1018, to enhance their immunogenicity. Inactivated whole-virus vaccines are immunogenic and also dosed with adjuvants to boost the immune response. No RNA [or DNA] vaccine has been approved for any human disease at this point, but the standardized approach enables agile development of new products in response to rapidly mutating viruses (albeit that SARS-CoV-2 does not currently appear to accrue mutation at a high rate). We are yet to see how the different SARS-CoV-2 vaccines compare in terms of which one confers the most long-lasting immunity.

L.C.: Theoretically, all the vaccine platforms — protein antigen, RNA or DNA plasmids, or viral shuttle vectors — are capable of eliciting protective antibodies. Evidence of this in NHP is seen with RNA vaccination, recombinant Ad26 [adenovirus serotype 26] vectors expressing SARS-CoV-2, and protein antigens. Whether these data in small-animal and NHP models translate to human infection and disease remains to be determined. I am cautiously optimistic and hopeful.

J.D.: It is too early to know whether a protein antigen or a nucleic acid expressing an antigen is more likely to induce protective antibodies. Given the need to create a safe vaccine as soon as possible, it is unlikely we will have conclusive evidence before the first SARS-CoV-2 vaccines are approved. In addition, vaccine potency depends on many interacting variables, such as the immunogen, its glycosylation pattern, its presentation, and the presence of specific adjuvants. As a result, it is unlikely that one vaccine class (for example, mRNA) will always be better than another (for example, protein antigen). That said, studies over the next few years will likely provide the answer for the first generation of CoV-2 vaccines; these data will inform the design of improved CoV-2 vaccines or vaccines against future coronaviruses.

Nick Jackson, CEPI.

Nick Jackson: In the absence of a correlate of protection, it is necessary to work on first principles and glean insights from immunological investigations in the MERS and SARS-CoV-1 fields. As such, the field is aligned that a specific, robust, rapid-onset and long-lived humoral neutralizing response could protect vaccinees against SARS-CoV-2 disease. Cell-mediated immune responses will likely supplement neutralizing antibody protection.

A plethora of early clinical data is emerging on all the different platforms, but an international standard with which to coordinate assays across laboratories is not yet available. It is also unclear how the level of assay variability of these assays impacts the interpretation of data. Thus, it remains impossible to make comparative assessments on the basis of available phase 1 data. Groups have attempted to calibrate assays by including convalescent sera as an internal control. In most cases, elicited responses appear to be in the range of convalescent sera. Given that efficacy trials are ongoing and expected to report interim results toward the end of 2020 and into 2021, the question of superior immunogenicity is arguably now superseded by point estimates of efficacy to prevent virologically confirmed disease. In totality, it is expected that the array of vaccine platforms being developed will likely result in a range of different estimations of efficacy.

J.M.: An adjuvanted subunit protein will surely be the strongest immunogen for inducing neutralizing antibodies. Recent macaque and human[5] immunogenicity data from Novavax fully support that statement. The single-dose adenovirus vectors don't do well, but in some cases there are improvements when a booster dose is given[6–8].

What aspects are important in the context of a goal of immunizing the largest fraction of the world's population?

G.A.: Immunogenicity, safety and tolerability are the most critical aspects for selecting globally relevant vaccines. Some vaccine platforms may be more immunogenic, but may induce more adverse reactions. Moreover, some platforms will drive different responses in children than adults. Furthermore, some platforms may not work well in immunocompromised patients or the elderly, due to their unusual and often less potent immune systems. Thus, testing is required across all populations to make the careful decisions for vaccine development. It is plausible that different solutions will work for distinct populations. Thus a single emergency authorization should not be regarded as global solution.

K.B: No vaccine, irrespective of format, should be administered anywhere in the world without a comprehensive safety dataset, approved by regulators. Prevalidated platforms and the adenoviral vector formats developed by Oxford (ChAdOx1; adenovirus serotype 6 vector) and Johnson & Johnson (Ad26 vector) can be engineered rapidly to include the relevant SARS-CoV-2 S protein sequence and scaled up quickly to produce hundreds of millions of doses of vaccine

relatively cheaply. Given the flexibility of their adeno-vaccine format, Oxford was able to start dosing clinical trial volunteers in April 2020, having only received the SARS-CoV-2 sequence in January. If these vaccines are proven safe and effective, AstraZeneca and Johnson & Johnson each seem set for global distribution in 2021 to produce ~2 billion doses of ChAdOx1 and Ad26, respectively.

The vaccine formats with the greatest potential for speed of scale up are RNA-based platforms, such as those from BioNTech, Curevac and Moderna. These can be made quickly because they use synthetic processes, without culture or fermentation, once the DNA template itself is made. Self-amplifying RNA (saRNA) vaccines, such as that being developed by VacEquity Global Health in Imperial College, have potentially greater advantages of manufacturing since the dose required for a saRNA vaccine is substantially lower than for other mRNA vaccines. But mRNA is naturally unstable and needs to be formulated in LNPs and stored frozen at below –20 °C, which will complicate the global shipping and clinical use of RNA vaccines, especially in the developing world. Although the relative cost of mRNA vaccines is currently high, I expect these costs to reduce once the mRNA vaccine technology is optimized and fully scaled.

Recombinant-subunit vaccines combined with adjuvants are relatively cheap to make, easily scaled, are widely used as vaccines throughout the world and are reasonably stable and so easier to manage for global distribution. There is widespread experience with these types of vaccines and supply chains are well established. However, they depend on biological processes and so have been slower to manufacture and develop, currently running about 6 months behind the adeno and mRNA leading vaccine candidates in development.

Whole inactivated virus-based vaccines are well understood and effective vaccine formats, but live virus Biosafety Level 3 (BSL-3) manufacture has not yet been scaled to volumes suitable for global distribution.

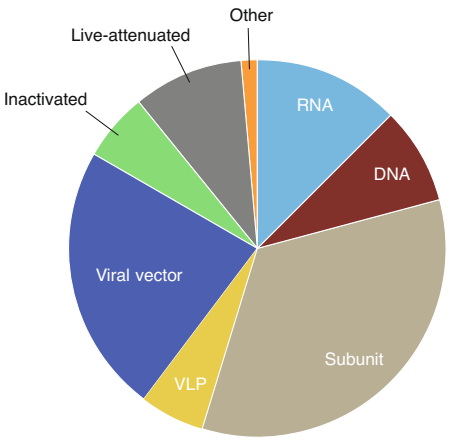
L.C.: I personally think a lot of different platforms are both desirable and necessary to achieve global immunization. Desirable because of the diversity of the population that needs to be immunized and necessary because there are manufacturing and logistical issues in rapidly making vaccine accessible to the vast population (seven billion people) who need to be vaccinated. Women of child-bearing age, children, older adults and pregnant women are unlikely to be best managed and vaccinated with just one vaccine. RNA vaccination has little experience in children and pregnant women — no evidence they are dangerous, but little evidence for proven safety. The protein–adjuvant platforms have long experience in children. The Johnson & Johnson Ad26 vector does have experience in pregnant women and women of child-bearing age and has excellent manufacturability. In the end, a diversity of platforms is best economically as well as to allow more rapid distribution throughout the world.

The one platform I think should not be pursued is that using Ad5 [adenovirus serotype 5] vectors. Ad5-based vaccines that lack HIV envelope have been associated with an increased risk of HIV-1 acquisition. I worry that Ad5 COVID-19 vaccines [for example, CanSino's] could duplicate that risk and feel that Ad5 vector should be used with caution and the risk of increased HIV acquisition should be a factor in its assessment.

N.J.: Historically, widespread successful immunization campaigns have required high volumes of vaccine drug product; thermal stable formulations that don't require a complex cold-chain distribution; a well characterized, simple immunization device; and low cost of goods. The current COVID-19 vaccine frontrunners have a variety of limitations. In the case of mRNA, the productivity of manufacturing remains low and cold-chain requirements will impose significant challenges for immunization campaigns in certain regions. As a result, the cost of goods is expected to be significant. Viral vectors are expected to yield higher annual volumes, in the hundreds of million doses range. However, certain vector platforms have thermal stability limitations.

Based on currently available data for protein vaccine approaches, it is expected that the annual manufacturing capacity could reach a billion or more doses, and more robust thermal stable formulations are being advanced. It is therefore reasonable to predict that protein-based vaccine approaches will ultimately reach a larger fraction of the world's population assuming other factors such as efficacy, safety and equitable access are equivalent.

R.R.: The key question will be which vaccines are effective in providing immunity against severe disease, infection and transmission — and how long that immunity is going to last. Although published data provide safety and efficacy data on all the different vaccine platforms, because a variety of non-standardized neutralizing assays were reported, direct comparison is impossible. But my feeling is that vaccines based on recombinant proteins and adjuvants may induce the highest level of neutralizing antibodies, followed by RNA vaccines and viral vectors.



COVID-19 vaccine candidates under development. Adapted with permission from ref. [17], Springer Nature.

The other important question will be vaccine safety. Viral vectors and RNA vaccines have never been used in millions of people, and we need to look carefully at this.

J.M.: There are practical concerns about the mRNA vaccines, given their thermal instability. [Moderna's vaccine needs to be kept at –20 °C, whereas the Pfizer/BioNTech vaccine needs to be at –70 °C.] A mass rollout may be problematic, given the apparent need for them to be shipped on dry ice and stored in ultra-cold freezers until just before use. But each of the various designs may end up playing a role in different settings, provided safety and efficacy is proven in the longer term in each case.

For nucleic acid vaccines, what is known about the effects of sequence/modifications, mode of vaccine delivery and host genetic factors on protein immunogen expression?

G.A.: For RNA vaccines, there are likely to be massive differences in the durability and level of protein expression depending on the cell type and organ where LNPs are delivered. The level of protein, its glycosylation, other post-translational modifications, and protein turnover will all vary. Conversely, viral vectors have tropism and take advantage of specific cell type protein production machinery, as well as antigen-presentation capacities that may have a critical effect on the quality and potency of the induced immune responses.

Novel chemical modifications to RNA and DNA vaccines may profoundly influence the quality of the immune responses induced by these novel vaccine

platforms. Nucleic acids not only carry the critical vaccine-message, but can also trigger immunity through pattern recognition receptors themselves. Thus, these emerging platforms may hold interesting and unexpected possibilities for immune programming that go beyond the vaccine insert.

Finally, one important consideration is efficiency of vaccine delivery. While viral vectors take advantage of millennia of evolution that endow viruses with the ability not only to target a particular cell type, but also to release viral nuclear material in a protected manner to the intracellular compartments where it may replicate, protein- and nucleic acid-based strategies are somewhat untargeted. Large amounts of protein-based vaccines are likely degraded, but some proteins are taken up and processed by antigen-presenting cells and represented to the immune system. Conversely, nucleic acid-based vaccines not only must get taken up by cells, but also must breach the endosomal compartment and release RNA into intracellular compartments that can drive translation for RNA vaccines, or even make into the nucleus to drive transcription for DNA vaccines. Thus, each platform may access the cellular machinery in very different ways that may alter antigenicity and immunogenicity.

K.B.: Optimizing protein expression is an essential part of vaccine development for any vaccine. One of the advantages of RNA vaccines is that this optimization is relatively easy. Clearly, the LNP is an integral part of any RNA vaccine and selection of an optimal lipid composition is essential for delivery. The mRNA cap sequences also need careful optimization so that the appropriate codons can be chosen to make the appropriate amino acids to ensure good expression levels. Future work will need to optimize the LNP to stabilize the mRNA product, minimize any degradation and avoid the need for a challenging cold chain in distribution.

I am not aware of data on changes in expression levels from RNA or DNA in different demographic populations, and I am not sure there would be expected to be any substantial differences.

J.D.: The expression level of mRNA vaccines delivered into cells by LNPs is influenced by the mRNA structure as well as LNP chemical composition. With respect to the mRNA, changes to its cap, 5′ UTR [untranslated region] and 3′ UTR and the inclusion of chemically modified nucleotides can increase the amount of protein produced per unit mRNA that enters the cell. These changes are additive and sometimes synergistic; an mRNA with a potent UTR can be further improved by including chemically modified bases. Finally, one underappreciated trait is the purification process used after mRNA is transcribed. Purification that reduces double-stranded RNA byproducts leads to higher quality mRNA.

The chemical composition of the LNP also potently affects mRNA delivery. LNPs are typically composed of four components: ionizable lipids, poly(ethylene glycol)-lipids, cholesterol and helper lipids. All four components work together to influence how efficiently LNPs deliver mRNA into cells. As a result, many are searching for an LNP mixture that maximizes protein production.

Finally, although evidence is still emerging, I am increasingly convinced that protein production requires us to understand cell signaling. Recent papers have shown that mTOR, PIP_3 [phosphatidylinositol 3,4,5-trisphosphate] and TLR [Toll-like receptor] signaling can influence nanoparticle-mediated mRNA delivery[9–11]. I would therefore hypothesize that certain cell 'states' are more amenable to mRNA production after LNP delivery than other cell states.

As yet, mRNA and DNA vaccines have not been tested at the scale of human populations, so we don't know about variation at this level due to demographics, genetic variation or environmental factors. It is even difficult to use preclinical data to guess; I am unaware of comprehensive datasets evaluating how mRNA or DNA vaccines work in non-human primates as a function of age or disease state. However, there may be an interesting opportunity to couple large biobanks (for example, the UK Biobank, which sequences samples from hundreds of thousands of people) with SARS-CoV-2 clinical data to see if there are genetic determinants that alter the efficacy of these vaccines.

N.J.: The level of protein expression and the subsequent elicited immune response are significantly impacted by the critical quality attributes (CQAs) of mRNA[12]. 5′ capping efficiency, 3′ UTR, poly(A) tail properties, coding sequence modification and the purity of the construct can all have a major impact on expression. In addition, the ability of the LNP formulation to successfully deliver the mRNA construct into the cytoplasm of the target cells is of paramount importance. To date, head-to-head comparisons of these CQAs in controlled clinical trials are lacking, as is the assessment of self-amplifying versus non-replicating constructs.

For viral vector vaccines, how much of a limitation is pre-existing immunity?

K.B.: There are two issues here: pre-existing immunity to the vector and pre-existing immunity (if any) to the antigen (that is, the vaccine sequence itself). Pre-existing immunity against Ad5 (a human cold virus) is widespread in the population, thus potentially hampering its clinical use as a vaccine vector (at least when delivered intramuscularly, since intranasal delivery may bypass pre-existing immunity). Recent CanSino clinical data showed that people who already had immunity to the Ad5 backbone of the vaccine had a reduced immune response to the COVID-19 S protein. Instead, simian adenoviruses (ChAdOx1 and Ad26) have been developed since they have minimal seroprevalence in humans. We don't yet know about pre-existing immunity to the SARS-CoV-2 S protein or other SARS-CoV-2 proteins, but pre-existing immunity to this could have all sorts of positive and negative implications.

N.J.: It has been demonstrated in several clinical trials that pre-existing immunity to certain viral vectors can reduce immunological potency. However, some viral vectors, such as measles-vectored candidate vaccines, do not appear to be impacted by varying levels of pre-existing immunity.

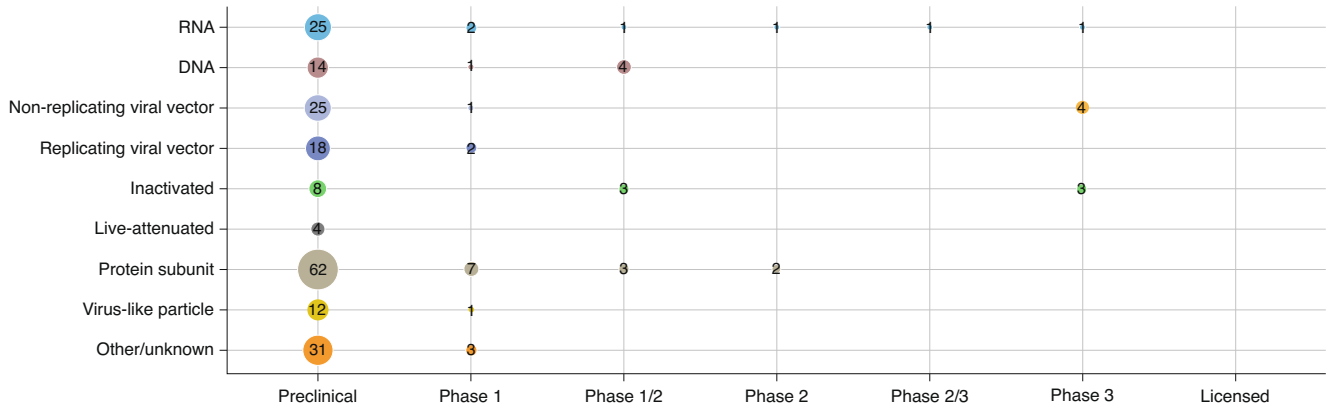
J.M.: For the CanSino Ad5 vector vaccine, being developed in China, pre-existing immunity does seem to be a substantial problem, which was entirely foreseeable based on what's known from studies in, for example, the HIV vaccine field. There are no signs that such problems are affecting the other adenoviral vectors, Ad26 and ChAdOx1, which were designed to overcome that particular problem.

Why are comparatively few inactivated or live-attenuated vaccines being developed against SARS-CoV-2?

G.A.: These are older approaches that have been replaced by super-high-end, cutting-edge, highly flexible vaccine platform technologies that are more controllable, predictable, safer, simpler and manufacturable.

K.B.: Developing a safe live-attenuated vaccine (LAV) takes a long time and has many more safety hurdles than protein, viral or mRNA/DNA-based vaccines. Regulatory-approved BSL-3 containment facilities are required to grow live virus for whole inactivated vaccines, and BSL-3 manufacturing capability in is very limited throughout the world.

N.J.: In China, there are actually several inactivated vaccines being developed, and one is currently undergoing phase 3 clinical assessment. Their limited application elsewhere may reflect concerns for the low levels of manufacturing yields, potentially lower immunogenicity in the elderly,



Stages of development of COVID-19 vaccine candidates. Adapted with permission from https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/, Vaccine Center at the London School of Hygiene and Tropical Medicine.

challenging manufacturing requirements and putative concerns over safety. LAVs are the basis of many successful, highly efficacious vaccines. However, the time to develop a LAV is typically protracted to find the right level of attenuation while maintaining sufficient immunogenicity. For these reasons, the field has few LAV currently in development.

J.M.: I suspect the simple answer is that the major American and European vaccine development companies have 'moved on' from those earlier generation concepts. The Chinese, however, have retained a substantial production capacity for killed-virus vaccines and are using it for COVID-19. For attenuated vaccines and RNA viruses, there's always a concern about reversion to virulence, and that may be a factor here.

What is the optimal vaccine immunogen against SARS-CoV-2?

G.A.: The S protein. There are multiple emerging sites of neutralizing antibody vulnerability across the S protein compared, beyond the RBD. In addition, extra neutralizing antibody functions (antibody-dependent cellular cytotoxicity, Fc-mediated phagocytosis, complement activation etc.) may all be critical for protection and can be targeted along the whole surface of the S protein.

K.B.: The current data suggest that antibodies against S protein are neutralizing. In theory, both S protein and its RBD domain should induce an immune response. The VTF is exploring second-wave vaccines incorporating other antigens to be combined with the S antigen, but these are not as advanced. LAV vaccines have multiple potential antigens. The T-cell responses when correlated to protection will tell us more about which viral proteins are required for protective cell- and antibody-mediated immunity.

N.J.: One way to answer to this is to look at the immune response upon natural infection and the targets of functional antibodies. These are largely directed to the S protein and, within it, to the RBD, the rationale being that blocking the RBD would prevent the virus from adhering to the receptor, a first step toward infecting a cell. A second requirement is to stabilize the S protein in a prefusion state, which is metastable in nature and in its trimer native form. Mutations within the S protein can actually stabilize it in a prefusion form and make it a stronger immunogen than the native S protein of the virus.

J.M.: I would choose RBD over S protein, which is why I prefer the Pfizer/BioNTech mRNA vaccine design to Moderna's. For one thing, there is less chance of inducing non-neutralizing antibodies that *may* be problematic in some scenarios. If T-cell helper responses are being sought, including (for example) the N [nucleocapsid] protein could be helpful, but not for inducing neutralizing antibodies directly.

How important is proper glycosylation and proper folding of the immunogen likely to be for vaccine efficacy?

G.A.: Glycans may influence, but are not critical for, RBD immunogenicity. Conversely, glycosylation on S will be critical, particularly given the unusual placement of glycans on the post-cell-fusion state of the protein. While emerging data point to the importance of glycan microheterogeneity at some sites for immunogenicity in HIV vaccine development, it is unclear whether glycan structures will alter SARS-CoV-2 vaccine immunogenicity.

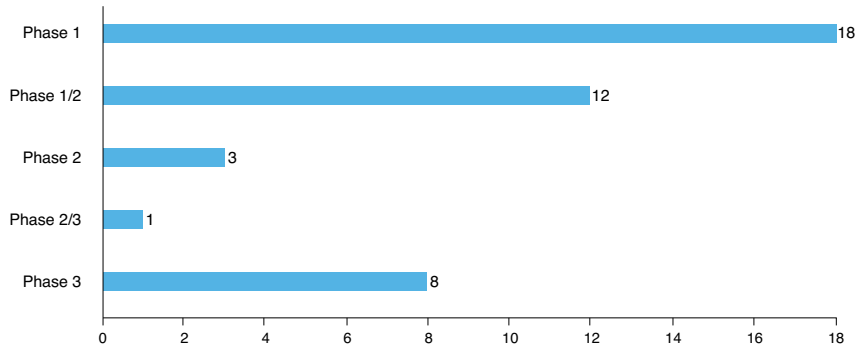
All viral-vectored and nucleic acid-based approaches leverage 'self' glycosylation [as they are expressed in the recipient's cells rather than an ex vivo system]. Recombinant antigen approaches, like Novavax's, will also have mammalian glycosylation [courtesy of Chinese hamster ovary (CHO) cell line expression]. The baculovirus- and plant-based recombinant systems may have some immunogenicity issues; on the other hand, their altered glycosylation patterns may enhance C-type lectin-driven processes that deliver immunogen to immune sensors as pattern recognition signals, so these type of recombinant vaccines may be self-adjuvanting.

Interestingly, host-cell glycans play a critical role for early viral attachment, before RBD attachment to ACE2. This early S interaction with cellular glycans helps the virus attach in a likely arduous respiratory environment, highlighting the importance of glycosylation both for vaccination and also in the context of natural infection/disease pathogenesis.

K.B.: Glycosylation is important for vaccine efficacy since it may affect which cells the SARS-CoV-2 virus can infect and could shield some epitopes from antibody neutralization. Recent data show that each protomer in the trimeric S protein has 22 glycosylation sites. For SARS-CoV-2 vaccines, the role of glycosylation in the immune response is not yet understood. In theory, production of the protein in mammalian or human cells should give rise to the most natural antigens with the right glycosylation patterns. It is clear that the conformation of the S protein is important, and the appropriate conformations have been designed into several of the vaccine candidates (for example, Moderna's encoded immunogen has the RBD binding arms up).

J.M.: If you had asked me before immunogenicity data emerged, I would have said these issues were very important

based on my experience in the HIV-1 envelope glycoprotein arena (equivalent to the SARS-CoV-2 S protein). However, that appears to be not (much) the case with the S protein and, in particular, its RBD. Some animal model studies have shown that high neutralizing antibody titers are rapidly induced almost irrespective of how the RBD is produced and what adjuvant is used[1], including at least one (complete Freund's) that is pretty harsh on protein conformation. The RBD is also relatively glycan free; insect-cell-produced S proteins, including the Novavax clinical candidate[5], seem to be quite immunogenic for anti-RBD neutralizing antibodies, despite their 'atypical' glycans when delivered with or without adjuvants.



COVID-19 clinical trials by stage of development. Source: London School of Hygiene and Tropical Medicine.

What types of adjuvant are likely to be most effective in eliciting not only neutralizing antibodies but also the right type of helper responses?

K.B.: All available adjuvants have been designed to be antigen dose sparing along with producing strong antibody and cellular responses in most cases. Until the combinations are tested with COVID-19 vaccines, it is not possible to say which combination makes for a safer, more efficacious vaccine. There have been safety issues with alum in the past, and we need to look at all aspects of preclinical and clinical immune response to ensure safety is managed appropriately. In addition, emerging data suggests previous exposure to adjuvants, such as AS03 in Shingrix [zoster vaccine recombinant, adjuvanted], may be important in providing protection against COVID-19.

N.J.: For protein-based vaccine candidates, the adjuvant brings a priori three things to the antigen(s). First, it stimulates and increases the immune response; second, it potentially reduces the amount of antigen needed; and third, it orients the immune response toward a T-helper 1 (T_H1) antibody response. Adjuvants known to orient the immune response toward T_H1 would therefore be prioritized, while those that orient the response toward a T_H2, such as alum, should be cautiously evaluated. A concern is the phenomenon known as the ADE, which occurs when antibodies enhance viral infection, possibly by increasing viral entry or promoting inflammation and tissue injury. This has been observed with other, non-COVID-19 vaccine candidates formulated toward a T_H2 response and can be evaluated in animal models.

J.M.: Adjuvants are only being used, so far, for the protein subunit vaccines. And, as noted above, a range of them appear to be effective, at least when used with the RBD. But what matters most is that only a very few adjuvants are approved for human use [for example, AS01/monophosphoryl lipid, M59/squalene and CpG], so it makes most sense to focus on those in the immediate future. Co-developing a new antigen and a new adjuvant would be more complicated, perhaps too much so in the relevant time frame. The Novavax S protein is combined with the Matrix M adjuvant, which the company has experience with in humans, it seems[5].

How likely do you think it is that SARS-CoV-2 vaccines will elicit serious side effects, such as ADE and vaccine-associated enhanced respiratory disease?

K.B.: ADE was found to be the cause of deaths and serious illness of children enrolled in a vaccine trial against respiratory syncytial virus in the 1960s. In one trial, several children who received the vaccine developed a serious illness when infected with the natural virus. However, we have no evidence so far of ADE occurring in human patients enrolled in SARS-CoV-2 vaccines trials. T_H2 immunopathology is implicated in ADE, but there is no evidence from studies of T-cell responses in infected individuals for any T_H2-biased responses. It is hypothesized that faulty T-cell responses trigger allergic inflammation and that low-potency antibodies form immune complexes, activating the complement system and potentially damaging the airways. To explore whether any SARS-CoV-2 vaccine is associated with ADE, NHP studies are used to evaluate safety before vaccines are dosed in human studies and mitigate the potential risks of ADE.

ADE and vaccine-associated enhanced respiratory disease are risks that must be considered as possible but unlikely events. Nevertheless, these risks will need to be monitored carefully throughout the development of the vaccines.

Everyone in the United Kingdom has a National Health Service number and almost everyone has electronic health records, and so the MHRA is able to review real-world data to support postauthorization phase 4 pharmacovigilance (safety) studies to evaluate vaccine safety in real-world populations, as well as other proactive enhanced evaluation of safety through well-established processes within the agency. Longer term safety will also be part of the ongoing phase 3 vaccine trials.

G.A.: I am unconvinced that vaccines will drive ADE. Limited data exist to suggest that SARS-CoV-2 can infect phagocytic cells following antibody opsonization; however, antibodies can certainly trigger inflammation that may contribute to disease pathology. However, emerging data from super-susceptible hamsters suggest that, at low monoclonal antibody titers, low levels of weight loss may occur. However, at higher antibody titers, no pathological effects are observed. Yet there are no data from monkeys or humans to suggest that pre-existing antibodies aggravate or enhance disease. As the rates of infection continue to accrue in some part of the world, studies in previously seropositive individuals or at durability time points in vaccine studies may provide insights on whether ADE may occur with waning antibody titers. But I believe the ADE effect observed with [vaccinia virus Ankara] MVA-CoV-1 that was published in 2019 raises a critical issue — that we must be vigilant, as different vaccines can induce different 'flavors' of antibodies, which may drive inflammation. These data suggest to me that Fc profiling, beyond ADE assays, must be embedded in all the vaccine development programs so we can learn rapidly and in real time to address any potential vaccine liabilities.

J.M.: Answers will only be possible once enough vaccine recipients have become

infected in phase 3 trials. There are, and will remain, concerns about these issues until hard data emerge. So far, the animal studies, particularly in macaques, have looked encouraging from the safety perspective. But, in the end, only human data from a substantial number of cases will alleviate nagging worries about postinfection adverse events, particularly for vaccines that induce neutralizing antibodies relatively poorly.

R.R.: The trials need to monitor ADE. There has been a lot of discussion about it, and there is no reliable in vitro or animal model. So the only way to study ADE is to look out for it in clinical trials. Personally, I do not believe this is a risk for the vaccines that induce good titer of neutralizing antibodies, but we need to monitor it and have a definitive answer for it.

How have vaccine developers gone about accelerating clinical development?

G.A.: It is important to convey that no corners are being cut. In fact, the large developers have now signed a pledge guaranteeing that safety will be a top priority. The major change here is that the pipeline is simply being accelerated and the sequence of activities has simply changed. The antiquated days of having multiple preclinical studies performed before phase 1, then phase 2, then phase 3 sequentially is gone. Efficiencies have been created in the system that still enable iterative learning. Combining phases with go/no-go decisions cuts months of vaccine trials. In addition, preclinical studies run in parallel offer a unique opportunity to blend in endpoint readouts as the trials progress. However, it is critical to note that this is all only possible because a large body of data already exists for many established vaccine platforms. Thus, this is not a total surprise. However, for the new products, the go/no-go decisions must be stricter.

It is also important to acknowledge the massive financial risks that pharmaceutical companies have undertaken to make millions or billions of doses of their vaccines before vaccine approvals. Massive investments from the NIH [US National Institutes of Health], CEPI [Coalition for Epidemic Preparedness Innovations], Gates Foundation and other national funding agencies have helped support the commitment that vaccine developers have made. This commitment ensures that any vaccine that looks promising can move forward.

Thus it is critical to remember that scrutiny has not gone away — the criteria have not relaxed. It is that data have to be collected faster and funding decisions have to be taken 'at risk'. Adaptive trials have also been implemented, enabling the integration of additional demographic populations, more/less vaccine boosting, and changes in regimen. Together, these changes are likely to reshape the way in which we develop vaccines, once taking decades.

K.B.: Assessment of safety remains the primary and fundamental goal of all vaccine trials, and then assessment of efficacy. The design of the SARS-CoV-2 vaccine studies are no different to any other vaccine trials, although the later phases of SARS-CoV-2 clinical development are currently being compressed and run in parallel. The reason for this parallel clinical development in the SARS-CoV-2 vaccine trials versus sequential development in traditional vaccine trials is that funding has been unlocked to accelerate clinical development to end the pandemic through vaccination as quickly as possible.

For example, unlike in traditional clinical development, SARS-CoV-2 vaccine phase 2 and phase 3 trials have been funded to start recruiting as soon as the initial phase 1 safety has been established. When the Oxford team published[8] their phase 1/2 neutralizing antibody results with ChAdOx1, they had by then already vaccinated 8,000 people in their large efficacy phase 2/3 trials, which was only possible due to unprecedented levels of international organization and cooperation. We need to try to continue this fabulous level of cooperation and speed in future vaccine development.

L.C.: No corners are being cut in the clinical development of coronavirus vaccines. Phase 1 and 2 trials are of normal size and numbers, and all safety and immune assessments are evaluated by study teams as well as the FDA before granting permission for the next stage of human testing. In general, the time from phase 2 to phase 3 of a trial is often a year. Here it's 7–14 days — all because the logistics and operational support of a large-scale phase 3 trial are in place at the time of the phase 2 discussion.

The primary endpoint for all the phase 3 vaccine trials is amelioration of COVID-19 disease. One can think of this as defining COVID-19 into severe and non-severe disease. Most vaccines have shown greater benefit in reducing the disease burden of persons with severe disease more effectively than mild disease. Thus, one goal of the phase 3 trial is to enroll persons at high risk of severe disease. The definition of disease severity is complex and is the crux of [vaccine strategy in] meeting this disease.

Who are the optimal target populations for phase 3 trials, and how important are genetic background, age and other factors in the general population in determining vaccine response?

G.A.: Age, genetics and sex all tune vaccine-induced immunity. Emerging data clearly demonstrate significant differences across the sexes with respect to disease pathology, with enhanced disease in age-matched men. Conversely, women tend to make stronger humoral immune responses following vaccination. Yet whether the correlates will differ as well following vaccination is unclear. Phase 3 trials in adults have been designed powered to define the influence of sex as a critical biological risk factor. Moreover, phase 3 trials have been designed to also test for protection in the elderly, a critical vulnerable population. Unfortunately, pregnant woman and infants are always last, together with immunocompromised populations and those [with underlying conditions] on medications, to be integrated into vaccine studies and thus will remain vulnerable for longer periods of time. Protection of this population will be key until safety can be ascertained in these immunologically distinct populations.

But we are in a unique situation with the SARS-CoV-2 vaccine development pipeline, where many vaccine strategies are being tested simultaneously, and some platforms may induce better immunogenicity/durability in pregnant women, other may work more robustly in the elderly, and another may be highly potent in infants. This flexibility and range of options is unparalleled and may help us understand platform advantages for SARS-CoV-2 and beyond.

K.B.: The MHRA have specified that phase 3 trials should include volunteers covering all age groups and demographics but that these trials should be enriched with the target populations at the greatest risk of severe illness and mortality from COVID-19. Almost all vaccine developers are not choosing to evaluate their SARS-CoV-2 vaccines in children less than 18 years old in their current large efficacy trials.

In the United Kingdom, the groups that have been prioritized for vaccination, if and when a vaccine is available, include frontline health and social care workers (who are at increased personal risk of exposure to infection and of transmitting that infection to patients in health and social care settings) and those people at increased risk of serious disease and death. This includes all adults over the age of 50 (with the risk increasing with age), 18- to 50-year-olds with underlying comorbidities including chronic heart disease, chronic kidney disease, chronic pulmonary disease, malignancy, diabetes, obesity and dementia, all shielded people (who are at greatest risk of severe illness) and certain Black and minority ethnic groups. (The reasons behind the apparently disproportionate effects

on certain ethnic minorities are complex, poorly understood and undergoing further investigation.)

The impact of genetics in determining response to vaccines is not yet known, and I hope the data may come out of the numerous trials worldwide. It is well known that aging negatively impacts the production of B and T cells and dampens the function of mature lymphocytes in secondary lymphoid tissues. As a result, the elderly do not typically respond to immune challenge as robustly as the young, so they need vaccines with adjuvants or other components to rejuvenate the immune system and evoke a strong immune response. Pre-existing exposure may also affect the vaccine response. Safety is the primary driver for vaccination of children. I expect there will ultimately be different vaccines for different population cohorts.

L.C.: Epidemiological data indicate the target populations must be older adults (over 65) and those with comorbidities, such as heart or lung disease, hypertension, diabetes and obesity. Black and Latinx populations are associated with severe infection, especially in the under-65-year-old population. This likely relates to high rates of exposure due to their occupations and living density.

Many protein-based vaccine platforms have reduced immunogenicity in older adults. Given that older adults have increased susceptibility clinically to both SARS-CoV-1 and SARS-CoV-2, as well as increased severity when facing SARS-CoV-2 in human and experimental challenge, whether disease enhancement with vaccines is seen in older adults is at present unknown. Early data from the RNA phase 1/2 [vaccine trial] indicate good responses to this vaccine in those over 65 years of age. We await further data to see whether this is associated with good efficacy.

J.M.: Too little information has been disclosed on these aspects so far for me (or anyone?) to know what to say here. And that's far from ideal as the questions are important ones. In the end, these vaccines do need testing in higher risk populations, including but not limited to older people. Vaccine immunogenicity is known to diminish with age, in general terms, and it's hard to see why that would be any different for COVID-19 vaccines. Recent data, published by Pfizer/BioNTech and in a Moderna, indicate that antibody responses are a few-fold weaker in people over 55 than in younger volunteers, but not to an extent that's a serious concern.

R.R.: One of the limitations of the trials may be whether we obtain data from a population that is genetically sufficiently different. However, trials can only be performed in those areas where there are enough cases. Hopefully, we will be able to establish correlates of protection that can be useful to extend the information also to other populations and to different ages, including children.

In the context of a pandemic, what standards should regulatory agencies use to assess a COVID-19 vaccine?

G.A.: Both efficacy and immunogenicity endpoints should be synchronized across all vaccine platforms. For many platforms that will be tested under the COVID-19 Prevention trials network, standardized tests will be used to quantify disease severity and vaccine immunogenicity. Additionally, efficacy will be evaluated by centralized statisticians with tremendous experience in vaccine efficacy analysis.

However, for most platforms, minimized disease severity will be used as a primary end point. Unquestionably, reducing severity will profoundly improve our capacity to manage this infection at a global level; however, multiple endpoints should be evaluated, including infection (seroconversion), viral RNA levels, and even secondary pathology such as cardiac complications. Unfortunately, the trials are not powered to encompass all these end points; however, post hoc analyses of these additional end points may provide additional insights across the platforms that may be vital for the downselection and evaluation of vaccines able to drive the most robust disease-modulating effects.

K.B.: The standards for a SARS-CoV-2 vaccines are no different from any other vaccine: this is outlined in the European Union guidelines. The time to regulatory approval may be shortened, but standards will not be compromised.

Seroconversion alone is not sufficient where the correlate of protection has not been established by prior work, such as from other COVID-19 vaccines. Once this has been established with a degree of certainty, which means having convincing efficacy and safety data from several vaccines, then approaches such as immune-bridging may be justified, alongside a safety database of subjects enriched in the target populations to be vaccinated. In the United Kingdom, the target groups for COVID-19 vaccination is specified by the Joint Committee on Vaccination and Immunisation (JCVI) and includes the elderly, adults with comorbidities, ethnic minorities and frontline workers, representing over 50% of the UK adult population.

The primary objective is typically to evaluate the rate of virologically confirmed (by PCR) COVID-19 symptomatic disease cases, regardless of severity, with the primary end point being the first COVID-19 disease episode occurring more than 14 days after the first dose. Other definitions for the primary endpoint may also be acceptable. Disease severity, including asymptomatic disease, is a key secondary endpoint. T-cell responses, while gaining interest, are not currently critical for approval as there are currently insufficient data to explain the implications of cellular responses, although emerging data classifying patients by TCR sequence suggest they may turn out to be as important as measuring antibody levels.

J.M.: If the COVID-19 vaccines are going to be widely used (and they will be of limited value if they are not), then the public must have strong confidence that they are both safe and effective. That means the approval process has to be both thorough and transparent and, above all, free of political interference. Multiple opinion polls now clearly show that vaccine uptake by the public would diminish significantly if there were a repeat of the hydroxychloroquine EUA [Emergency Use Authorization], in which election politics dominated a transparent and trusted scientific process. A vaccine that's not trusted is a vaccine that's not used. And a vaccine that's not used is a vaccine that's not effective.

R.R.: I believe it is imperative to demonstrate efficacy for severe disease and also for infection of the upper respiratory tract. It will be very important to use this information to establish correlates of protection. Indeed, it will not be possible to perform efficacy trials for all vaccines in development, and correlates of protection will be the only road for licensing several vaccines.

Should regulators gather cross-trial data from all vaccine trials to make decisions on best comparative evidence, as has been proposed[13]?

G.A.: Cross-comparative analysis will be very difficult, and the urgency for a SARS-CoV-2 vaccine should not 'break the system'. Cross-comparative data are not as critical as the ultimate development of a safe and effective vaccine. For each vaccine a Drug Safety Monitoring Board (DSMB) will be assembled. We have to have confidence in these experts that data will be reviewed thoughtfully, objectively and with extreme rigor. These confidential, closed meetings, along with the FDA and other regulatory bodies, will provide the evaluation of the vaccine results that are required to move a promising product safely into humans. In the meantime, public disclosures in the form of presentations,

Table 2 | Peer-reviewed papers describing clinical trial results from SARS-CoV-2 vaccines in late-stage development

Sponsor(s)	Vaccine type	Clinical stage	Peer-reviewed papers
Wuhan Institute of Biological Products, Sinopharm	Inactivated virus	Phase 3	Ref. [14]: "Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes. Interim analysis of 2 randomized clinical trials"
Moderna, NIAID, Lonza, Catalent, Rovi, Medidata, Bioqual	RNA-based vaccine (nucleoside-modified mRNA) encoding codon-modified S protein encapsulated in ionizable LNPs, containing heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy) hexyl)amino)octanoate (Lipid 8), 1,2-distearoyl phosphatidylcholine, cholesterol and polyethylene glycol lipid in 50:10:38.5:1.5 ratio	Phase 3	Ref. [15]: "An mRNA vaccine against SARS-CoV-2 — preliminary report"
CanSino Biologics, Beijing Institute of Biotechnology, National Research Council of Canada	Non-replicating viral vector (Ad5 vector encoding S protein)	Phase 2	Ref. [6]: "Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial"; ref. [7]: "Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomized, double-blind, placebo-controlled, phase 2 trial"
Novavax	Recombinant subunit vaccine with full-length prefusion spike protein in a nanoparticle, Matrix M adjuvant	Phase 1/2	Ref. [5]: "Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine"
Gamaleya Research Institute of Epidemiology and Microbiology	Two-component vaccine: recombinant Ad26 and Ad5, both carrying spike protein	Phase 1/2	Ref. [16]: "Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia"
University of Oxford, Oxford Biomedica, AstraZeneca	Non-replicating viral vector (chimpanzee adenoviral vector encoding S protein; AZD 1222; formerly ChAdOx1)	Phase 1/2	Ref. [8]: "Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial"

public forums and published manuscripts will be important for the public's ability to evaluate the data.

K.B.: Head-to-head trials would only be possible if there were a vaccine already licensed. And even then, early vaccines would likely have conditional approval so may not be considered appropriate comparators. The European Medicines Agency's guidelines suggest that if one vaccine is already approved for prevention of the disease then it may be difficult to identify a study population that still has a sufficient incidence of disease to allow for reliable estimates of efficacy to be made.

Typically regulators, including the UK's MHRA, do not compare data from different vaccines unless there is a specific reason, such as immuno-bridging comparisons. The main consideration for regulators is to assess whether any vaccine meets the requirements for a license; it is not the role of the regulators to choose one vaccine over another.

Common oversight is possible, however. For example, the AstraZeneca/Oxford University vaccine effort has a single DSMB for their UK, Brazil and South African clinical trials, but I'm not aware of DSMBs being common across different companies or products.

The UK VTF, however, does want to compare the data generated in different vaccine trials so that the JCVI can make more informed recommendations on vaccine selection and advise the UK government on strategy. So we are investing in building standardized, accredited assays, including quantitative high-throughput S-protein ELISA assays, live viral neutralization assays and T-cell assays. We are fortunate to be able to work with Public Health England Porton Down to build on their viral neutralization assay capability, which is already being used to support clinical trials. Once accredited, these assays will be available to any vaccine developer or country to use.

J.D.: I support the idea of a cross-trial DSMB. In order for people to take the vaccine, they need to trust information they have received. The best way to create trust is through a coordinated, coherent and transparent public conversation. It will be critical to accurately state the benefits and risks of the vaccine because even a single severe side effect will be covered and shared extensively on social media. Put another way, the 'credibility' of the vaccine cannot depend on it being a perfect product without any chance of side effects.

J.M.: They should, but will they? Companies who may fear/know their products will fare poorly in a head-to-head matchup may well find reasons to not take part.

What are the pros and cons of each vaccine modality in terms of large-scale manufacture?

K.B.: Scale-up to large-scale manufacturing of all COVID-19 vaccine modalities is a challenge, given the speed of all the programs. Manufacture is better understood for some vaccine modalities than others. For example, viral-vector vaccines are very similar to gene-therapy technology, a modality that has more history than, for example, mRNA vaccines. The United Kingdom has plenty of experience manufacturing gene therapy vectors for therapeutic use. RNA vaccines are less well known in general, and to date no RNA vaccines have yet been registered for commercial use. An additional manufacturing complexity of mRNA vaccines is the LNP technology required to

stabilize them, but ultimately this should not be an obstacle.

There are differences in the productivity of different modalities, and each modality has different dose requirements as a vaccine. Protein and adeno vaccine modalities can generally produce millions of doses from 2,000-liter to 4,000-liter scale, but the productivity/yield depends largely on the individual vaccine, the process parameters, and the skills and capability of the people developing and making them.

The mRNA and self-amplifying RNA vaccines are very active in very small quantities so many millions of doses can be produced in relatively small volumes. However, these vaccines need to be formulated in LNPs, which is a challenging process that currently reduces the overall productivity. The human capability is extremely important, particularly in the rapid scale-up processes underway today, which is why the UK VTF has invested funds to meet the specialist skills demand for vaccine manufacture in the United Kingdom.

N.J.: RNA is fast to clinic, but not of high productivity in manufacturing to date. The issue is the maturity of the platform and hence the lack of established large-scale manufacturing. This is an obstacle that can be overcome with time, but meanwhile scale-up will be expensive. Cost of goods is also high as the batch sizes are small and raw materials are not available in large quantities with the sufficient purity. Finally, RNA products may require ultra-low cold chain to maintain stability of the RNA and/or LNP delivery vehicle.

DNA is fast to clinic, but requires rather high doses, making manufacturing a challenge. Also, the DNA vaccine requires manufacture of an electroporation device for delivery of the product, which adds significant cost and further limits supply availability. The production process is mature, so many CMOs [contract manufacturing organizations] exist that can make large quantities.

Live viral vectors are proven technology, are generally scalable and have good yields. The process is fairly simple and the downstream purification is minimal, allowing higher yields/recovery. One drawback is that these vectors generally require cold chain (−20 to −80 °C) to preserve the viral activity.

Manufacturing for subunit protein vaccines is well established, and for S protein in the trimeric form the proteins are very stable, even at elevated temperatures. They require an adjuvant to boost immune response, and in most cases capacity of adjuvant is more limiting than our capacity to make the recombinant protein. The products are highly purified, which reduces yield of production to some extent, but the processes are still able to exceed 1,000 doses per liter (up to 5,000 doses per liter).

R.R.: Manufacturing of hundreds of millions or billions of doses will be a big challenge for all vaccines, especially for the new ones, such as those based on nucleic acids and viral vectors, that have never been manufactured in large quantities. Fortunately, an unprecedented amount of money is being invested at risk to accelerate the scale-up of these platforms. However, we know that industrialization of vaccine manufacturing takes time, and it is not done until it is done. So, while we all hope that we will be successful, we need to continue to be prepared for surprises.

What are the challenges in terms of vaccine filled and finished product, cold chain, storage/stability, distribution and administration for the various vaccines?

K.B.: While there are challenges in the fill–finish process itself, there is a global shortage of fill–finish capacity and of some components to support all the vaccine development efforts at a global scale right now. Anticipating this, we have acquired several million doses of fill–finish capacity so we can receive bulk drug substance for fill–finish in the United Kingdom.

Because vaccines are being developed in real time, there is no historical stability data, so stability data are being generated for the regulator as the development process proceeds. It is not possible to accelerate stability testing to extrapolate to a potentially longer shelf life, so in the short term, while a longer stability is verified, it will be a big challenge to match delivery of vaccines with the capacity to administer. For the vaccines stable at 2–8 °C, such as adeno and adjuvanted protein vaccines, this will be somewhat easier; however, those that require very cold storage will need a very well thought-through deployment strategy.

J.M.: RNA vaccines have to tackle the issue of thermal fragility; it's also quite hard to imagine how a DNA-vaccine electroporation device could be used on anything more than niche applications. It would be a tough sell even in well-equipped hospitals, let alone in more challenging low-resource environments. For it to be worth going there, the DNA vaccine would have to be far superior to its competitors. It's hard to see that happening. All things being equal, and they may not be, the vaccine that's easiest to distribute and use may be the vaccine that's most useful on a global scale.

R.R.: A challenge underestimated by many is the capacity to fill billions of doses of vaccines. In any case, vaccines in large quantities are likely to become available only in the second half of 2021, and until then, it will be important to prioritize the people at risk who will need the vaccines first.

How should we think about the question of achieving herd immunity through vaccination?

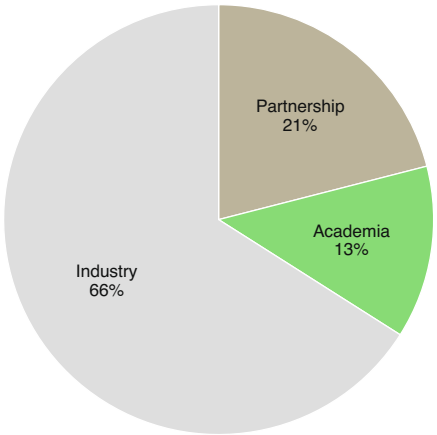
G.A.: Social network analyses could guide the strategic generation of herd immunity. It is simple nowadays to define the individuals who sit at the center of most social networks. Using these strategies, individuals on the front lines (for example, teachers, drivers, hospital works, grocery store workers, hairdressers, dentists) will likely be the hubs of most networks and should get a top-tier status for vaccination. Additionally, once a vaccine is approved, vulnerable populations at the center of networks (for example, nursing homes) should gain priority. This would be a sociological experiment, but could help make deployment equitable and guide rational deployment protocols — similar to ring vaccine efficacy trials.

K.B.: Clinically vulnerable populations should be prioritized for vaccination, but vaccinating these populations alone is unlikely to achieve population herd immunity to control the pandemic worldwide. Herd immunity is likely to be derived from vaccination and continuing infections. I think it is unlikely that we will reach a level of herd immunity that is required, owing to the large number of asymptomatic patients where the induction of lasting immunity (including T cells) is unknown.

If a vaccine were shown to be safe and provide durable protective immunity, then it is possible that the risk/benefit balance will allow all adults to be vaccinated, rather than just those who are clinically vulnerable. In that case, herd immunity could be achieved. We need to vaccinate the majority of the population to keep [the reproduction number] R below 1.

However, there are several issues to consider regarding herd immunity, including longevity of response, type of response required for herd immunity, and kinetics and pattern of herd immunity (epidemiology), which are complicated and not currently well understood.

J.M.: To achieve herd immunity requires vaccinating a major proportion of the population (maybe as high as 70% in some models) with a product that's substantially protective. Logically, one would try to first protect those most at risk of infection and severe disease, but while we know some of the parameters influencing disease, we have little idea of the risk factors involved



Vaccine developers. Adapted with permission from ref. [17], Springer Nature.

in acquiring and spreading the virus. I hope there actually is a plan, but I have read only proposals and opinions so far.

What are the best mechanisms to achieve equity in vaccinating under-resourced and high-risk communities?

K.B.: The United Kingdom is committed to ensuring that people around the world have fair access to a safe and effective COVID-19 vaccine. It is highly unlikely that any one country will develop the only successful vaccine and be able to manufacture all its component parts at sufficient speed and scale for global use.

This is not a time for nationalist politics. China, the United States, Europe and the United Kingdom need to work together. We need to collaborate internationally to pool risks and costs, address barriers to access, and scale up manufacturing capacity internationally to produce sufficient doses of any COVID-19 vaccine.

The United Kingdom is therefore a strong supporter of COVAX, a multilateral initiative to support discovery, manufacture and fair distribution of COVID-19 vaccines. We are working to set this up with a broad alliance of some 180 nations and international organizations including GAVI (the Global Alliance for Vaccines and Immunization, a global health partnership of public- and private-sector organizations that delivers childhood vaccinations to almost half of the world's children), CEPI (Coalition for Epidemic Preparedness Innovations) and the WHO (World Health Organization) to ensure equitable access of COVID-19 vaccines to low-income countries and high-risk as well as middle- and high-income countries.

The United Kingdom supports this global approach for equitable access to vaccines and is one of the largest country funders of both CEPI and the GAVI alliance.

As in all global health matters, there are multiple stakeholders with many competing interests trying to balance the challenge of national and global interests. The COVID-19 pandemic has affected all countries, both rich and poor, and unusually in this first phase of the pandemic, high-income countries have been more affected than low-income countries, which changes the balance of national interests, global interests, domestic funding and overseas development-aid-style funding.

So the best mechanism to help end the global COVID-19 pandemic is for the high-income countries to come together to provide funding and support to ensure that a COVID-19 vaccine should be made available as rapidly and widely as possible — to high-, medium- and low-income countries — for the health of the global economy and global population. It is highly unlikely that any one country will develop the only successful vaccine and be able to manufacture all its component parts at sufficient speed and scale for global use.

J.D.: Vaccine distribution will almost certainly become a political flashpoint. I am especially worried that vaccine distribution will be turned into 'us versus them', both across countries (that is, vaccine nationalism) as well as within a country (that is, vaccine partisanship). The United States is already a partisan powder keg, and a contentious election is around the corner. As a result, there is a real possibility that under-resourced communities will not receive enough vaccines, even if their communities are high-risk. This will need to be combatted actively, and to that end, I favor a weighted lottery system, wherein people who are more likely to be exposed are more likely to receive the vaccine

N.J.: Making vaccines available to those who need them most is the fastest, as well as the fairest, way to bring the pandemic to an end. We anticipate that initial demand for COVID-19 vaccines is going to vastly outstrip supply; every country on the planet will need access to vaccines at the same time, to protect their most vulnerable populations. But that is already leading to a race between countries to secure vaccine supply for their own population. This approach will push countries to the back of the queue if they can't afford to make deals with manufacturers and leave many of those who are most vulnerable to the virus unprotected.

To address this challenge, CEPI, alongside GAVI and the WHO, launched COVAX as part of the Access to COVID-19 Tools (ACT) Accelerator on 4 May 2020, with the aim of ending the acute phase of the pandemic by the end of 2021. COVAX is a global initiative that aims to provide an end-to-end solution to the challenge of vaccine development, manufacture and supply in this pandemic, bringing together the skills, expertise and resources of the public, private and philanthropic sectors on a global scale.

COVAX is the only solution that will deliver fair, equitable and necessary access to vaccines for every country that participates. It aims to produce two billion doses of vaccine and distribute them according to an equitable allocation formula in 2021. Countries of all income levels can participate in the COVAX Facility, a financing mechanism established by the COVAX partners. All participating countries, of every income level, will get doses for at least 20% of their populations. That covers those most at risk: health workers, older people, and adults living with health conditions.

J.M.: Build data-driven trust that the vaccine is both safe and effective, which requires a thorough and transparent approval process. And then provide the financial and logistical resources needed to roll out the vaccine everywhere it's most needed. In the face of a global pandemic, 'vaccine nationalism' is an abhorrent concept, but it will be hard to counter.

How do you compare the vaccine choices made by Operation Warp Speed and the UK Vaccine Taskforce?

K.B.: I have regular conversations with Moncef Slaoui, who runs Operation Warp Speed (OWS), and the United States is astonishingly fortunate to have such a remarkable and thoughtful expert in vaccines, with deep experience and compassion, to help develop and deliver COVID-19 vaccines at speed. The choices that OWS have made overlap in part with those made by the UK VTF, and I hope that several vaccines are successful this and next year.

An important positive outcome of the COVID-19 pandemic that I have observed is the open, regular and transparent interactions between governments, companies, regulators and academic institutions, all of which have served not only to bring together the best brains in the world with immediate funding but also to accelerate the development of COVID-19 vaccines that can both help stop this pandemic and restore global

economic health and growth. We must ensure this level of collaboration and global cooperation continues.

J.D.: I do not have concerns with the VTF. I am concerned about politics influencing OWS. The number of lies told by the US administration is shocking, and a growing number of statements (for example, overselling the benefits of plasma) and actions (for example, changing guidelines so asymptomatic patients do not necessarily need to be tested) by scientific institutions clearly demonstrates that the executive branch is choosing politics over truth. I am therefore concerned that OWS will be pressured to make politically driven decisions. That said, I am hopeful that the leading scientists helping with OWS will resist this pressure.

J.M.: Both countries seem to have adopted the 'get there the firstest with the mostest' philosophy. In other words, something that can be made 'tomorrow' was emphasized over what could be produced 'next week'. That's peachy if it all works, but there's always a concern about cutting corners when there's a need for speed.

An additional dynamic is that the various companies are competing with each other, which is understandable, given the financial stakes and the prestige involved (the latter particularly for the academic collaborators). Again, that could lead to corner-cutting, particularly by smaller companies that are 'one-trick ponies'. Cooperation would be much more constructive and, in some scenarios, might be necessary (for example, for combination vaccines, a 'plan B' option).

R.R.: From what I can see from the media, the choices made by OWS and the VTF reflect the uncertainty of the field. In the absence of sufficient data about safety, efficacy, large-scale manufacturing, and the stability of the different vaccines in development, they tried to book vaccines from several different platforms, hoping that some of them will be the right choice — a wise strategy given the limited information we have.

What are your closing thoughts and best-case scenario for public health control of SARS-CoV-2?

G.A.: We need to understand the nature of reinfection. Natural correlates of exposure could significantly change the game and give us insights to drive vaccine development and, more importantly, to prioritize particular vaccines for those that are most vulnerable to disease. In the meantime, social distancing will be a reality for the foreseeable future. This should be emphasized. We will not be out of masks for a long while. The economy continues to suffer, and we need creative solutions to help our population and world heal. This will not be the last pathogen, and if we learn only one lesson, let us continue to make diagnostics and vaccines a priority, so we can stop emerging infections in their tracks and prevent a pandemic from paralyzing our globe again.

K.B.: The best-case scenario for public health control of SARS-CoV-2 is that we find a cheap, stable sterilizing vaccine. Assuming that doesn't happen (immediately), the next best case is we have multiple vaccines for different at-risk populations, which are disease modifying, lessen the severity of the infection, and (together with effective therapeutics) reduce mortality from COVID-19. I am optimistic this will happen.

However, we have to recognize that we are likely to face future evolution of the biology of the SARS-CoV-2 virus and also of future viruses. So this means we need to improve our global public health preparedness, where vaccines are just one piece of the pie.

J.D.: My best-case scenario for public health control of SARS-CoV-2 is not scientific. Instead, it is social: a return to truth-based conversations. Politicians must acknowledge and appreciate the value of objective scientific evidence. Until we return to these norms, SARS-CoV-2 will remain a social and political issue and, as a result, scientific and public health solutions to COVID-19 will be encumbered.

In the United States, scientific and medical professionals must continue to highlight the need for everyone to wear masks. I am in awe of our frontline medical workers, many of whom have spent time away from family, gotten sick, or died. Frontline medical professionals are willing to make the ultimate sacrifice for us, and yet many of us will not make the small sacrifice of wearing a mask for them.

J.M.: My best-case scenario is that several vaccines are proven to be safe and effective and can be very widely used throughout 2021. Combined with better therapies, and also with more traditional methods (masks, social distancing, lockdowns), vaccines could end the pandemic next year.

Company executives at vaccine manufacturers (and politicians) really need to pay much more attention to the need to boost public confidence in their products. Vaccine hesitancy is a real thing, and it's becoming worse during the ultrapoliticized COVID-19 pandemic. Creating a vaccine that is effective but not widely used because it's not trusted would be a very expensive Pyrrhic victory …. In other words, some companies may need to rein in their ambitions to be first, as they will need the support of the vaccine science and public health communities. If the latter believe or suspect that shortcuts have been taken with safety, that support may not be a given.

Interviewed by Laura DeFrancesco

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CORONAVIRUS

3 vaccine executives say that after approval, distribution will be the main challenge

Pfizer, Moderna and Johnson & Johnson are working to produce enough doses and ensure fair distribution through the uneven U.S. health care system.

A lab technician sorts blood samples at a lab for a Covid-19 vaccine study at Research Centers of America in Hollywood, Fla., on Aug. 13. Chandan Khanna / AFP - Getty Images file

Dec. 3, 2020, 11:49 PM CET

By David Ingram

The top executives of Pfizer, Moderna and Johnson & Johnson said in an NBC News interview that even after their companies developed potential Covid-19 vaccines at a breakneck pace, some of their biggest challenges still lie ahead, including quickly producing enough doses and ensuring fair distribution through the uneven U.S. health care system.

"We have never done anything like this," Johnson & Johnson CEO Alex Gorsky said, speaking of the logistics of reaching billions of people with potential vaccines.

The executives – Gorsky, Pfizer CEO Albert Bourla and Moderna President Stephen Hoge – spoke in an exclusive joint interview with NBC News' Lester Holt. The interview is scheduled to air Thursday on "Dateline NBC" at 10 p.m. ET.

This report is part of NBC News' in-depth coverage on the "Race for a Vaccine," a network-wide, weeklong series airing across all programs and platforms, including "NBC Nightly News," "TODAY," "Dateline NBC," MSNBC, NBCNews.com and NBC News NOW.

Gorsky said he was especially concerned about access to potential vaccines within Black and Hispanic communities, which not only have been hit especially hard by the coronavirus but in many cases also have been underserved by the health care system. He said governments and the drug companies would need to respond with massive distribution systems and education.

"How do we actually make sure that we can get distribution [and] administration safely, effectively, and do the logistics of trying to reach hundreds of millions, let alone billions, of people around the world?" Gorsky asked.

More than 274,000 people in the U.S. have died in the pandemic, which has shuttered businesses nationwide and put millions out of work. The winter months could be even more difficult, federal officials have warned.

Lester Holt interviews Pfizer CEO Albert Bourla, Moderna President Stephen Hoge and Johnson & Johnson CEO Alex Gorsky. Dateline

But the potential that Covid-19 vaccine shots will soon be available has spurred optimism, even before there's a definite date for the first Americans who weren't part of clinical trials to get them.

An advisory committee of the Food and Drug Administration is scheduled to meet Dec. 10 to consider whether to grant emergency use authorization to Pfizer for its vaccine candidate. The FDA itself would weigh in next. FDA scientists are also reviewing data about another vaccine candidate made by Moderna, and a third candidate from Johnson & Johnson is in a late-stage trial. Some states have said they also want to conduct their own reviews.

A member of an FDA advisory committee, Dr. Paul Offit, director of the Vaccine Education Center at Children's Hospital of Philadelphia, said in a separate interview: "The standard we're going to hold this to is: Would I give this vaccine to myself or my own family? And if the answer to that question is 'I'm not sure,' then we're not going to move forward."

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The United Kingdom formally approved the vaccine from Pfizer and its partner, BioNTech, on Wednesday, becoming the first country to have done so.

Hoge said Moderna already faced a significant setback in September because of the lack of trust that some communities of color have in the health care system. He said the company realized that the people who had enrolled in its late-stage vaccine trial weren't diverse enough to give Moderna the data it needed, so the company had to broaden its outreach.

"We said, 'We're going to take the time to do that now,'" Hoge said. "Because it's absolutely essential that this trial provide data that provides confidence to all of those communities, particularly those that are disproportionately impacted by Covid, and make sure they can have confidence that the vaccine works for them, as well.

"In the end, we were able to work with the investigators to build that trust and recruit the trial over the subsequent six to eight weeks. But it was a hard decision and a lot of work," he said.

The initial vaccine rollouts could be swift. If Pfizer receives approval, Bourla said, it has a logistics network in place, including specialized insulated boxes to keep doses cold "to send vaccines within 24 hours basically in any place in the U.S."

Bourla said it's still unknown whether people who've been vaccinated could still be carriers of the virus, able to transmit it to others.

"I think this is something that needs to be examined. We are not certain about that right now," he said.

Bourla said researchers and regulators ought to find a way to quickly vaccinate participants in clinical trials who received placebo doses, an idea Pfizer said it was exploring last month. "It is a moral and ethical dilemma and obligation, I think, that we have to these people," he said.

The executives said many factors contributed to making the vaccine candidates possible on timelines never before imagined. In particular, they cited the willingness of governments to buy doses of unproven candidates, which sped manufacturing and freed the companies of some financial worry.

"What's really the ingredient that's been taken out over the course of the past year is some of the financial and business caution that normally slows the development of drugs," Hoge said. He said the standards of quality for the vaccine trials weren't compromised.

The executives said they were kept in the dark as their companies collected data from the trials, in keeping with standard practice. Hoge said he didn't sleep for the 24 hours from when he was told he would finally see the results to when he saw them.

"They notified us of the vaccine efficacy and the number of cases that had happened on placebo – and the very small number that had happened on the vaccine. And I don't think I remember another thing for about 20 minutes," Hoge said.

"From the moment of hearing that result, there was this overwhelming sense of relief for the past – for that 24 hours, for the past year, for the past 10 years of work," he said.

David Ingram

David Ingram covers tech for NBC News.

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by Taboola

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IMAGE: **YouTube**/EPP

COVID-19

Pfizer CEO says there is 'encouraging' data on whether its vaccine stops Covid transmission

"We know that in animals, [there is] significant protection from transferring the virus," Dr Albert Bourla told an the EPP Group health event.

40 57.3k Jan 13th 2021, 3:12 PM

THE CEO OF Pfizer has said that there is "encouraging" data on whether the Pfizer BioNTech vaccine stops transmission.

Dr Albert Bourla said at the EPP Group health event that "more concrete data" would be available by February.

Studies to date have shown that its vaccine is highly effective at preventing a person who gets SARS-CoV-2 from becoming seriously ill with Covid-19, but separate research needs to be carried out as to its effectiveness at preventing transmission itself.

"Right now we want to see to the vaccine, in addition to protecting people, is also preventing transferring the virus," Dr Bourla said.

"This is not conclusive yet. We know that in animals, [there is] significant protection from transferring the virus…. We haven't [proven that in] humans yet."

When asked how long the vaccine would give immunity to Covid-19 for, Bourla said that people who have been vaccinated for 6-7 months "are maintaining a very high level of protection".

Dr Bourla also told the EPP Group event that it looks like there is a "very, very high efficacy" of the Pfizer-BioNTech vaccine against the two variants that appear to be able to transmit easier than other variants.

Studies have suggested that two variants – one found in the UK and another in South Africa – could be between 50-75% more transmissible.

Dr Bourla said that after a number of in vitro experiments, it appears that it will have a very high efficacy against these variants.

On the safety of the vaccine for children, he said that the Pfizer-BioNTech vaccine has been licenced for people aged 16 years old and above.

Pfizer are running clinical trials to examine the safety of the vaccine among children aged from 12-16, and Dr Bourla expects them to conclude in a few months, "maybe the first quarter".

He said that any bottlenecks that there are currently in the production of the vaccine are a result of the vaccine not having been made before, coupled with the vaccines being needed in "extraordinary quantities".

"We feel confident that we will dramatically increase the production of our vaccines."

Right now, we expect this year to deliver 2 billion doses against the 1.3 billion [previously planned for this year]. And the efforts [to increase production] are not stopping.

When asked if the contract for vaccines with the European Union would be published, Dr Bourla said that they would look at publishing a version of the deal that keeps some information confidential "because I think it's become quite sensitive" to make some of the information public.

Franz-Werner Haas, CEO of CureVac which is also developing a Covid-19 vaccine, said that the importance of a Europe-wide and global approach to battling the Covid-19 pandemic is that the virus doesn't recognise borders, nationality, or the colour of skin.

The CureVac vaccine is in the third testing phase; if it cannot apply for authorisation by this Spring, it aims to produce the BioNTech vaccine.

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Comirnaty

COVID-19 mRNA vaccine (nucleoside modified)

What is Comirnaty and what is it used for?

Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 16 years and older.

Comirnaty contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2, the virus that causes COVID-19. Comirnaty does not contain the virus itself and cannot cause COVID-19.

Detailed information about this vaccine is available in the product information, which includes the package leaflet.

How is Comirnaty used?

Comirnaty is given as two injections, usually into the muscle of the upper arm, at least 21 days apart.

Arrangements for the supply of the vaccine will be the responsibility of national authorities. For more information about using Comirnaty, see the package leaflet or consult a healthcare professional.

How does Comirnaty work?

Comirnaty works by preparing the body to defend itself against COVID-19. It contains a molecule called mRNA which has instructions for making the spike protein. This is a protein on the surface of the SARS-CoV-2 virus which the virus needs to enter the body's cells.

When a person is given the vaccine, some of their cells will read the mRNA instructions and temporarily produce the spike protein. The person's immune system will then recognise this protein as foreign and produce antibodies and activate T cells (white blood cells) to attack it.

If, later on, the person comes into contact with SARS-CoV-2 virus, their immune system will recognise it and be ready to defend the body against it.

The mRNA from the vaccine does not stay in the body but is broken down shortly after vaccination.

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What benefits of Comirnaty have been shown in studies?

A very large clinical trial showed that Comirnaty was effective at preventing COVID-19 in people from 16 years of age.

The trial involved around 44,000 people in total. Half received the vaccine and half were given a dummy injection. People did not know whether they received the vaccine or the dummy injection.

Efficacy was calculated in over 36,000 people from 16 years of age (including people over 75 years of age) who had no sign of previous infection. The study showed a 95% reduction in the number of symptomatic COVID-19 cases in the people who received the vaccine (8 cases out of 18,198 got COVID-19 symptoms) compared with people who received a dummy injection (162 cases out of 18,325 got COVID-19 symptoms). This means that the vaccine demonstrated a 95% efficacy in the trial.

The trial also showed around 95% efficacy in the participants at risk of severe COVID-19, including those with asthma, chronic lung disease, diabetes, high blood pressure or a body mass index ≥ 30 kg/m^2.

Can people who have already had COVID-19 be vaccinated with Comirnaty?

There were no additional side effects in the 545 people who received Comirnaty in the trial and had previously had COVID-19.

There were not enough data from the trial to conclude on how well Comirnaty works for people who have already had COVID-19.

Can Comirnaty reduce transmission of the virus from one person to another?

The impact of vaccination with Comirnaty on the spread of the SARS-CoV-2 virus in the community is not yet known. It is not yet known how much vaccinated people may still be able to carry and spread the virus.

How long does protection from Comirnaty last?

It is not currently known how long protection given by Comirnaty lasts. The people vaccinated in the clinical trial will continue to be followed for 2 years to gather more information on the duration of protection.

Can children be vaccinated with Comirnaty?

Comirnaty is not currently recommended for children below 16 years of age. EMA has agreed with the company on a plan to trial the vaccine in children at a later stage.

Can immunocompromised people be vaccinated with Comirnaty?

There are limited data on immunocompromised people (people with weakened immune systems). Although immunocompromised people may not respond as well to the vaccine, there are no particular safety concerns. Immunocompromised people can still be vaccinated as they may be at higher risk from COVID-19.

Can pregnant or breast-feeding women be vaccinated with Comirnaty?

Animal studies do not show any harmful effects in pregnancy, however data on the use of Comirnaty during pregnancy are very limited. Although there are no studies on breast-feeding, no risk for breast-feeding is expected.

The decision on whether to use the vaccine in pregnant women should be made in close consultation with a healthcare professional after considering the benefits and risks.

Can people with allergies be vaccinated with Comirnaty?

People who already know they have an allergy to one of the components of the vaccine listed in section 6 of the package leaflet should not receive the vaccine.

Allergic reactions (hypersensitivity) have been seen in people receiving the vaccine. A very small number of cases of anaphylaxis (severe allergic reaction) have occurred since the vaccine started being used in vaccination campaigns. Therefore, as for all vaccines, Comirnaty should be given under close medical supervision, with the appropriate medical treatment available. People who have a severe allergic reaction when they are given the first dose of Comirnaty should not receive the second dose.

How well does Comirnaty work for people of different ethnicities and genders?

The main trial included people of different ethnicities and genders. Efficacy of around 95% was maintained across genders, racial and ethnic groups.

What are the risks associated with Comirnaty?

The most common side effects with Comirnaty in the trial were usually mild or moderate and got better within a few days after vaccination. These included pain and swelling at the injection site, tiredness, headache, muscle and joint pain, chills and fever. They affected more than 1 in 10 people.

Redness at the injection site and nausea occurred in less than 1 in 10 people. Itching at the injection site, pain in the limb, enlarged lymph nodes, difficulty sleeping and feeling unwell were uncommon side effects (affecting less than 1 in 100 people). Weakness in muscles on one side of face (acute peripheral facial paralysis or palsy) occurred rarely in less than 1 in 1,000 people.

Allergic reactions have occurred with Comirnaty, including a very small number of cases of severe allergic reactions (anaphylaxis) which have occurred when Comirnaty has been used in vaccination campaigns. As for all vaccines, Comirnaty should be given under close supervision with appropriate medical treatment available.

Why has EMA recommended the authorisation of Comirnaty?

Comirnaty offers a high level of protection against COVID-19 which is a critical need in the current pandemic. The main trial showed that the vaccine has a 95% efficacy. Most side effects are mild to moderate in severity and are gone within a few days.

The Agency therefore decided that Comirnaty’s benefits are greater than its risks and that it can be recommended for authorisation in the EU.

EMA has recommended a conditional marketing authorisation for Comirnaty. This means that there is more evidence to come about the vaccine (see below), which the company is required to provide. The Agency will review any new information that becomes available and this overview will be updated as necessary.

What information is still awaited for Comirnaty?

As Comirnaty is recommended for a conditional marketing authorisation, the company that markets Comirnaty will continue to provide results from the clinical trial, which is ongoing for 2 years. This trial and additional studies will provide information on how long protection lasts, how well the vaccine prevents severe COVID-19, how well it protects immunocompromised people, children and pregnant women, and whether it prevents asymptomatic cases.

In addition, independent studies of COVID-19 vaccines coordinated by EU authorities will also give more information on the vaccine's long-term safety and benefit in the general population.

The company will also carry out studies to provide additional assurance on the pharmaceutical quality of the vaccine as the manufacturing continues to be scaled up.

What measures are being taken to ensure the safe and effective use of Comirnaty?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Comirnaty have been included in the summary of product characteristics and the package leaflet.

A risk management plan (RMP) for Comirnaty is also in place and contains important information about the vaccine's safety, how to collect further information and how to minimise any potential risks. A summary of the RMP is available.

Safety measures will be implemented for Comirnaty in line with the EU safety monitoring plan for COVID-19 vaccines to ensure that new safety information is rapidly collected and analysed. The company that markets Comirnaty will provide monthly safety reports.

As for all medicines, data on the use of Comirnaty are continuously monitored. Suspected side effects reported with Comirnaty are carefully evaluated and any necessary action taken to protect patients.

Other information about Comirnaty

Comirnaty was recommended by EMA's human medicines committee (CHMP) on 21 December 2020 for a conditional marketing authorisation valid throughout the EU. The European Commission will issue a decision shortly.

Detailed recommendations for the use of this product are described in the product information, which will be available in all official European Union languages after a decision on the marketing authorisation has been issued by the European Commission.

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FDA NEWS RELEASE

FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine

Action Follows Thorough Evaluation of Available Safety, Effectiveness, and Manufacturing Quality Information by FDA Career Scientists, Input from Independent Experts

For Immediate Release:

December 11, 2020

Español (/news-events/press-announcements/la-fda-toma-accion-clave-en-la-lucha-contra-el-covid-19-al-emitir-una-autorizacion-de-uso-de)

Today, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The emergency use authorization allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the U.S.

"The FDA's authorization for emergency use of the first COVID-19 vaccine is a significant milestone in battling this devastating pandemic that has affected so many families in the United States and around the world," said FDA Commissioner Stephen M. Hahn, M.D. "Today's action follows an open and transparent review process that included input from independent scientific and public health experts and a thorough evaluation by the agency's career scientists to ensure this vaccine met FDA's rigorous, scientific standards for safety, effectiveness, and manufacturing quality needed to support emergency use authorization. The tireless work to develop a new vaccine to prevent this novel, serious, and life-threatening disease in an expedited timeframe after its emergence is a true testament to scientific innovation and public-private collaboration worldwide."

The FDA has determined that Pfizer-BioNTech COVID-19 Vaccine has met the statutory criteria for issuance of an EUA. The totality of the available data provides clear evidence that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19. The data also support that the known and potential benefits outweigh the known and potential risks, supporting the vaccine's use in millions of people 16 years of age and older, including healthy individuals. In making this determination, the FDA can assure the public and medical community that it has conducted a thorough evaluation of the available safety, effectiveness and manufacturing quality information.

The Pfizer-BioNTech COVID-19 Vaccine contains messenger RNA (mRNA), which is genetic material. The vaccine contains a small piece of the SARS-CoV-2 virus's mRNA that instructs cells in the body to make the virus's distinctive "spike" protein. When a person receives this vaccine, their body produces copies of the spike protein, which does not cause disease, but triggers the immune system to learn to react defensively, producing an immune response against SARS-CoV-2.

"While not an FDA approval, today's emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine holds the promise to alter the course of this pandemic in the United States," said Peter Marks, M.D., Ph.D., Director of the FDA's Center for Biologics Evaluation and Research. "With science guiding our decision-making, the available safety and effectiveness data support the authorization of the Pfizer-BioNTech COVID-19 Vaccine because the vaccine's known and potential benefits clearly outweigh its known and potential risks. The data provided by the sponsor have met the FDA's expectations as conveyed in our June and October guidance documents. Efforts to speed vaccine development have not sacrificed scientific standards or the integrity of our vaccine evaluation process. The FDA's review process also included public and independent review from members of the agency's Vaccines and Related Biological Products Advisory Committee. Today's achievement is ultimately a testament to the commitment of our career scientists and physicians, who worked tirelessly to thoroughly evaluate the data and information for this vaccine."

FDA Evaluation of Available Safety Data

Pfizer BioNTech COVID-19 Vaccine is administered as a series of two doses, three weeks apart. The available safety data to support the EUA include 37,586 of the participants enrolled in an ongoing randomized, placebo-controlled international study, the majority of whom are U.S. participants. These participants, 18,801 of whom received the vaccine and 18,785 of whom received saline placebo, were followed for a median of two months after receiving the second dose. The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so it is important for vaccination providers and recipients to expect that there may be some side effects after either dose, but even more so after the second dose.

It is mandatory for Pfizer Inc. and vaccination providers to report the following to the Vaccine Adverse Event Reporting System (VAERS) for Pfizer-BioNTech COVID-19 Vaccine: all vaccine administration errors, serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS), and cases of COVID-19 that result in hospitalization or death.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the EUA include an analysis of 36,523 participants in the ongoing randomized, placebo-controlled international study, the majority of whom are U.S. participants, who did not have evidence of SARS-CoV-2 infection through seven days after the second dose. Among these participants, 18,198 received the vaccine and 18,325 received placebo. The vaccine was 95% effective in preventing COVID-19 disease among these clinical trial participants with eight COVID-19 cases in the vaccine group and 162 in the placebo group. Of these 170 COVID-19 cases, one in the vaccine group and three in the placebo group were classified as severe. At this time, data are not available to make a determination about how long the vaccine will provide protection, nor is there evidence that the vaccine prevents transmission of SARS-CoV-2 from person to person.

The EUA Process

On the basis of the determination by the Secretary of the Department of Health and Human Services on February 4, 2020, that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and then issued declarations that circumstances exist justifying the authorization of emergency use of unapproved products, the FDA may issue an EUA to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent COVID-19 when there are no adequate, approved, and available alternatives.

The issuance of an EUA is different than an FDA approval (licensure) of a vaccine. In determining whether to issue an EUA for a product, the FDA evaluates the available evidence and assesses any known or potential risks and any known or potential benefits, and if the benefit-risk assessment is favorable, the product is made available during the emergency. Once a manufacturer submits an EUA request for a COVID-19 vaccine to the FDA, the agency then evaluates the request and determines whether the relevant statutory criteria are met, taking into account the totality of the scientific evidence about the vaccine that is available to the FDA.

The EUA also requires that fact sheets that provide important information, including dosing instructions, and information about the benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine, be made available to vaccination providers and vaccine recipients.

The company has submitted a pharmacovigilance plan to FDA to monitor the safety of Pfizer-BioNTech COVID-19 Vaccine. The pharmacovigilance plan includes a plan to complete longer-term safety follow-up for participants enrolled in ongoing clinical trials. The pharmacovigilance plan also includes other activities aimed at monitoring the safety profile of the Pfizer-BioNTech COVID-19 vaccine and ensuring that any safety concerns are identified and evaluated in a timely manner.

The FDA also expects manufacturers whose COVID-19 vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and effectiveness information and pursue approval (licensure).

The EUA for the Pfizer-BioNTech COVID-19 Vaccine was issued to Pfizer Inc. The EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19 is terminated, and may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Related Information

- Pfizer-BioNTech COVID-19 Vaccine EUA Letter of Authorization (https://www.fda.gov/media/144412/download)
- Pfizer-BioNTech COVID-19 Vaccine EUA Fact Sheet for Healthcare Providers (https://www.fda.gov/media/144413/download)
- Pfizer-BioNTech COVID-19 Vaccine EUA Fact Sheet for Patients (https://www.fda.gov/media/144414/download)
- COVID-19 Vaccines (/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines)
- Emergency Use Authorization for Vaccines Explained (/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained)
- Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry (/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19)
- Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19)

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This is an archived version of this Interim Guidance which has since been updated. The latest version can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1

Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing

Interim guidance

8 January 2021

World Health Organization

Background

This interim guidance has been developed based on the advice issued by the Strategic Advisory Group of Experts on Immunization (SAGE) at its 5 January 2021 extraordinary meeting [1].

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing or updating recommendations [2]. Specifically for COVID-19 vaccines, a detailed description of the methodological processes can be found in the SAGE evidence framework for COVID-19 vaccines. This framework is intended to offer guidance for considering data emerging from clinical trials in support of issuing vaccine-specific evidence-based recommendations [3].

General goal and strategy for the use of the mRNA vaccine BNT162b2 against COVID-19 (Pfizer–BioNTech)

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There is an urgent global need for effective and safe vaccines. On 31 December 2020, WHO listed the COVID-19 mRNA vaccine BNT162b2 for emergency use, making the Pfizer–BioNTech vaccine the first to receive emergency validation from WHO since the outbreak began a year earlier. The WHO Emergency Use Listing Procedure (EUL) is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a public health emergency.

BNT162b2, an mRNA vaccine against COVID-19 developed by BioNTech and Pfizer, has been shown to have an efficacy of approximately 95%, based on a median follow-up of two months. The data reviewed by WHO at this time support the conclusion that the known and potential benefits of BNT162b2 outweigh the known and potential risks. As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, countries are recommended to use the WHO Prioritization Roadmap [4] and the WHO Values Framework [5] as guidance for their prioritization of target groups. As long as vaccine supplies are very limited (stage I in the WHO Prioritization Roadmap), in settings with community transmission, the Roadmap recommends that priority be given initially to health workers at high risk and older people with and without comorbidities. Protecting high-risk health workers has a threefold purpose: (i) to protect the individual health workers; (ii) to protect critical essential services during the COVID-19 pandemic, and (iii) to prevent onward transmission to vulnerable people. Protecting older people will have the greatest public health impact in terms of reducing the number of deaths. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap [4], taking into account national epidemiological data and other relevant considerations.

Intended use

Persons aged 16 years and above.

Administration

The recommended schedule is two doses (30 µg, 0.3 ml each) given intramuscularly into the deltoid muscle. An interval of 21–28 days between the doses is recommended. If the second dose is inadvertently administered less than 21 days after the first, the dose does not need to be repeated. If administration of the second dose is inadvertently delayed it should be given as soon as possible thereafter, according to the manufacturer's instructions. It is currently recommended that individuals receive no more than two doses in total.

Considerations for deferring the second dose

WHO acknowledges that a number of countries face exceptional circumstances of vaccine supply constraints combined with a high disease burden. Some countries have therefore considered delaying the administration of the second dose to allow for a higher initial coverage. This is based on the observation that efficacy has been shown to start from day 12 after the first dose and reached about 89% between days 14 and 21, at the time when the second dose was given. No data on longer term efficacy for a single dose of the mRNA vaccine BNT162b2 currently exist, as the trial participants received 2 doses with an interval between doses in the trial ranging from 19 to 42 days. Of note, neutralizing antibody responses are modest after the first dose and increase substantially after the second dose.

Countries experiencing exceptional epidemiological circumstances may consider delaying for a short period the administration of the second dose as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. WHO's recommendation at present is that the interval between doses may be extended up to 42 days (6 weeks), on the basis of currently available clinical trial data. Should additional data become available on longer intervals between doses, revision of this recommendation will be considered. Countries should ensure that any such programme adjustments to dose intervals do not affect the likelihood of receiving the second dose.

Booster doses

There is currently no evidence on the need for a booster dose or booster doses of the vaccine after the current two-dose vaccine series is complete. The need for and timing of booster doses will be evaluated as further data accumulate.

Interchangeability with other vaccines

No data are available on the interchangeability of this vaccine with other mRNA vaccines or other COVID-19 vaccine platforms. It is currently recommended that the same product should be used for both doses. If different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended at this time. Recommendations may be updated as further information becomes available on interchangeability.

Co-administration with other vaccines

There should be a minimum interval of 14 days between administration of this vaccine and any other vaccine against other conditions, until data on co-administration with other vaccines become available.

Contraindications

A history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine is a contraindication to vaccination. In particular, BNT162b2 should not be administered to individuals with a known history of severe allergic reaction to polyethylene glycol (PEG) or related molecules as PEG is a component of the vaccine.

Precautions

Anaphylactic reactions after administration of BNT162b2 vaccine have been reported outside of clinical trials. A history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is considered as a precaution but not a contraindication to vaccination. For such persons, a risk assessment should be conducted to determine the type and severity of reaction and the reliability of the information. Such individuals may still receive vaccination, but they should be counselled about the risks of developing a severe allergic reaction and the risks should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health care settings where anaphylaxis can be immediately treated.

In general, persons with an immediate allergic reaction to the first dose should not receive additional doses. For the purposes of this guidance, an immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms, such as anaphylaxis, urticaria, angioedema, respiratory distress (e.g. wheezing, stridor), that occur within hours of administration. However, subject to individual risk-benefit assessment, specialist services for immunization may allow BNT162b2 to be provided under close medical supervision if it is the only available option for persons at high risk of severe COVID-19.

As a small number of anaphylactic reactions have also been reported in vaccinees without a history of severe allergic reactions, WHO recommends that BNT162b2 vaccine should be administered only in settings where anaphylaxis can be treated. Until more data and insights are available with regard to severe allergic reactions to BNT162b2 vaccination, all vaccinees should be observed for at least 15 minutes after vaccination.

Food, contact, or seasonal allergies are not considered a precaution. The vial stoppers are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, as BNT162b2 does not contain eggs or gelatin, there is no contraindication or precaution to vaccination for persons with allergies to these substances.

Anyone with an acute febrile illness (body temperature over 38.5 ºC) should postpone vaccination until they are afebrile.

Vaccination of specific populations

Populations for which supportive data are available from phase 2/3 clinical trials

Older people

The risk of severe COVID-19 and death increases steeply with age. Data from the phase 3 trial indicate that the efficacy and safety of the vaccine are comparable across all age groups (above the age of 16). Vaccination is recommended for older persons.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. Phase 2/3 clinical trials have demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in phase 2/3 clinical trials include hypertension; diabetes; asthma; and pulmonary, liver and kidney disease; as well as chronic (stable and controlled) infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19.

Populations for which limited or no data exist from phase 2/3 clinical trials

Persons above 85 years of age

Persons above the age of 85 years and very frail older persons were not included in the clinical trials. However, the safety and immunogenicity data obtained in a large subset of older people with and without comorbidities suggest that the benefits of vaccination outweigh the potential risks. Vaccination is recommended for older persons without an upper age limit.

Children and adolescents below the age of 16 years

There are currently no efficacy or safety data for children or adolescents below the age of 16 years. Until such data are available, individuals below 16 years of age should not be vaccinated.

Pregnant women

Pregnant women are at higher risk of severe COVID-19 compared to women of child-bearing age who are not pregnant, and COVID-19 has been associated with an increased risk of preterm birth. The available data on BNT162b2 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, it should be noted that the BNT162b2 vaccine is not a live virus vaccine, the mRNA does not enter the nucleus of the cell and is degraded quickly.

Developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects in pregnancy. Further studies are planned in pregnant women in the coming months. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, WHO recommends not to use BNT162b2 in pregnancy, unless the benefit of vaccinating a pregnant woman outweighs the potential vaccine risks, such as in health workers at high risk of exposure and

pregnant women with comorbidities placing them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided. WHO does not recommend pregnancy testing prior to vaccination.

Lactating women

Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. However, there are no data on the safety of COVID-19 vaccines in lactating women or on the effects of mRNA vaccines on breastfed children. As the BNT162b2 vaccine is not a live virus vaccine and the mRNA does not enter the nucleus of the cell and is degraded quickly, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g. health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination.

Persons living with HIV

Persons living with HIV may be at higher risk of severe COVID-19. Among the phase 2/3 clinical trial participants with well controlled HIV, there were no reported differences in safety signals. HIV-positive persons who are well controlled on highly active antiretroviral therapy and are part of a group recommended for vaccination can be vaccinated. Available data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy or safety for persons living with HIV who are not well controlled on therapy. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

Immunocompromised persons

Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment.

Persons with autoimmune conditions

No data are currently available on the safety and efficacy of BNT162b2 in persons with autoimmune conditions, although these persons were eligible for enrolment in the clinical trials. Persons with autoimmune conditions who have no contraindications to vaccination may be vaccinated.

Persons with a history of Bell's palsy

Cases of Bell's palsy were reported following vaccination in participants in the Pfizer-BioNTech clinical trials. However, there is currently no conclusive evidence that these cases were causally related to vaccination. Post-authorization safety surveillance will be important to assess any possible causal association. In the absence of such evidence, persons with a history of Bell's palsy may receive BNT162b2 unless they have a contraindication to vaccination.

Persons who have previously had SARS-CoV-2 infection

Vaccination may be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing for prior infection is not recommended for the purpose of decision-making about vaccination. Available data from the phase 2/3 trials indicate that BNT162b2 is safe in people with evidence of prior SARS-CoV-2 infection. The added protection of vaccinating previously infected individuals is yet to be established. Despite the potential for reinfection, currently available data indicate that symptomatic reinfection within 6 months after an initial infection is rare. Thus, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may delay vaccination until near the end of this period. When more data on duration of immunity after natural infection become available, the length of this time period may be revised.

Persons with current acute COVID-19

Vaccination of persons with acute symptomatic SARS-CoV-2 should be deferred until they have recovered from acute illness and the criteria for discontinuation of isolation have been met. There are no data to support a recommendation of a minimal interval between onset of symptoms and vaccination.

Persons who previously received passive antibody therapy for COVID-19

Currently there are no data on the safety or efficacy of vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. Hence, as a precautionary measure, vaccination should be deferred for at least 90 days to avoid interference of the antibody treatment with vaccine-induced immune responses.

Special settings

Persons in settings such as refugee and detention camps, prisons, slums, and other settings with high population densities, where physical distancing is not implementable, should be prioritized for vaccination as outlined in the WHO Prioritization Roadmap [4], taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap, national programmes should give special consideration to groups that are disproportionately affected by COVID-19 or that face health inequities as a result of social or structural inequities. Such groups should be identified, barriers to vaccination should be addressed, and programmes should be developed to enable equitable access to vaccines.

In the current period of very limited vaccine supply, preferential vaccination of international travelers would counter the principle of equity. Because of this and the lack of evidence on whether vaccination reduces the risk of transmission, WHO currently does not recommend COVID-19 vaccination of travelers (unless they are also part of a high-risk group or in epidemiological settings identified in the WHO Prioritization Roadmap [4]). With increasing vaccine supply, these recommendations will be revisited.

Other considerations

SARS-CoV-2 tests

Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. However, it is important to note that currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains mRNA that encodes the spike protein; thus, a positive test for spike protein IgM or IgG could indicate either prior infection or prior vaccination. To evaluate for evidence of prior infection in an individual who has received the BNT162b2 vaccine, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing is not currently recommended to assess immunity to COVID-19 following BNT162b2 vaccination.

Role of vaccines among other preventive measures

As there is not yet any evidence of an effect of the vaccine on transmission, non-pharmaceutical interventions must continue, including use of face masks, physical distancing, handwashing and other measures based on the epidemiology of SARS-CoV-2 in particular settings. Government advice on non-pharmaceutical interventions should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

Community engagement, effective communication, and legitimacy

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. Prioritization decisions should be made through transparent processes that are based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore, communication about the mechanism of action of mRNA vaccines, and efficacy and safety data derived from clinical trials and post-marketing studies, needs to be strengthened. Strategies should include: (1) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (2) active community engagement and involvement of community opinion leaders

and trusted voices to improve awareness and understanding of such communications, and (3) inclusion of diverse and affected stakeholder opinions in decision-making. Such efforts are especially important in subpopulations who may be unfamiliar with or distrustful of health care systems and immunization.

Vaccination logistics

The BNT162b2 vaccine currently requires ultra-cold-chain distribution and storage conditions that will be challenging in many country settings. When assessing the feasibility of deploying BNT162b2, immunization programmes should consider the cold-chain requirements, the current minimum number of doses per shipment, the need to administer a whole batch of vaccine within a short time frame after removal from cold storage, and the need to ensure bundling with an adequate independent supply of the correct diluent. Conditions must be met to avoid exposure of vials to sunlight and ultraviolet light

When scheduling vaccination for occupational groups, e.g. health workers, consideration should be given to the reactogenicity profile of BNT162b2 observed in clinical trials, leading to time off work in the 24-48 hours following vaccination.

Appropriate medical treatment to manage anaphylaxis must be immediately available. Hence, this vaccine should only be administered in settings with the necessary resources and trained health workers, and in settings that allow for at least 15 minutes of post-vaccination observation.

In considering the programme implications of implementing these recommendations, particular attention should be given to equity, including the feasibility, acceptability, and effectiveness of the programme in resource-constrained settings (for example, how to ensure ultra-cold chain storage and the need to be able to provide treatment for anaphylaxis).

Recommendations on addressing current knowledge gaps through further research

In order to confirm the safety profile demonstrated in the clinical trials in the short term, active surveillance of large numbers of vaccinated individuals is necessary in the general population studied for a longer duration, as well as of specific at-risk subpopulations. It is essential for Pfizer–BioNTech and vaccination providers to report the following to adverse event reporting systems in countries: all vaccine administration errors, serious adverse events, cases of multisystem inflammatory syndrome (MIS) following vaccination, anaphylaxis and other serious allergic reactions, Bell`s palsy, and cases of COVID-19 following vaccination that result in hospitalization or death.

WHO recommends the following research and post-authorization monitoring activities:

- vaccine effectiveness over time;
- ongoing collection of safety data in vaccine recipients;
- surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline);
- safety data from inadvertently vaccinated pregnant women during trials and post-authorization;
- safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers;
- prospective studies on the safety of BNT162b2 in pregnant women;
- impact on infants of vaccination of breastfeeding mothers;
- safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease;
- impact of delayed second dose as currently implemented by certain countries;
- clinical trials on the efficacy and safety of vaccination of children below the age of 16 years;
- immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
- studies to determine how protection changes with time since vaccination and whether protection can be prolonged by booster doses;
- studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
- stability of vaccine under alternative cold-chain distribution and storage conditions;
- effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions;
- interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms;
- global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed;
- head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

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WHO: Annelies Wilder-Smith, Joachim Hombach, Melanie Marti, Susan Wang, Katherine O'Brien.

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/BNT162b2/2021.1

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Fact Check: Preventing transmission never required for COVID vaccines' initial approval; Pfizer vax did reduce transmission of early variants

By Reuters Fact Check
February 12, 20249:48 PM GMT+1Updated 3 days ago

Social media users are circulating video clips of testimony by a Pfizer executive, who is said to "admit" that the company and its partner BioNTech did not test whether their mRNA-based COVID-19 vaccine reduced virus transmission prior to rolling it out – which is something the companies were not required to do for initial regulatory approval, nor did they claim to have done.

To get emergency approval, companies needed to show that the vaccines were safe and prevented vaccinated people from getting ill. They did not have to show that the vaccine would also prevent people from spreading the virus to others. Once the vaccines were on the market, independent researchers in multiple countries studied people who

received the Pfizer-BioNTech vaccine and did show that vaccination reduced transmission of variants circulating at the time.

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As these results on transmission were emerging in early 2021, national health authorities in many countries implemented or proposed vaccine-passport-style regulations that prompted ongoing debate (https://www.science.org/doi/10.1126/science.abi5245, opens new tab) over the ethical and legal basis of the rules.

The misleading posts imply that national restrictions such as vaccine passports were based on a promise of vaccines blocking virus spread that neither the companies nor EU regulators made before the vaccines were marketed.

'COMPLETE NONSENSE'

In one of the recent tweets, shared more than 10,000 times (https://twitter.com/calvinrobinson/status/1579781402396348416, opens new tab), one user wrote "Pfizer director admits 'vaccine' wasn't tested for transmissibility. Pfizer 'vaccine' wasn't intended to prevent transmission. Politicians and MSM spread misinformation. Vaccine mandates/passports were immoral, unscientific, and should've been illegal."

Other posts containing portions of the Pfizer executive's testimony with similar claims can be seen (https://twitter.com/itsmercadante/status/1580217286312734720, opens new tab) (https://twitter.com/truenorthcentre/status/1579830040858329089, opens new tab) (https://twitter.com/jamessmithPT_/status/1579944795837198337, opens new tab)

The testimony clips appear to originate in a longer video tweeted on October 11 by European Member of Parliament [redacted] Roos of the Netherlands, with the caption "BREAKING: Vaccine never tested on preventing transmission This means the COVID passport was based on a big lie" which has been shared more than 170,000 times (https://twitter.com/Rob_Roos/status/1579759795225198593, opens new tab).

In the video shared by Roos, he addresses the camera and states that the Dutch prime minister and health minister told the Dutch people that "if you don't get vaccinated, you're antisocial" and that "you don't get vaccinated just for yourself, but also for others." Roos continues, "Today, this turns out to be complete nonsense. In a COVID hearing in the European Parliament, one of the Pfizer directors just admitted to me: at

the time of introduction, the vaccine had never been tested on stopping the transmission of the virus. This removes the entire legal basis for the COVID passport."

In the video, Roos then introduces the testimony clip showing himself first asking a person identified as J. Small of Pfizer for a "clear" yes or no answer to the question, "Was the Pfizer COVID vaccine tested for stopping transmission of the virus before it entered the market?"

Small responds, "No" and explains, "we had to really move at the speed of science to understand what is taking place in the market."

The European Parliament Multimedia Centre makes a longer compilation of excerpts from the full hearing available online (https://multimedia.europarl.europa.eu/en/video/lessons-learned-and-recommendations-for-the-future-extracts-from-the-exchange-of-views-ep-special-committee-on-the-covid-19-pandemic_I231213, opens new tab). The hearing is identified as having taken place on Oct. 10, 2022, and included testimony from "Janine Small, President of Developed Markets, Pfizer."

The hearing's focus was the transparency of negotiations between Pfizer and the European Union over advance-purchase orders for 200 million vaccine doses that were placed before the vaccine had gained regulatory approval, according to Reuters reporting (https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-exec-says-ceo-did-not-negotiate-eu-covid-vaccine-contract-via-text-2022-10-10/)

NOT REQUIRED, NOT PROMISED

In the video clip shared online, the Pfizer executive accurately states that studies of the vaccine's effect on virus transmission from person to person were not performed during the original clinical trials of the company's vaccine.

At the time governments were negotiating advance purchases of vaccine in 2020, the European Medicines Agency had already laid out requirements for an application for conditional marketing authorization of a COVID-19 vaccine, clinical trials were underway, and tests to show the vaccine prevented onward transmission were not required of any vaccine maker.

In a presentation later that year (https://www.ema.europa.eu/en/events/public-stakeholder-meeting-development-authorisation-safe-effective-covid-19-vaccines-eu#video-recording-section, opens new tab), the EMA listed vaccine benefits that clinical trials were intended to demonstrate (slide 8), which included only safety and at least 50% efficacy against "symptomatic disease"

(https://www.ema.europa.eu/documents/presentation/presentation-how-are-covid-19-vaccines-developed-marco-cavaleri_en.pdf, opens new tab).

The same presentation slide describes "Other benefits likely uncertain at approval and only clearer after the vaccine is used" to include the vaccine's "long term protection," "prevention of infection (asymptomatic cases)," and "prevention of virus transmission in the community - needs specific studies post-approval necessary to show."

The U.S. Food and Drug Administration laid out similar expectations for vaccine trials in June of 2020, and did not require data regarding the effect on virus transmission. (https://www.fda.gov/media/139638/download, opens new tab)

A Pfizer spokesperson confirmed to Reuters Fact Check that the company was not asked by regulators to assess the transmission question in the original trials of the vaccine (known as BNT162b2 while in development and later marketed as Comirnaty).

"Our landmark phase 3 clinical trial (protocol published November 2020) was designed and powered to evaluate efficacy of BNT162b2 to prevent disease caused by SARS-CoV2, including severe disease," the spokesperson said in an email. "The pivotal BNT162b2 clinical trial met two critical endpoints including the efficacy end-point which is prevention of confirmed symptomatic COVID-19 infection and the secondary end-point was prevention of severe disease. The BNT162b2 trials were not designed to evaluate the vaccine's effectiveness against transmission of SARS-CoV-2."

A KNOWN UNKNOWN

As clinical trial data on vaccine efficacy against the main endpoints – symptomatic and severe disease -- began to be released in November 2020 (https://www.reuters.com/article/us-health-coronavirus-vaccines-pfizer-em/eu-drug-regulator-says-it-is-assessing-early-data-from-pfizer-covid-vaccine-idINKBN27P1X5), researchers and regulators made clear in public statements that the vaccines' effect on virus transmission remained unknown (https://www.reuters.com/article/health-coronavirus-vaccines-pfizer-scien/pfizer-biontech-initial-vaccine-results-impress-but-scientists-remain-cautious-idUSKBN27P2PI).

The Pfizer/BioNTech vaccine began rolling out immediately after receiving emergency use authorization in the U.S. on Dec. 11, 2020 and conditional marketing authorization in the EU on Dec. 21 (https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#authorisation-details-section, opens new tab).

In a summary of its vaccine assessment published on Dec. 21, 2020, the EMA states: "The impact of vaccination with Comirnaty on the spread of the SARS-CoV-2 virus in the

community is not yet known. It is not yet known how much vaccinated people may still be able to carry and spread the virus." (https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-comirnaty_en.pdf, opens new tab).

BioNTech also stated publicly at the time that answering the transmission question would require at least three to six more months of study, according to Reuters reporting (https://www.reuters.com/article/health-coronavirus-israel-vaccine-int/israeli-studies-find-pfizer-covid-19-vaccine-reduces-transmission-idUSKBN2AJ08J).

Further undermining the idea that Pfizer "admitted" something in the recent hearing that was not already widely known, in January, 2021, Pfizer CEO Albert Bourla continued to state that the company did not know if the vaccine would prevent transmission. He told online news site The Journal that the preliminary data on transmission in the broader population were "encouraging" but that "This is not conclusive yet. We know that in animals, (there is) significant protection from transferring the virus…. We haven't (proven that in) humans yet." (https://www.thejournal.ie/pfizer-ceo-5323949-Jan2021/, opens new tab)

VACCINE DID REDUCE TRANSMISSION

Within months of the vaccine hitting the market, researchers in the UK (https://www.reuters.com/article/uk-health-coronavirus-pfizer-vaccine-tra-idUKKBN2AQ1A7) and Israel (https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762, opens new tab(21)00127-7/fulltext) began publishing studies suggesting that the Pfizer vaccine was reducing transmission of the virus.

In February 2021, for example, Israeli data (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736, opens new tab(21)00448-7/fulltext) showed a sharp drop in infections among healthcare workers within 15-28 days of receiving the two-shot Pfizer vaccine series, indicating the vaccine was not just preventing symptomatic disease, but also preventing the virus from being passed from person to person.

"Whether it is 75 or 90 percent reduction doesn't matter - it is a big drop in transmission," Michal Linial, a professor of molecular biology and bioinformatics at Jerusalem's Hebrew University, told Reuters at the time. "It means that not only is the individual vaccinated protected, the inoculation also provides protection to his or her surroundings" (https://www.reuters.com/article/health-coronavirus-israel-vaccine-int/israeli-studies-find-pfizer-covid-19-vaccine-reduces-transmission-idUSKBN2AJ08J)

Evidence continued to build in 2021 that the mRNA-based vaccines prevented infections and onward transmission of the virus (https://www.science.org/doi/10.1126/science.abl4292, opens new tab). But with the advent that year of the coronavirus Delta variant, plus waning immunity from vaccines delivered at the start of the year, protection against infection and transmission was seen to be dropping, although not eliminated, as previously described by Reuters Fact Check (https://www.reuters.com/article/factcheck-coronavirus-vaccines-idUSL1N2SA1FZ).

The newest family of Omicron variants has further eroded vaccine effectiveness against infection and transmission (https://www.reuters.com/business/healthcare-pharmaceuticals/how-omicron-highlights-fading-hope-herd-immunity-covid-2022-01-20/) . But even Omicron does not escape vaccine protection completely.

A recent study in U.S. prisons, for example, found that vaccinated people who experience an Omicron breakthrough infection still have lower odds of passing the virus to their contacts (https://www.gavi.org/vaccineswork/new-research-proves-covid-19-vaccines-can-slow-spread-disease-even-omicron, opens new tab). The protection was seen to start waning quickly, though, the journal Nature reported: “For every 5 weeks that passed since a person’s last vaccine dose, the risk of transmitting the infection to a close contact increased by 6%” (https://www.nature.com/articles/d41586-022-02328-0, opens new tab)

[redacted]Roos told Reuters in an email that his tweet was not making a point about Pfizer: "My message isn't about Pfizer at all. My message is about governments using a misleading argument to infringe on fundamental rights. Governments worldwide have introduced COVID mandates and passports that had an enormous impact on millions of people. They did so by explicitly arguing that vaccinated people cause less transmission of the virus. Ms. Small's response to my question proves this was an assumption by governments for which no evidence had been provided."

Updated Oct. 17 to add statement by[redacted]Roos.

Updated Jan. 26 to correct the name of Pfizer CEO Albert Bourla in paragraph 27.

VERDICT

Misleading. Social media posts claiming that a Pfizer executive “admitted” the company did not test its COVID vaccine’s ability to prevent virus transmission before receiving marketing approval imply that the company had been required to do so or claimed to have done so, which is false. National policies requiring vaccination to access public spaces or to enter a country that were implemented in early 2021 may have been based

in part on data emerging at that time showing the vaccine did, in fact, prevent transmission of the variants then circulating.

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European Centre for Disease Prevention and Control

Risk of SARS-CoV-2 transmission from newly-infected individuals with documented previous infection or vaccination

Surveillance and monitoring

29 Mar 2021

Cite:

Translate this page

The aim of this document is to provide a summary of the available scientific evidence on the risk of SARS-CoV-2 transmission to susceptible contacts from infected individuals with documented previous infection or vaccination.

Executive summary

More than one year into the SARS-CoV-2 pandemic, over 120 million people have been infected with the virus across more than 200 countries. Reinfections following natural infections with the same or a new SARSCoV-2 variant have been reported sporadically and questions remain concerning the duration of immunity following natural infection, and whether asymptomatic reinfected individuals may be able to transmit the virus.

COVID-19 vaccines have been evaluated for their efficacy and effectiveness against symptomatic COVID-19 infection and for reducing and/or preventing mild, moderate, or severe COVID-19 disease, including mortality. However, the vaccine trials have not been designed to measure reduction in transmission risk from infected vaccinated individuals to susceptible contacts.

In this context, it is important to understand the available scientific evidence on the extent to which previous SARS-CoV-2 infection or COVID-19 vaccination prevents onward transmission from infected individuals to susceptible contacts. Therefore, ECDC has conducted a review of published and pre-print literature on duration and characteristics of immunity following a natural SARS-CoV-2 infection due to any variant or after COVID-19 vaccination with any of the EU-authorised vaccines now available.

The review of evidence on natural immunity and possibilities for transmission from previously infected to susceptible contacts found that:

- Evidence from studies specifically designed to assess the impact of previous infection on the risk of transmission is currently lacking. Infection with SARS-CoV-2 does not provide sterilising immunity for all individuals and some who are reinfected might still be able to transmit SARS-CoV-2 infection to susceptible contacts.
- There is evidence that reinfection remains a rare event. Results from cohort studies confirm that the protective effect of previous SARS-CoV-2 infection ranges from 81% to 100% from Day 14 following initial infection, for a follow-up period of five to seven months. Protection against reinfection is lower in individuals aged 65 years and older.
- These studies were carried out before the emergence of SARS-CoV-2 variants of concern (VOCs) and therefore there is limited preliminary evidence that immunity induced against previously circulating SARS-CoV-2 variants may not have the same potency or duration against the VOCs identified to date (in particular the B.1.351 and P.1 variants.)
- As the number of individuals acquiring natural immunity increases, the total number of infections is expected to decrease significantly, leading to decreased transmission overall, unless the genetic changes in the circulating variants induce significant immune escape.

The review of evidence on immunity and possibilities for transmission from infected, previously-vaccinated individuals to susceptible contacts found that:

- Direct evidence of the impact of vaccination on the risk of transmission is only available from one study, a large register-based household transmission study from Scotland. This study suggests that vaccination of a household member reduces the risk of infection in susceptible household members by at least 30%.
- There is evidence that vaccination significantly reduces viral load and symptomatic/asymptomatic infections in vaccinated individuals, which could translate into reduced transmission, although the vaccine efficacy varies by vaccine product and target group. In light of this fact, the total number of infections is expected to decrease significantly as vaccination coverage increases, provided that there is a match between the vaccine strains and the circulating virus strains. This will lead to decreased transmission overall.
- Follow-up periods for vaccinated persons are not yet sufficiently long enough to draw conclusions on the duration of protection against infection long-term. Antibody titres in vaccinated individuals peak at 3–4 weeks following vaccination.
- Many of the vaccine efficacy studies were carried out before the emergence of SARS-CoV-2 VOCs. In studies that address the variants, there is limited preliminary evidence of reduced vaccine efficacy, in particular for B.1.351 and possibly also for P.1.

Follow-up of cohorts with previous SARS-CoV-2 infection and vaccination is needed to better assess the magnitude and duration of protection from reinfection leading to asymptomatic/symptomatic disease, and the effect of protection against further transmission to contacts.

As an RNA (ribonucleic acid) virus, SARS-CoV-2 will continue to evolve over time and its potential to escape human immune defences induced by natural infection or vaccination has already been documented. It is likely that in the future VOCs will continue to evolve and play a significant role in placing immunological pressure on the circulating viruses. It is not possible to predict when and where this will occur, however, cocirculation of the three VOCs (B.1.1.7, B.1.351 and P.1) has been noted in several EU/EEA countries.

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 30 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a purple cap and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older
Comirnaty is administered intramuscularly after dilution as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population
There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population
No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis
There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness
Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders
As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals
The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals.

Duration of protection
The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness
As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

Excipients

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Comirnaty has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

Participants 16 years of age and older – after 2 doses
In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses
In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 12 years of age and older – after booster dose
A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

Participants 12 years of age and older – after subsequent booster doses
The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain (> 70%), fatigue (> 60%), headache (> 40%), myalgia and chills (> 20%), and arthralgia (> 10%).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), myalgia and chills (> 10%).

Booster dose following primary vaccination with another authorised COVID-19 vaccine
In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy[a]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, pruritus, urticaria[b], angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[d]; lethargy
	Rare	Acute peripheral facial paralysis[c]
	Not known	Paraesthesia[d]; hypoaesthesia[d]
Cardiac disorders	Very rare	Myocarditis[d]; pericarditis[d]
Gastrointestinal disorders	Very common	Diarrhoea[d]
	Common	Nausea; vomiting[d]
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; night sweats
	Not known	Erythema multiforme[d]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia
	Uncommon	Pain in extremity[e]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[h]
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia[f]; injection site swelling
	Common	Injection site redness
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb[d]; facial swelling[g]

a. In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster (≤ 2.8%) dose than after primary (≤ 0.9%) doses of the vaccine.
b. The frequency category for urticaria and angioedema was rare.
c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
d. Adverse reaction determined post-authorisation.
e. Refers to vaccinated arm.
f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.
g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
h. Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis
The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine N[a] = 18 198 Cases n1[b] Surveillance time[c] (n2[d])**	**Placebo N[a] = 18 325 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)[c]**
All participants	8 2.214 (17 411)	162 2.222 (17 511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13 549)	143 1.710 (13 618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3 848)	19 0.511 (3 880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3 074)	14 0.406 (3 095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

Table 3. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine N[a]=20 998 Cases n1[b] Surveillance time[c] (n2[d])	Placebo N[a]=21 096 Cases n1[b] Surveillance time[c] (n2[d])	Vaccine efficacy % (95% CI[e])
All participants[f]	77 6.247 (20 712)	850 6.003 (20 713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15 519)	710 4.654 (15 515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4 192)	124 1.202 (4 226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3 350)	98 0.966 (3 379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19
Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 4. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n1[a] Surveillance time (n2[b])	Placebo Cases n1[a] Surveillance time (n2[b])	Vaccine efficacy % (95% CI[c])
After Dose 1[d]	1 8.439[e] (22 505)	30 8.288[e] (22 435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21 649)	21 6.404[g] (21 730)	95.3 (70.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).
* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen ≤ 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 5.

Table 5. SARS-CoV-2 neutralization assay - NT50 (titre)† (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population±

	N	1 month after booster dose (95% CI)	1 month after primary series (95% CI)	1 month after booster dose - 1 month after primary series (97.5% CI)	Met noninferiority objective (Y/N)
Geometric mean 50% neutralizing titre (GMT[b])	212[a]	2 466.0[b] (2 202.6, 2 760.8)	755.7[b] (663.1, 861.2)	3.26[c] (2.76, 3.86)	Y[d]
Seroresponse rate (%) for 50% neutralizing titre†	200[e]	199[f] 99.5% (97.2%, 100.0%)	190[f] 95.0% (91.0%, 97.6%)	4.5%[g] (1.0%, 7.9%[h])	Y[i]

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

† SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

± All eligible participants who had received 2 doses of Comirnaty as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80.

e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.

g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is > -10%.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a

data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 6. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	Comirnaty N[a]=4 695 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4 671 Cases n1[b] Surveillance Time[c] (n2[d])**	**Relative Vaccine Efficacy[e] % (95% CI[f])**
First COVID-19 occurrence from 7 days after booster vaccination	6 0.823 (4 659)	123 0.792 (4 614)	95.3 (89.5, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the immunogenicity subset data see Table 7.

Table 7. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

		Substudy D (18 to ≤ 55 years of age)		Substudy E (> 55 years of age)	
		Comirnaty 30 mcg		Comirnaty 30 mcg	
GMT	**Dose/ sampling time point[a]**	**N[b]**	**GMT (95% CI[d])**	**N[b]**	**GMT (95% CI[d])**
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre)	1/Prevax	226	315.0 (269.0, 368.9)	167	67.5 (52.9, 86.3)
	1/1 Month	228	1 063.2 (935.8, 1 207.9)	163	455.8 (365.9, 567.6)
SARS-CoV-2 neutralization assay – reference strain – NT50 (titre)	1/Prevax	226	3 999.0 (3 529.5, 4 531.0)	179	1 389.1 (1 142.1, 1 689.5)
	1/1 Month	227	12 009.9 (10 744.3, 13 424.6)	182	5 998.1 (5 223.6, 6 887.4)
Seroresponse rate at 1 month post-Dose 4		**N[c]**	**n[e] (%) (95% CI[f])**	**N[c]**	**n[e] (%) (95% CI[f])**
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre)	1/1 Month	226	91 (40.3%) (33.8, 47.0)	149	85 (57.0%) (48.7, 65.1)
SARS-CoV-2 neutralization assay – reference strain – NT50 (titre)	1/1 Month	225	76 (33.8%) (27.6, 40.4)	179	88 (49.2%) (41.6, 56.7)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

a. Protocol-specified timing for blood sample collection.
b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium phosphate dihydrate
Sucrose
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

Frozen vial
2 years when stored at -90 °C to -60 °C.
Within the 2-year shelf life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial
1 month at 2 °C to 8 °C within the 2-year shelf life.
Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.
Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Handling of temperature excursions once removed from the freezer
Stability data indicate that the unopened vial is stable for up to:

- 24 hours when stored at temperatures from -3 °C to 2 °C
- a total of 4 hours when stored at temperatures from 8 °C to 30 °C; this includes the 2 hours at up to 30 °C detailed above

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Transfers of frozen vials stored at ultra-low temperature (< -60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation, has been demonstrated for 6 hours at 2 ºC to 30 ºC after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.45 mL concentrate in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a purple flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **purple plastic cap** and the product **name is Comirnaty 30 micrograms/dose concentrate for dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- The vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195-vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

- The unopened vial can be **stored for up to 1 month at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
- Allow the thawed vial to come to room temperature. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Gently invert the vial 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.8 mL of sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 ºC to 30 ºC and use within **6 hours**, including any transportation time.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.3 mL doses

- After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of Comirnaty.
  Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose concentrate for dispersion for injection
Adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given the vaccine if:
- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children
Comirnaty 30 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding
If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines
Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people
- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people
- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people
- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people
- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)
- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C. Unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C; not exceeding the printed expiry date (EXP).

Store in the original package in order to protect from light.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Transfers of frozen vials stored at ultra-low temperature (< -60 °C)
- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C
- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at

2 °C to 8 °C, up to 48 hours may be used for transportation. Prior to use, the unopened vaccine can be stored for up to 2 hours at temperatures up to 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store and transport the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
  - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
  - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
  - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
  - cholesterol
  - potassium chloride
  - potassium dihydrogen phosphate
  - sodium chloride
  - disodium phosphate dihydrate
  - sucrose
  - water for injections
  - sodium hydroxide (for pH adjustment)
  - hydrochloric acid (for pH adjustment)

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a purple flip-off plastic cap with aluminium seal.

Pack size: 195 vials

Marketing Authorisation Holder

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Productie 39

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	27034
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	November 20, 2020
Receipt Date	November 20, 2020
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Nabil Al-Humadi, Ph.D., Toxicology reviewer, OVRR/DVRPA; Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Laura Fontan, Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	December 11, 2020
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.3 mL Suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 16 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	chemistry, manufacturing, and controls
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA for a COVID-19 vaccine after determining that certain statutory requirements are met.

On November 20, 2020, the Sponsor (Pfizer, on behalf of Pfizer and BioNTech) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 and in preventing COVID-19 following the first dose, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020, data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ⩾55 years of age (⩽ 2.8%) as compared to younger participants (⩽4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the

vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis will be further evaluated as part of the pharmacovigilance plan for the vaccine.

Non-clinical toxicology studies with BNT162b did not raise specific safety concerns, and other non-clinical studies support the vaccine's immunogenicity, reduction of SARS-CoV-2 pulmonary viral load in animal challenge models, and absence of findings suggesting risk of vaccine-enhanced disease.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on December 10, 2020. Following a discussion of the data presented, the VRBPAC voted 17-4 (with one abstention) in favor of the determination that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 10, 2020, meeting, the review team concludes that:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine (BNT162b) may be effective to prevent such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

- The known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.
- There is no adequate, approved, and available alternative to the product for preventing COVID-19 caused by SARS-CoV-2.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of HHS declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. Available Therapies for COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use

authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.3. EUA Request for the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 μg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A Phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 μg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.4. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least

one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

2.5. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6] These considerations are summarized below.

Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse

events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk review and assessment to support continuation of the EUA.

Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

3. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

3.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

3.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older."

4. FDA Review of Clinical Safety and Effectiveness Data

4.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 µg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

4.2. Study C4591001

4.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a Phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In Phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels

in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from Phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into Phase 2/3.

In Phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion. The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary efficacy endpoints

Study C4591001 has two primary endpoints:

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

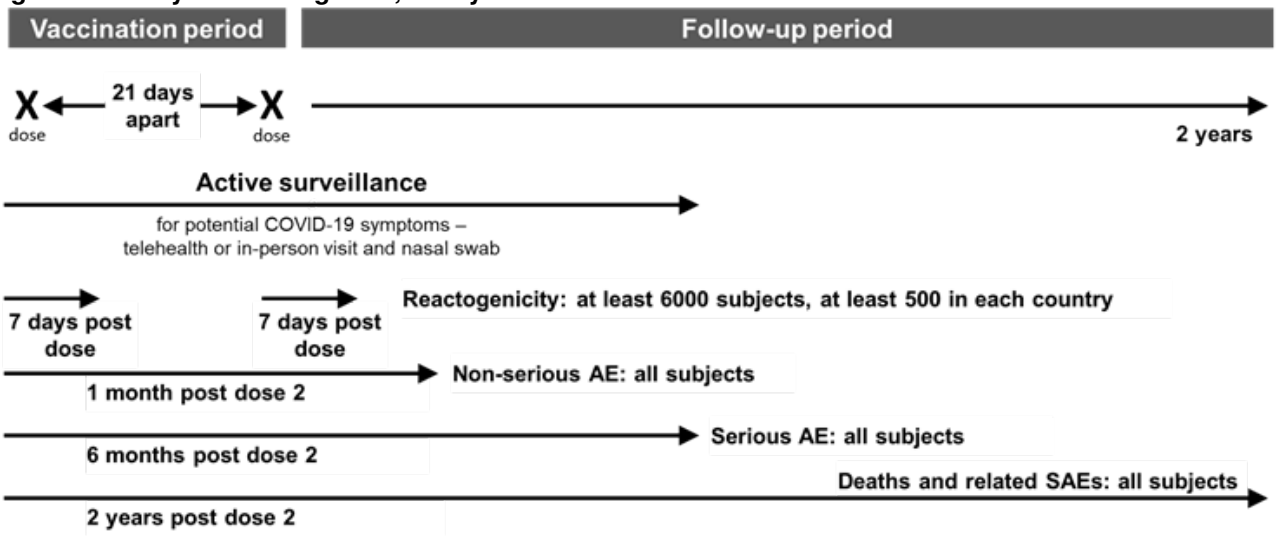
- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All Phase 1 participants (n=30), and then 6653 U.S. participants (360 Phase 2, 6293 Phase 3) and the first ~500 Phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. For all participants, unsolicited adverse events (AEs) were collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. As of the data cutoff date, reactogenicity assessed as solicited reactions and events are available from a limited number of adolescents 16 and 17 years of age, since enrollment for this age group began with implementation of Protocol Amendment 6 (finalized September 8, 2020) and the Phase 2/3 safety population only participants 16 and 17 years of age enrolled by October 9, 2020. Adolescents enrolled after implementation of Protocol Amendment 9 (finalized 29 October 2020) were included in the reactogenicity subset. For any Phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 Phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were

insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in Phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In Phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The

percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the Phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

4.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the Phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the Phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller Phase 2/3 safety population.

4.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (Phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment

groups. Of 43,448 participants in the Phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

Table 2. Efficacy Populations, Treatment Groups as Randomized

Population	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a] n = Number of participants with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
[c] Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Population	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the Phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020, data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the Phase 2/3 safety population analyses.

4.2.4. Demographics and Other Baseline Characteristics

Overall, the Phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The population for the analysis of the primary efficacy endpoint (evaluable efficacy population) included, 36,621 participants 12 years of age and older (18,242 in the Pfizer BioNTech COVID-19 Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. The demographic characteristics among vaccine and placebo participants in the each of the efficacy populations were similar. The demographics of the evaluable efficacy population used for the second primary endpoint is displayed in Table 4.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 N[a]=20033 n[b] (%)	Placebo N[a]=20244 n[b] (%)	Total N[a]=40277 n[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity only (BMI ≥30 kg/m^2).

Overall, the Phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and Phase 2/3 safety population with median 2-month follow-up.

Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or Other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

4.2.5. Vaccine Efficacy

Primary efficacy analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 to 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
>55 years	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7).

The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With and Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup analyses of vaccine efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or Other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f] At risk is defined as having at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity (BMI ≥30 kg/m^2).
[g] Obese is defined as BMI ≥30 kg/m^2.
[h] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 N[a]=8 n[b] (%)	Placebo N[a]=162 n[b] (%)	Total N[a]=170 n[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity only (BMI ≥30 kg/m^2).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection). However, available data are insufficient to determine whether such individuals could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

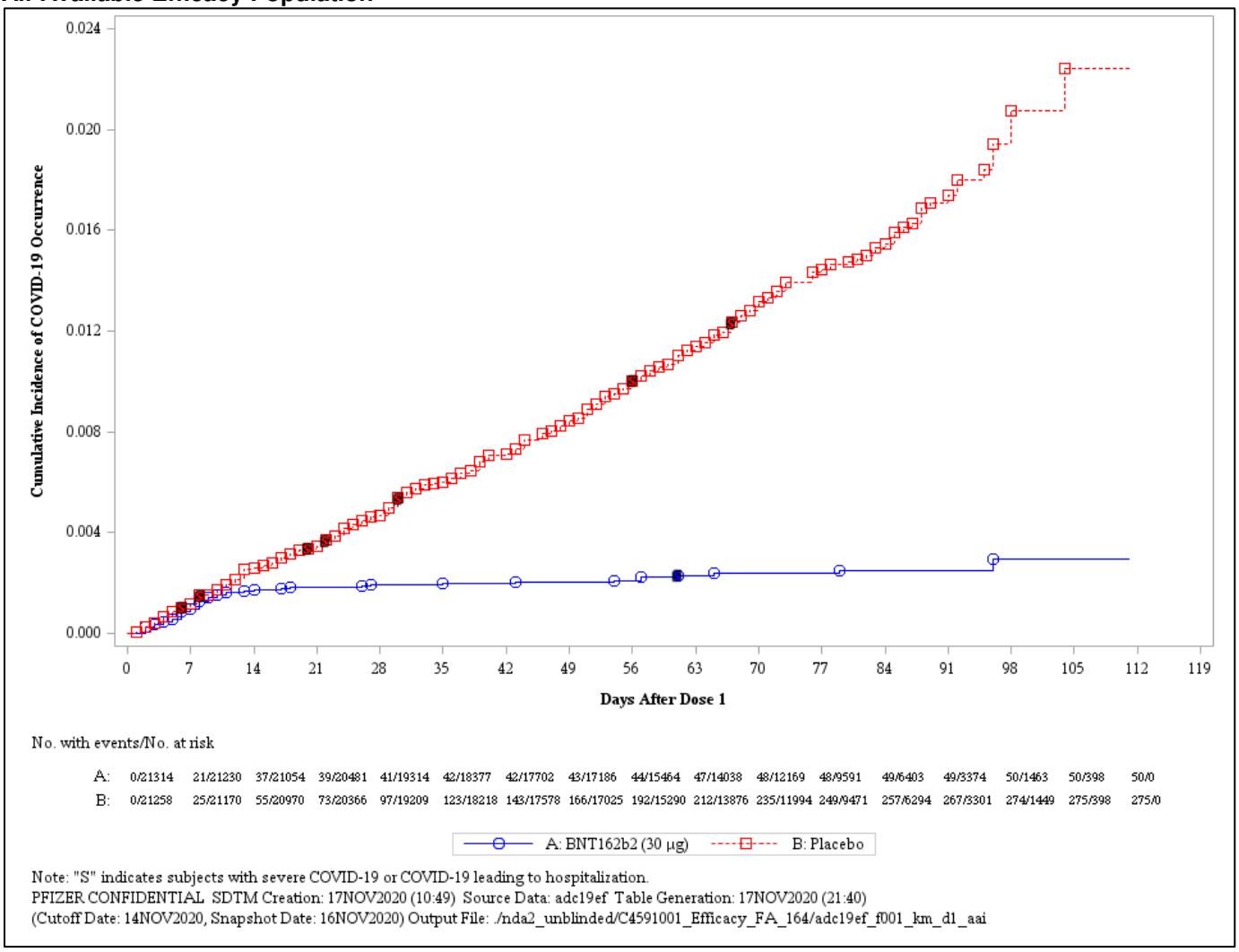
Efficacy Endpoint Subgroup	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or BMI ≥30 kg/m2.

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Secondary efficacy analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2, Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 6 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional efficacy analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint, All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after	50	275	82.0
Dose 1 – Dose 1	4.015 (21314)	3.982 (21258)	(75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 6 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned final primary efficacy analysis, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (⩾93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

4.2.6. Safety

Overview of adverse events

Table 14 below presents an overview of all adverse events in the Phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview, Ages 16 Years and Older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the Phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the Phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited local reactions and systemic adverse events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population, 18 to 55 Years of Age*

Local Reaction	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
*Includes <10 participants 16 and 17 years of age.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population, 18 to 55 Years of Age*

Adverse Event	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Fever				
≥38.0℃	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0℃ to ≤38.4℃	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4℃ to ≤38.9℃	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9℃ to ≤40.0℃	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0℃	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

Adverse Event	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
*Includes <10 participants 16 and 17 years of age.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to ≤38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to ≤38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to ≤40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the Phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020, data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited Local Reactions and Systemic Adverse Events Reported Within 7 Days After Each Dose, Phase 2/3 Safety Population, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 Dose 1 N=53 n (%)	Placebo Dose 1 N=50 n (%)	BNT162b2 Dose 2 N=53 n (%)	Placebo Dose 2 N=50 n (%)
General disorders and administration site conditions	4 (7.5%)	4 (8.0%)	5 (9.4%)	2 (4.0%)
Injection site pain	3 (5.7)	2 (4.0)	3 (5.7)	0 (0.0)
Fatigue	1 (1.9)	1 (2.0)	1 (1.9)	1 (2.0)
Pyrexia	1 (1.9)	0 (0.0)	4 (7.5)	0 (0.0)
Chills	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)
Headache	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 N=4058 n (%)	Placebo N=4043 n (%)	Total N=8101 n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)

System Organ Class Preferred Term	BNT162b2 N=4058 n (%)	Placebo N=4043 n (%)	Total N=8101 n (%)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the Phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

During review of the EUA request, FDA became aware of two cases of anaphylactic reactions in vaccine recipients during the start of the vaccination campaign in the United Kingdom following authorization of the vaccine in that country (approximately 15,000 individuals vaccinated). These reactions were reported to have occurred in the immediate post-vaccination period in individuals with medical history of anaphylactic reactions and required treatment with epinephrine. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. On further review of hypersensitivity-related adverse events in the BNT162b development program, none occurred during the immediate post-vaccination period, none required epinephrine treatment, and none were otherwise classified as serious (i.e., no reported events of anaphylactoid reactions in the clinical trials). Participants in clinical trials were excluded if they had a history of significant allergic reaction to any vaccine or component of BNT162b but were not excluded for history of other significant allergic reactions.

Immediate AEs (Phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%). For both study groups, no participant reported an immediate allergic reaction related to vaccination or to the saline placebo.

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs

in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious adverse events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other participant had pre-existing atherosclerotic disease and baseline obesity and died 3 days after vaccination #1 The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study

intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3,410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1,594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020, (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 6 participants (4 vaccine, 2 placebo), within 30 days after LMP in 10 participants (4 vaccine, 6 placebo), >30 days after LMP in 2 participants (0 vaccine, 2 placebo), and date of LMP not known in 5

participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise unknown at this time.

Clinical laboratory evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 Phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 Phase 1 participants who received the 30-µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 2/3 safety population (N=37,586; 18,801 vaccine,18,785 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations described in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43,448; 21,720 vaccine, 21,728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest 60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine.

4.3. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, Phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was September 17, 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was September 18, 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

5. FDA Review of Other Information Submitted in Support of the EUA

5.1. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

5.2. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include anaphylaxis (including anaphylactic reactions) as an important potential risk and missing information in pediatric

participants less than 16 years of age. Division of Epidemiology recommendations are as follows:

- Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
  - Vaccine administration errors whether or not associated with an adverse event
  - Serious adverse events (irrespective of attribution to vaccination)
  - Cases of Multisystem Inflammatory Syndrome in children and adults
  - Cases of COVID-19 that result in hospitalization or death
- The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
  - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest (AESIs)
  - Newly identified safety concerns in the interval
  - Actions taken since the last report because of adverse experiences (for example, changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)
- Pfizer, Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of AESIs, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general US population (16 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, and subpopulations with specific comorbidities. The study should be conducted in large scale databases with an active comparator. Pfizer, Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates. The Sponsor has proposed the following three planned active surveillance studies:
  - Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry about AESI, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents will receive follow-up surveys for a 30-month period.
  - Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated subjects will be compared to unvaccinated comparators. The study will be conducted for 30 months.
  - Study Protocol Number C4591012. This study is an active surveillance study for AESIs and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated subjects will be compared to unvaccinated subjects or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Mandatory reporting by vaccination providers to VAERS for the following events:
  - Vaccine administration errors whether or not associated with an adverse event
  - Serious adverse events (irrespective of attribution to vaccination)
  - Cases of Multisystem Inflammatory Syndrome in children and adults
  - Cases of COVID-19 that result in hospitalization or death

- Active surveillance of vaccine recipients via the v-safe program. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

5.3. Non-Clinical Studies

Toxicology studies

To support their EUA request, Pfizer submitted the following general toxicology studies:

- Repeat-dose toxicity study of three LNP-formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Wistar Han rats. Study number: 38166. Reviewed under IND 19736 amendments 0 and 32.

- 17-day intramuscular toxicity study of BNT162B2 (V9) and BNT162B3C In Wistar Han rats with a 3-week recovery. Study number: 20GR142. Reviewed under IND 19736 amendment 141.

Based on nonclinical toxicity assessments, there are no significant safety issues to report. The following DART study is still in progress and will be reviewed when submitted: Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat.

Other non-clinical studies

Several nonclinical studies in mice and rhesus macaques were conducted to support the safety and efficacy of BNT162b2. BNT162b2 was highly immunogenic in mice with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4+ response, as well as an IFNγ+, IL-2+, CD8+ T-cell response, after a single immunization. BNT162b2 was also assessed for immunogenicity and for protection against an infectious SARS-CoV-2 challenge in rhesus macaques. Rhesus macaques immunized intramuscularly had readily detectable S1-binding IgG and SARS-CoV-2 neutralizing titers (NT_{50}) as early as 14 days after a single immunization, with substantial increases following the second immunization. Animals were challenged with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-

WA1/2020) and there was a significant decrease in viral RNA detection in bronchoalveolar lavage fluid in the BNT162b2-immunized macaques as compared with the control-immunized rhesus macaques. Further, there was no radiographic evidence of vaccine-elicited enhanced disease in immunized animals. Based on current hypotheses regarding the etiology of vaccine-associated enhanced disease, the provided data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice and rhesus macaques; (2) the Th1 bias in T cell responses; and (3) the lack of disease in vaccinated rhesus macaques challenged with SARS-CoV-2.

5.4. Chemistry, Manufacturing, and Control (CMC) Information

The manufacturing process for the BNT162b2 drug substance (DS) consists of two major steps: (b) (4) . The BNT162b2 drug product (DP) is manufactured by mixing the modRNA DS with lipids during lipid particle (LNP) formulation followed by fill/finish. To support the EUA request, in-process, release, and characterization data for a minimum of three process performance qualification (PPQ) DS batches for each DS manufacturing facility were provided. Certificates of Analysis (CoAs) for a minimum of three GMP commercial-scale DP lots from each DP manufacturing node were requested from the Sponsor to demonstrate DP process performance and consistency. DP data from four manufacturing nodes were available during the EUA review. In addition, to support vaccine supply and availability, data from two additional nodes will be submitted to the EUA between December 17 and December 23, 2020. Once authorized, the Sponsor will submit the CoAs of DP lots to be distributed under EUA for review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent changes during vaccine development. (b) (4) A comprehensive analytical comparability assessment has been performed and the submitted data support the comparability of (b) (4) with (b) (4) for the manufacture of BNT162b2 DS. (b) (4) For DP, the manufacturing process was changed from a Classical process to an Upscale process involving an increase in batch size (capable of accommodating larger RNA input) to meet commercial need. A comparison of available DP batch release data and an in-depth analytical comparability assessment between six representative Classical process DP batches and one Upscale process DP batch support the use of the Upscale process for DP manufacture under emergency use. A more comprehensive comparability assessment encompassing additional lots from multiple DP manufacturing nodes is ongoing and the results will be provided to the EUA upon completion of the study.

Stability studies have been designed to support the use of vaccine under the EUA. All available stability data generated using the BNT162b2 DS and DP lots support the emergency deployment of the Pfizer-BioNTech COVID-19 Vaccine. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of BNT162b2 DS and DP include tests to ensure their identity, purity, quality, and potency. The assays are appropriate and acceptable to be used for the control of DS/DP quality. All analytical procedures used for the release of emergency supply DS and DP have been adequately

qualified. The summaries of the qualification results demonstrate precision, accuracy, sensitivity, specificity, and reproducibility for each evaluated analytical assay, indicating that they are suitable for the intended use.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.
- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also reviewed the inspectional histories of each facility in addition to all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine under an Emergency Use Authorization.

5.5. Clinical Assay Information

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. The Cepheid Xpert Xpress RT-PCR assay is used to assess viral infection of the subjects before vaccination and to confirm COVID-19 cases during study follow-up. The Roche Elecsys Anti-SARS-CoV-2 assay is used to assess serostatus of the subjects before vaccination. Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended use in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

5.6. Inspections of Clinical Study Sites

Bioresearch Monitoring (BIMO) inspections were conducted at six domestic clinical investigator sites participating in the conduct of study protocol C4591001. Based on the preliminary review of the inspection reports, the inspections did not reveal problems impacting the data submitted in support of this EUA.

5.7. EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

6.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

6.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such

as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination. Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection).

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term

effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[12-15] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

6.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) ($\underline{\leq}$2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the Phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically

reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis will be further evaluated as part of the pharmacovigilance plan for the vaccine.

6.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Meeting Summary

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on December 10, 2020, to discuss Pfizer's EUA request. The meeting agenda included: an overview by FDA on EUA and considerations specific to COVID-19 vaccines; updates from

CDC on COVID-19 epidemiology, plans for further evaluation of vaccine safety and effectiveness monitoring during use under an EUA, and operational distribution plans; a presentation on conduct of placebo-controlled studies in the event that a vaccine becomes available under EUA; a public comment period; presentations of data from studies of the Pfizer-BioNTech COVID-19 Vaccine by representatives of Pfizer, an FDA presentation of its independent review of the data submitted in support of the EUA request, and a discussion and vote by the VRBPAC.

The VRBPAC was asked to discuss the following points, with no vote:

- Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.
- Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech Vaccine under an EUA.

The committee discussed potential implications of loss of blinded, placebo-controlled follow-up in ongoing trials including how this may impact availability of safety data to support a biologics license application. Some pointed out the importance of long-term safety data for the Pfizer-BioNTech COVID-19 Vaccine as it is made using a technology not used in previously licensed vaccines. In response to the question whether the ongoing Phase 3 study would still be sufficiently powered if eligible placebo recipients would be vaccinated, Pfizer asserted that even with an anticipated loss of placebo-controlled follow-up of 20%, the study would maintain adequate statistical power and would be positioned to accrue additional data on vaccine efficacy, including efficacy against severe disease, as well as safety, although unblinding of the study would reduce interpretability of results. It was pointed out that non-random loss of placebo recipients from the study, as would be expected when unblinded placebo recipients would receive vaccination based on Advisory Committee on Immunization Practices (ACIP) recommendations, would further reduce interpretability of results. There was also discussion of a blinded trial design proposed by Dean Follman, Ph.D. of NIH in which duration of efficacy would be compared in clinical trial participants originally vaccinated with the vaccine to those later administered the vaccine as part of a planned cross-over. Pfizer stated that this design was considered but would present logistical challenges including the need for reconsenting subjects and additional study visits.

The lack of data on how the vaccine impacts asymptomatic infection and viral shedding was also pointed out and that this should be addressed prior to study unblinding. Other committee members were concerned about limited data available in certain subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2 and certain demographic groups.

The committee inquired about information regarding anaphylactoid reactions occurring in 2 individuals vaccinated with the Pfizer-BioNTech vaccine in the UK. Pfizer briefly summarized the available information, i.e., the two cases of anaphylactoid reactions were in individuals with a strong past history of allergic reactions both of whom carried an epinephrine auto injector. These individuals developed symptoms of anaphylactoid reaction shortly after receiving the vaccine. Both recovered after appropriate treatment. FDA referred to its analysis of safety data derived from the ongoing pivotal trial that excluded subjects with allergic reactions to previous vaccine administrations but did not exclude subjects with non-vaccine related allergies. A slight

numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group compared with the placebo group (137 vs. 111). None of these were considered to be serious, and none of these events occurred in the immediate post-vaccination period. FDA noted that the fact sheet and prescribing information for Pfizer-BioNTech COVID-19 vaccine will include information under the contraindications section that the vaccine should not be administered to individuals with known history of a severe allergic reaction to any component of the vaccine. Under the warning section, there will be a statement that appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Following this discussion, the VRBPAC was asked to vote on whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

In reference to the voting question, and prior to the committee members casting their votes committee members asked FDA's perspective on use of the vaccine in pregnancy. FDA explained that data from the preclinical developmental and reproductive toxicity study for this product are expected soon. Even though there are insufficient data to inform vaccine-associated risks in pregnancy, there are also no data warranting a contraindication. Some committee members expressed concerns about including adolescents 16 and 17 years of age in the indication for the vaccine because of the limited amount of safety and efficacy data available in this population. Other committee members encouraged authorization of the vaccine under EUA in adolescents because this would support initiating pediatric clinical trials and because benefits would be expected to outweigh any theoretical risks in this population. Inclusion of vaccines against COVID-19 in the pediatric vaccination schedule will ultimately likely be needed to increase the uptake of the vaccine and to reach herd immunity. Pfizer is planning studies in pediatric subjects using an age-stratified step-down approach. Some committee members raised concerns about the small number of severe COVID-19 cases and limited conclusions about the prevention of severe disease based on the study endpoints. FDA pointed out that vaccine development has a long history and that FDA is not aware of an example of any vaccine that is effective against mild disease that is not also effective against severe disease and that even though limited, data for Pfizer-BioNTech COVID-19 Vaccine suggest efficacy against severe disease.

The results of the vote were as follows: Yes = 17, No = 4, Abstain = 1. Thus, the committee voted in favor of a determination that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 10, 2020 meeting, the review team concludes that:

- As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2. In the planned final primary efficacy analysis of an ongoing randomized, blinded, placebo-controlled Phase 1/2/3 clinical trial, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the larger group of participants with or without prior infection. Efficacy outcomes were consistently robust (≥93%) across demographic subgroups. Secondary and post-hoc efficacy analyses also suggested efficacy against severe COVID-19, efficacy against COVID-19 in the time period between Dose 1 and Dose 2, and against COVID-19 in subjects with evidence of SARS-CoV-2 vaccination prior to vaccination.

- Based on the data summarized in Sections 4 and 5 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2, reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2, and reduction in the risk of confirmed severe COVID-19 any time after Dose 1. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up (including further evaluation of risk of Bell's palsy and allergic reactions following vaccination), risks associated with vaccination of specific populations such as children younger than 16 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, and available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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10. Appendix A. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, /AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

Productie 40

Medicines &
Healthcare products
Regulatory Agency

Decision

Summary of the Public Assessment Report for COVID-19 Vaccine Pfizer/BioNTech

Updated 22 December 2023

Applies to England, Scotland and Wales

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Summary of the Public Assessment Report

Lay summary, COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection (BNT162b2 RNA)

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This publication is available at https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine

The Public Assessment Report summarises the initial assessment at the time of approval in December 2020. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and the Summary of Coronavirus Yellow Card reporting (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine)

Summary of the Public Assessment Report

Authorisation for Temporary Supply, COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA) concentrate for solution for injection

Department of Health and Social Care (DHSC), Pfizer Limited & BioNTech Manufacturing, GmbH

Lay summary, COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection (BNT162b2 RNA)

This is a summary of the Public Assessment Report (PAR) for COVID-19 mRNA Vaccine BNT162b2. It explains how this product was assessed and authorised under Regulation 174 of the Human Medicine Regulations, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

The product will be referred to as BNT162b2 in this lay summary for ease of reading.

For practical information about using BNT162b2 injections (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine)

patients should read the Information for UK recipients or contact their doctor or healthcare practitioner.

What is BNT162b2 and what is it used for?

BNT162b2 is a vaccine indicated for active immunisation to prevent COVID-19 caused by the SARS-CoV-2 virus, in individuals 12 years of age and older.

How does BNT162b2 work?

When a person is given BNT162b2, it triggers the body to naturally produce antibodies and stimulates immune cells to protect against COVID-19.

How is BNT162b2 used?

The pharmaceutical form of this medicine is an injection. Following dilution with saline, BNT162b2 is given to you by an authorised practitioner as an intramuscular injection into the muscle at the top of the upper arm (deltoid muscle). You should receive two doses (each 0.3mL) given 21 days apart.

Further information for healthcare professionals on how BNT162b2 is used (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and information for UK recipients on how BNT162b2 is used (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine) is available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This vaccine can only be obtained with a prescription.

If a person has any questions concerning the vaccine, they should ask the administering healthcare practitioner.

What benefits of BNT162b2 have been shown in studies?

BNT162b2 has been studied in approximately 43,000 individuals 16 years of age and older who were equally allocated to the vaccine or a placebo. Those who received vaccination with BNT162b2 had a reduction in the rate of COVID-19 illness compared to those who received placebo (8 cases of COVID-19 illness in the vaccinated group compared to 162 cases in the placebo group). These results were observed 7 days following the second dose in study participants with no evidence of prior SARS-CoV-2 infection.

A similar benefit of the vaccine was observed in subjects with one or more other medical conditions that increase the risk of severe COVID-19 disease, such as obesity, hypertension, diabetes, or asthma.

What are the possible side effects of BNT162b2?

The most common side effects with BNT162b2 (which may affect more than 1 in 10 people) were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain and fever. Adverse events were usually mild or moderate in intensity and resolved within a few days after vaccination.

Why was BNT162b2 approved?

It was concluded that BNT162b2 has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects observed with use of this vaccine are considered to be similar to those seen with other vaccines. Therefore, the MHRA concluded that the benefits are greater than the risks and recommended that this medicine can be authorised for temporary supply during the COVID-19 pandemic.

What measures are being taken to ensure the safe and effective use of BNT162b2?

All new medicines approved require a Risk Management Plan (RMP) to ensure they are used as safely as possible. An RMP has been agreed for the use of BNT162b2 in the UK. Based on this plan, safety information has been included in the Information for UK Healthcare Professionals

(https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and the safety information for UK recipients (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine), including the appropriate precautions to be followed by healthcare professionals and patients.

All side effects reported by patients/healthcare professionals are continuously monitored. Any new safety signals identified will be reviewed and, if necessary, appropriate regulatory action will be taken. The MHRA has also put in place an additional proactive safety monitoring plan for all COVID-19 vaccines to enable rapid analysis of safety information which is important during a pandemic.

Other information about BNT162b2

Authorisation for the temporary supply of BNT162b2 was granted in the UK on 1 December 2020.

The full public assessment report for BNT162b2 follows this summary.

This summary was last updated in June 2021.

A marketing authorisation was granted for the Pfizer/BioNTech vaccine (Comirnaty) following a European Commission (EC) decision on 21 December 2020 (PLGB 53632/0002).

1. Introduction

This report is based on the information provided by the company in a rolling data submission procedure and it covers the authorisation for temporary supply of BNT162b2. At the time of writing, the main clinical study is still on-going and additional data is being collected. Due to differences in the collection date, the data and information in this report may differ from that contained in documents relating to BNT162b2 released by other regulatory authorities. Quality aspects of the vaccine are reviewed on a batch-specific basis.

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China and in January 2020, a novel coronavirus was discovered as the underlying

cause. Infections by the virus, named SARS-CoV-2, and the resulting disease, COVID-19, have spread globally. On 11 March 2020, the WHO declared the COVID-19 outbreak to be a pandemic.

At the time of this report, the number of COVID-19 cases in the UK is estimated at 1.64 million and more than 60,000 deaths have been attributed to the disease. These numbers continue to rise. The elderly and those with pre-existing medical conditions are at an increased risk of severe disease and death from COVID-19. Vaccination is the most effective medical intervention to decrease risk and reduce spread of the SARS-CoV-2 virus.

The Department of Health and Social Care (DHSC) is leading the Government's deployment of vaccinations against COVID-19. In order to save lives, and to reduce the number of people who need hospital treatment due to COVID-19, the DHSC have sought to deploy a safe and effective vaccination as soon as possible. In a letter dated November 17th 2020, the DHSC requested authorisation, on a temporary basis, of its proposed supply of a vaccine manufactured by Pfizer/BioNTech collaboration, named "COVID-19 mRNA Vaccine BNT162b2", under Regulation 174 of the Human Medicines Regulations 2012 (https://www.legislation.gov.uk/uksi/2012/1916/contents/made), ("the Regulations").

Following an extensive review of the quality, safety and efficacy data, COVID-19 mRNA Vaccine BNT162b2 has been authorised for temporary supply in the UK for the following indication: active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The active substance of the COVID-19 mRNA Vaccine BNT162b2 is a multi-dose concentrate of RNA-containing lipid nanoparticles formulated in saline and sucrose to be diluted for intramuscular (IM) administration. A single vial contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles).

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free in vitro transcription from the corresponding DNA templates.

COVID-19 mRNA Vaccine BNT162b2 encodes a mutant viral spike (S) protein of SARS-CoV-2, with two point mutations inserted to lock S in an antigenically preferred prefusion conformation (P2 S). It is formulated as an RNA-lipid nanoparticle of nucleosidemodified mRNA containing N1-methylpseudouridine instead of uridine. Encapsulation into lipid nanoparticles enables transfection of the mRNA into host cells after intramuscular injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the lipid nanoparticles are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated into the encoded viral protein. The viral spike (S) protein antigen induces an adaptive immune response through neutralising antibodies. Furthermore, as the expressed spike (S)

protein is being degraded intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific T cell-mediated immune response with activity against the virus and infected cells.

The authorisation is for an identified batch of the vaccine (provided certain conditions are met), together with future batches, which will each be approved by MHRA on a batch-specific basis. [The conditions that covid-19 injections must meet] (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine) are published on the MHRA website.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

This batch, and any future batches, of COVID-19 mRNA Vaccine BNT162b2 are subject to Qualified Person (QP) certification and batch evaluation by an independent control laboratory before the vaccine is released into the UK.

The COVID-19 Vaccine Benefit Risk Expert Working Group (Vaccine BR EWG) have met several times to review and discuss the quality, safety and efficacy aspects in relation to batches of COVID-19 mRNA Vaccine BNT162b2. The manufacturer, Pfizer/BioNTech, was also invited to a separate meeting with the quality subgroup of the Vaccine BR EWG to review and discuss questions related to manufacture and control of the product.

The Vaccine BR EWG gave advice to the Commission of Human Medicines (CHM) on 11th September 2020, 8th October 2020, 27th October 2020, 28th November 2020 and 30th November 2020, regarding the requirements for authorisation for the temporary supply of COVID-19 mRNA Vaccine BNT162b2. The requirements for quality, safety and efficacy were considered, taking into account the urgent public health need and risk to life, the pandemic situation and a lack of COVID-19 vaccines. As well as data on quality, safety and efficacy, specific mitigations and conditions on the product were discussed to ensure adequate standards of quality and safety are met.

The CHM concluded that the proposed supply of COVID-19 mRNA Vaccine BNT162b2 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older, is recommended to be suitable for approval under Regulation 174 provided the company meets the conditions set out by the MHRA.

Authorisation for the temporary supply of COVID-19 mRNA Vaccine BNT162b2 was granted in the UK on 1 December 2020. This report covers data received and reviewed for this authorisation only. This authorisation is valid until expressly withdrawn by MHRA or upon issue of a marketing authorisation.

Whilst an acceptable level of information has been received to provide assurance that appropriate standards of quality, safety and efficacy have been met for authorisation of specific batches for temporary supply under Regulation 174 of the Regulations, it should be noted that COVID-19 mRNA Vaccine BNT162b2 remains under review as MHRA continues to receive data from the company as it becomes available. This will include, for example, long-term follow-up efficacy and safety data. Further information that is received by the MHRA will be reviewed as part of the ongoing assessment for this product and updates will be made to this PAR to reflect that in due course.

On 4 June 2021 the MHRA granted an extension of indication to 'the active immunisation to prevent COVID-19 caused by the SARS-CoV-2 virus, in individuals 12 years of age and older'.

2. Quality aspects

2.1 Introduction

This product is a white to off-white solution provided in a multidose vial and must be diluted before use. One vial contains 5 doses of 30 micrograms of BNT162b2 RNA embedded in lipid nanoparticles (LNPs). COVID-19 mRNA Vaccine BNT162b2 is provided in a pack size of 195 vials.

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) in lipid nanoparticles (LNPs). The mRNA is produced by cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

In addition to BNT162b2 RNA this product also contains the excipients ALC-0315 = (4- hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3 phosphocholine, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water for injections.

The finished product is packaged in a 2 mL clear vial (type I glass) with a stopper (coated bromobutyl) and a plastic flip-off cap with aluminium seal. Container closure components comply with the relevant regulatory requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current Ph. Eur. quality standards

2.2 Active substance

Drug Substance (BNT162b2 RNA)

BNT162b2 drug substance is a single-stranded, 5'-capped mRNA encoding the full-length viral S (S1S2) protein of SARS-CoV-2. The optimised codon sequence encoding the spike glycoprotein antigen of the SARS-CoV-2 virus results in a protein expressed with two proline mutations that fix the S1S2 spike protein in a pre-fusion conformation to increase potential to elicit virus neutralising antibodies. In addition, the RNA contains common structural elements optimised for mediating high RNA stability and translational efficiency (5'-cap, 5'-UTR, 3'-UTR, poly(A) – tail). Uridine is replaced by modified N1- methylpseudouridine (m1ΨTP) in the RNA synthesis which increases RNA persistence invivo through dampening of innate immune response to itself. The 5 prime end is capped with a structure which will not activate the innate immune system.

Chemical Name: messenger RNA (mRNA), 5'-capped, encoding a full-length, codonoptimised pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, GenBank: MN908947.3) spike (S) glycoprotein, flanked by 5' and 3' untranslated regions and a 3' poly(A) tail; contains N1-methylpseudouridine instead of uridine (all-U>m1 Ψ). Immunological agent for active immunisation (anti-SARS-CoV-2)

Appearance: Clear to slightly opalescent, colourless to slightly brown liquid

BNT162b2 RNA is not the subject of a European Pharmacopoeia monograph (Ph. Eur.) or other pharmacopoeial monograph.

Overall, production of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and adequate starting material specifications are applied.

The starting materials are adenosine triphosphate, cytidine triphosphate, guanosine triphosphate, modified uridine triphosphate, 5' Cap and the DNA template from which the RNA is transcribed.

The DNA template from which the RNA is transcribed is critical for the fidelity of the mRNA. The manufacture of the DNA template has been described. It is manufactured through fermentation in an established and well-controlled Escherichia coli cell line, extracted and purified. The specifications controlling the quality of the DNA template are satisfactory. Batch data for the DNA template have been supplied for several batches for which an acceptable level of batch to batch consistency is observed. The genealogy of the finished product can be traced back to the batch of originating DNA template.

The in vitro enzymatic RNA transcription process has been adequately described. The 5'cap and poly(A) tail are co-transcribed with the S1S2 spike protein codon. It is noted that the operating parameters for this process span a wide range however this does not raise any immediate concerns for the batch under review.

Full scale validation data for RNA transcription demonstrates consistency and repeatability of the process operation and is accepted as qualifying the process operated at its target set points.

The manufacturer has performed a comparability assessment of drug substance batches used in the clinical trial programme and batches representative of the subsequent manufacturing changes occurring during product development, such as introduction of new manufacturing sites, manufacturing process changes and increase in batch scale, including full scale validation batches. The drug substance batch release data for essential parameters that control the quality of the active RNA and several extended characterisation test parameters were considered. These data demonstrate consistency between the drug substance described for this application and those used in the pivotal clinical study.

Analytical procedure methods have been described and are considered appropriately qualified to control this batch in the context of a batch specific approval.

The shelf-life for BNT162b2 RNA (drug substance) has been provided and is satisfactory in relation to the cadence of drug substance to drug product manufacture.

2.3 Drug product

The data submitted to describe the drug product have been evaluated.

Pharmaceutical development

The manufacturer has described the finished product development strategy. This utilised principles described in ICH Q8 Pharmaceutical Development and was based on the available scientific knowledge and the manufacturer's prior experience with similar RNA-lipid nanoparticle vaccines, as well as risk assessments and development studies.

The characteristics of the drug product were provided, as well as formulation development and process characterisation studies. The development history, including process changes have been summarised. The manufacturer has described their approach to defining critical quality attributes and the rationale for their criticality decisions, as well as their process risk assessment strategy and methodology, which was accompanied by a description of the manufacturer's product development and characterisation strategy. Operating ranges have been defined and the manufacturer is working on the validation of the final commercial process, which follows process optimisation.

A quality target product profile for the finished product has been established taking into consideration the World Health Organization's Target Product Profiles for COVID19 Vaccines (https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines).

Development studies have been submitted which support the compatibility of the vaccine with the container closure and the unpreserved sodium chloride 0.9% diluent as well as commonly used needles and syringes.

The manufacturer has performed a comparability assessment of batches used in the clinical trial programme and batches representative of manufacturing changes occurring during product development, such as introduction of new manufacturing sites, process changes and increase in batch scale. In addition to release testing, the manufacturer also investigated several extended characterisation test parameters. These data will be supplemented as further experience with the manufacturing process accumulates. The recommendation for the batch which is the subject of this assessment was based on a direct comparison of the batch release results with the results for the clinically qualified batches.

Manufacture of the product

A description of the manufacturing method for COVID-19 mRNA Vaccine BNT162b2 has been provided and consists of: thawing and dilution of the drug substance, lipid nanoparticle formation upon mixing organic and aqueous phases (where specialised equipment is used for LNP formation), buffer exchange, concentration, filtration, formulation, sterile filtration, aseptic filling, visual inspection, labelling and freezing, and storage packaging and shipment.

In-process monitoring and control are performed. In-process controls and process parameters for each manufacturing step are provided and criticality has been

assigned. Further in-process details are expected from the manufacturer however the information provided to date are acceptable.

As part of the control of the product, once vials are manufactured, they undergo 100% visual inspection for defects.

A condition of authorisation under this regulation is that the manufacturer will provide further data on the drug product manufacturing process as it is scaled up.

Excipients

The excipients sucrose, sodium chloride, potassium chloride, dibasic sodium phosphate dihydrate, monobasic potassium phosphate and water for injection are all of Ph. Eur. grades, which are acceptable.

In addition to those excipients, the vaccine contains four lipids, of which two are used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine, hereafter termed DSPC) and two are considered novel in that they have not been used in an authorised medicinal product in the UK:

- ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate))
- ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

The lipids are intended to encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles.

ALC-0315 is the functional cationic lipid component of the drug product. When incorporated in lipid nanoparticles, it helps regulate the endosomal release of the RNA. During drug product manufacturing, introduction of an aqueous RNA solution to an ethanolic lipid mixture containing ALC-0315 at a specific pH leads to an electrostatic interaction between the negatively charged RNA backbone and the positively charged cationic lipid. This electrostatic interaction leads to encapsulation of RNA drug substance resulting with particle formation. Once the lipid nanoparticle is taken up by the cell, the low pH of the endosome renders the LNP fusogenic and allows the release of the RNA into the cytosol.

The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the LNP which contributes to storage stability and reduces nonspecific binding to proteins. As higher PEG content can reduce cellular uptake and interaction with the endosomal membrane, PEG content is controlled.

Cholesterol is included in the formulation to support bilayer structures in the lipid nanoparticle and to provide mobility of the lipid components within the lipid

nanoparticle structure. The specification for the conventional lipid, cholesterol, is considered acceptable for the purpose of this application.

DSPC is a phospholipid component intended to provide a stable bilayer-forming structure to balance the non-bilayer propensity of the cationic lipid. DSPC is a non-pharmacopeial excipient and an adequate specification has been provided.

The controls in place for the excipients are considered suitable for this application.

Excipients of human and animal origin

No excipients of animal or human origin are used in the finished product.

Novel excipients

ALC-0315 is a cationic lipid and is critical to the self-assembly process of the particle itself, the ability of the particle to be taken up into cells and the escape of the RNA from the endosome. ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid).

Finished product control

The product specification includes relevant control parameters considering the nature of the product and its manufacturing process.

Batch release data for this batch have been evaluated comparing the results with the clinically qualified ranges from batches used in the clinical trial programme.

Independent batch testing

Independent batch testing is required for vaccines and provides additional assurance of quality before a batch is made available to the market. Independent batch testing is a function that is undertaken by an Official Medicines Control Laboratory (OMCL) and, under Regulation 174A, the UK's National Institute for Biological Standards and Control (NIBSC) is responsible for this function. Each batch will be independently tested prior to deployment.

Independent batch testing is product-specific and highly technical: it requires specific materials and documentation from the manufacturer and comprises laboratory-based testing and review of the manufacturer's test data. If all tests meet the product specifications a certificate of compliance is issued by the OMCL.

Characterisation of impurities

The impurity profile of the BNT162b2 drug product is based primarily on the impurity profile of the materials used for its manufacture.

The manufacturer has described four identified drug product manufacturing process-related impurities. A safety risk assessment for each of these four potential impurities has been performed and they are below the safety threshold given the intended product administration schedule.

Process-impurities from the sucrose, phosphate and chloride salts used in the final drug product formulation are controlled through testing and specifications ensuring compliance to relevant compendial monographs. This is acceptable.

The lipid impurities are controlled through the acceptance criteria used for their manufacture.

No critical issues have been identified with respect to the lipids that would preclude the emergency use of the vaccine.

Reference standards or materials

The manufacturer has defined reference materials that are used in the determination of drug product content and in the determination of lipid content for the four lipids used for nanoparticle formation. These methods are considered conventional and uncomplicated to perform.

Container closure system

Overall, the container closure system has been well described and complies with the relevant quality standards of the Ph.Eur. The vaccine requires storage at ultra-low temperature conditions and the rubber septum is punctured at least 6 times to reconstitute the product and recover 5 doses from the vial. The manufacturer has provided details of adequate testing to provide evidence that the self-sealing capacity of the elastomeric closure is retained upon freezing and repeated thawing of product, even though the storage requirements do not permit this. The testing also accounted for the recommended needles for diluent addition.

Stability

The manufacturer has provided all stability data available to date. Information on the stability of batches used in clinical trials has been used to support conclusions on product storage and storage conditions.

Based on the stability information currently available, a shelf-life of 6 months at -80°C to -60°C can be accepted for this vaccine, with the following storage conditions:

- Store in a freezer at -80°C to -60°C
- Store in the thermal container at -90ºC to -60ºC

Store in the original package in order to protect from light.

After removal from frozen storage, the undiluted vaccine can be stored for up to 5 days (120 hours) at 2°C to 8°C and up to 2 hours at temperatures up to 25°C, prior to use. Once thawed, the vaccine cannot be re-frozen.

During storage, it is recommended that exposure to room light is minimised, and exposure to direct sunlight and ultraviolet light avoided. Thawed vials can be handled in room light conditions.

After dilution with unpreserved normal saline, the vaccine should be stored at 2°C to 25°C and used as soon as practically possible. Since the vaccine does not contain a preservative, once the stopper has first been punctured on addition of the diluent, the vial should be used within 6 hours as is recommended by WHO guidance. After 6 hours, any unused vaccine left in the vial should be discarded.

Deployment of this vaccine is subject to the conditions of this Regulation 174 approval.

Suitable post approval stability commitments have been provided to continue stability testing on batches of COVID-19 mRNA Vaccine BNT162b2, including for the batch concerning this Regulation 174 application. The manufacturer has committed to provide these data to the MHRA on an on-going basis as it becomes available.

Handling of Pfizer Vaccine BNT162b2

Lipid nanoparticles (LNPs) are complex particles made of four lipid components that entrap the mRNA. Because of this complexity LNPs are potentially fragile to degradation and damage through inappropriate handling.

The published storage conditions are qualified by the data reviewed by the MHRA.

- Long term storage: It must be stored frozen at ultra-low temperature (ULT).

After removal from frozen storage, it has a shelf life of up to 120 hours at 2-8 ºC before being diluted (label to be added once box removed from freezer).

In addition to the 120-hour period at 2-8 ºC, an undiluted vial can be stored for 2 hours at up to 25 ºC. This is intended to qualify removing the vial from the fridge for up to two hours immediately before it is diluted in preparation for use. It is not intended to qualify ad hoc removal from fridge within the 120-hour period with a view to then replacing back into stock were it not to be used.

Once thawed, the vaccine cannot be refrozen.

Before dilution the vial must be inverted gently 10 times without shaking (to avoid foaming). Once the specified diluent is added, the vial must be inverted gently 10 times without shaking (to avoid foaming).

Once diluted, the vials should be marked with the dilution date and time.

Transportation by motor vehicle of diluted vaccine away from the site of dilution is not currently supported by any relevant stability data.

After dilution the vaccine should be used as soon as is practically possible and within 6 hours of dilution; it can be stored at 2-25 ºC during this period. It would not normally be considered good practice to store diluted product for 6 hours at 25ºC before being administered.

Similarly, there are no data supporting multiple temperature cycling within that 6 hours that would qualify the product being repeatedly removed and replaced into a fridge, as doses are administered over the course of 6 hours.

Following dilution, vials should be used in the shortest time period possible.

2.4 Regulation 174

Authorisation for temporary supply of COVID-19 mRNA Vaccine BNT162b2 under this Regulation 174 has been given following review of batch analytical data by MHRA.

Independent batch release by the National Institute for Biological Standards and Control (NIBSC) will be performed on all batches to be supplied to the UK.

The quality data currently available for COVID-19 mRNA Vaccine BNT162b2 can be accepted as sufficient with specific conditions in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174 of the Human Medicine Regulations.

3. Non-clinical aspects

3.1 Introduction

COVID-19 mRNA Vaccine BNT162b2 has been developed for use in healthy subjects to prevent COVID-19 on exposure to SARS-CoV-2. The vaccine has as its active agent messenger ribonucleic acid (mRNA), made by transcription of a DNA template, encoding for the full-length spike (S) protein of SARS CoV-2 with two point mutations, to lock S in an antigenically preferred prefusion conformation.

COVID-19 mRNA Vaccine BNT162b2 is given as two intramuscular injections (IM), 21 days apart, of the same dose of 30 µg mRNA.

COVID-19 mRNA Vaccine BNT162b2 is made up of the mRNA component with 4 lipid components forming nanoparticles, of which two are novel and not used before in pharmaceutical products in the UK. The lipids function to encapsulate, stabilise the mRNA and mediate its delivery to cells.

The following non-clinical studies were submitted with this application:

Pharmacology

- Study 20-0211: In vitro expression of BNT162b2 drug substance and drug product
- Study R-20-0085: COVID-19: Immunogenicity of BNT162b2 in mice
- Study R-20-0112: Characterizing the immunophenotype in spleen and lymph node of mice treated with SARS-CoV-2 vaccine candidates
- Study VR-VTR-10671: BNT162b2 immunogenicity and evaluation of protection against SARS-CoV-2 challenge in rhesus macaques

Pharmacokinetics

- Study PF-07302048: Single dose pharmacokinetics study of ALC-0315 and ALC-0159 following intravenous bolus injection of a nanoparticle formulation in rats
- Study R-20-0072: Biodistribution of BNT162b2 using the luciferase protein as a surrogate marker protein after intramuscular injection in mice. Toxicology
- Study 38166: Repeat-dose toxicity study of three LNP-formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Wistar Han rats
- Study 20GR142: 17-day Intramuscular Toxicity Study of BNT162b2 and BNT162b3 in Wistar Han Rats

These studies were conducted in accordance with current Good Laboratory Practice (GLP).

3.2 Pharmacology

This vaccine acts by intracellular translation of mRNA to the SARS-CoV-2 S protein to induce an immune response, a humoral neutralizing antibody response and Th1-type CD4+ and CD8+ cellular response, to block virus infection and kill virus infected cells, respectively.

The vaccine was tested for its ability to result in S protein expression in a mammalian cell population in vitro, for its immunogenicity in mice in two studies, and in one study in rhesus monkeys, including its capacity to prevent disease after challenge with SARS Cov-2 virus in rhesus monkeys. The vaccine also induced an immune response in rats in the two toxicity studies.

Study 20-0211 analysed SARS-CoV-2 P2 S expression in HEK293T cells. The initial demonstration of in vitro expression in HEK293 cells confirmed that transfection and subsequent protein expression could take place, including in cells incubated with the nanoparticle presentation of the vaccine.

In Study R-20-085, four groups of eight female mice were immunised once by the IM route on day 0 with 0.2 µg, 1 µg or 5 µg RNA/animal of COVID-19 mRNA Vaccine BNT162b2, or with a control. Antibody response was assessed at days 7, 14, 21 and 28.

Study R-20-0112 aimed to characterise T- and B-cell responses in the spleen, lymph nodes and blood of BNT162b2 immunised mice. It characterised changes in the myeloid cell compartment, determined the ability of CD8+ T-cells to react to cells presenting the vaccineencoded antigen, and determined antibody responses.

In Studies R-20-085 and R-20-0112 in mice, a dose-response effect was seen in the IgG responses specific for the SARS CoV-2 S1 protein fragment and its receptor binding domain.

A high and dose-dependent pseudovirus neutralising antibody response was confirmed. CD4+ and CD8+ T cell cellular responses with a Th1 pattern of response (e.g. production of IFN-γ) were observed. Booster responses were not evaluated in these studies.

Study VR-VTR-10671 was performed in male rhesus macaques aged 2-4 years vaccinated with 30 µg COVID-19 mRNA Vaccine BNT162b2, 100 µg COVID-19 mRNA Vaccine BNT162b2 or a control.

Results showed COVID-19 mRNA vaccine BNT162b2 was immunogenic, eliciting IgG responses after a single dose, which were boosted by a second dose. It also showed a dose response. At 30 µg BNT162, the neutralising geometric mean titre in a SARS-CoV-2 neutralization assay was compared to that seen in convalescent serum (HCS) from humans recovered from SARS CoV-2 infection/COVID-19 and

found to be ~8-times higher. Seven days after Dose 2 of 100 µg, the neutralising GMT reached 18-times that of the HCS panel and remained 3.3-times higher than this benchmark five weeks after the last immunisation. In monkeys, the cellular immune response was characterised as a strongly Th1-biased CD4+ T cell response with a concurrent interferon-γ (IFNγ)+ CD8+ T cell response.

For the challenge portion of the study, SARS-CoV-2 challenge was performed on the COVID-19 mRNA Vaccine BNT162b2-immunised animals (100 µg/animal dose level) and on animals dosed with a control. Upon challenge with SARS CoV-2, the resulting clinical pattern in monkeys was unremarkable and no signs of clinical illness resulted from this exposure. Total viral RNA (genomic and subgenomic RNA) was detected in bronchoalveolar lavage fluid of control monkeys but not detected in monkeys immunised with BNT162b2; in the nasal swabs viral RNA was detected in monkeys given BNT162 but clearance was faster than in controls. This is evidence of the beneficial effect of this vaccine. In lung tissues, control monkeys had evidence of some pulmonary disease indicated by their increased scores on computed tomography scans with a suggestion of recovery in those scores at day 10 that were less than those at day 3; in contrast, the monkeys given COVID-19 mRNA Vaccine BNT162b2 had lower scores than controls.

The absence of secondary pharmacology and safety pharmacology studies is acceptable for a vaccine and is in line with relevant regulatory guidance (WHO Guidelines on nonclinical evaluation of vaccines, 2005). The guidance does not mention secondary pharmacodynamics: however, it does state that if data from other studies suggest that the vaccine may affect physiological functions (central nervous system, renal, respiratory or cardiovascular system functions), safety pharmacology studies should be incorporated into the toxicity assessment. This does not apply for COVID-19 mRNA Vaccine BNT162b2.

There are no major public health concerns identified. Since this authorisation the manufacturer has provided further information on the methodology used to determine antispike protein antibodies in mice which has been reviewed as part of the ongoing assessment for this product. These data are not discussed here.

3.3 Pharmacokinetics

The active substance of COVID-19 mRNA Vaccine BNT162b2 is N1-methylpseudouridine instead of uridine containing mRNA expressing full-length SARS-CoV-2 spike protein with two proline mutations (P2 S) to lock the transmembrane protein in an antigenically optimal prefusion conformation. The vaccine is formulated in lipid nanoparticles (LNPs). The LNP is composed of 4

lipids: ALC-0315, ALC-0159, 1,2-distearoyl-sn-glycero-3-phosphocoline (DSPC), and cholesterol. Of the four lipids used as excipients in the LNP formulation, two are naturally occurring (cholesterol and DSPC) and will be metabolised and excreted like their endogenous counterparts.

Pharmacokinetic studies have not been conducted with COVID-19 mRNA Vaccine BNT162b2 and are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005; WHO, 2014).

The ADME profile of COVID-19 mRNA Vaccine BNT162b2 included evaluation of the PK and metabolism of the two novel lipid excipients (ALC-0315 and ALC-0159) in the LNP and potential in vivo biodistribution using luciferase expression as a surrogate reporter.

Absorption

No absorption studies were conducted for COVID-19 mRNA Vaccine BNT162b2 since the route of administration is intramuscular (IM).

The “Single dose pharmacokinetics study of ALC-0315 and ALC-0159 following intravenous bolus injection of a nanoparticle formulation in rats” was conducted to assess the PK and metabolism of the two novel lipid excipients (ALC-0315 and ALC-0159). This study used LNPs containing surrogate luciferase RNA, with the lipid composition being identical to BNT162b2, to investigate the in vivo disposition of ALC-0159 and ALC-0315.

Concentrations of ALC-0159 dropped approximately 8000- and >250-fold in plasma and liver, respectively, during this 2-week study. For ALC-0315, the elimination of the molecule from plasma and liver was slower, but concentrations fell approximately 7000- and 4-fold in two weeks for plasma and liver, respectively. Overall, the apparent terminal t½ in plasma and liver were similar in both tissues and were 2-3 and 6-8 days for ALC-0159 and ALC0315, respectively. The apparent terminal t½ in plasma likely represents the re-distribution of the respective lipids from the tissues into which they have distributed as the LNP, back to plasma where they are eliminated.

Distribution

Study R-20-0072 evaluated the in vivo potential biodistribution of COVID-19 mRNA Vaccine BNT162b2 in mice using luciferase expression as a surrogate reporter. Protein expression was demonstrated at the site of injection and to a lesser extent, and more transiently, in the liver after mice received an IM injection of RNA encoding luciferase in an LNP formulation like BNT162b2. Luciferase expression was identified at the injection site at 6 hours after injection and diminished to near baseline levels by day 9. Expression in the liver was also

present at 6 hours after injection and was not detected by 48 hours after injection. Information regarding the potential distribution of the test articles to sites other than the injection site following IM administration has been provided and is under review as part of the ongoing rolling assessment.

Metabolism

The in vitro metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The in vivo metabolism was examined in rat plasma, urine, faeces, and liver samples from the PK study. Metabolism of ALC-0315 and ALC-0159 appears to occur slowly in vitro and in vivo. ALC-0315 and ALC-0159 are metabolised by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

Excretion

No excretion studies have been conducted with COVID-19 mRNA Vaccine BNT162b2. In the PK study, it appears that 50% of ALC-0159 was eliminated unchanged in faeces. Metabolism played a role in the elimination of ALC-0315, as little to no unchanged material was detected in either urine or faeces. Investigations of urine, faeces and plasma from the rat PK study identified a series of ester cleavage products of ALC-0315. The manufacturer has proposed that this likely represents the primary clearance mechanism acting on this molecule, although no quantitative data is available to confirm this hypothesis. In vitro, ALC-0159 was metabolised slowly by hydrolytic metabolism of the amide functionality.

Pharmacokinetic drug interactions

No PK drug interaction studies have been conducted with COVID-19 mRNA Vaccine BNT162b2. This is acceptable and in line with relevant guidelines (WHO 2005; WHO 2014).

3.4 Toxicology

Single dose toxicity

No single dose toxicity studies have been performed. This is acceptable and in line with relevant guidelines (WHO 2005; WHO 2014).

Repeat-dose toxicity

Study 38166 was a GLP-compliant repeat-dose study performed in rats to evaluate toxicity of the LNP and mRNA platform used in BNT162b2.

Study 20GR142 was a GLP-compliant repeat-dose study performed in rats to evaluate toxicity of COVID-19 mRNA Vaccine BNT162b2.

In Study 38166, male and female Wistar rats were given BNT162b2 as IM injection(s) into the hind limb on three occasions each a week apart (dosing days 1, 8 and 15). Different doses (10, 30, and 100 µg) were tested; the lower doses were given as a single injection of 20-70 µL, while the highest dose (100 µg) and controls were given as two injections (one in each hindlimb) of 100 µL each. The control was phosphate buffered saline/300 mM sucrose, corresponding to the storage buffer of the vaccine product. Each group had 18 male and 18 female rats, assigned as 10 to the main study, 5 for recovery groups and 3 as additional animals for cytokine analyses. The recovery period was 3 weeks after the last dose. Necropsy was performed on study day 17, ~48 hours after the last dose, and after the 3-week recovery period.

No unscheduled deaths were observed.

Dosing was considered well tolerated and did not present any signs of systemic toxicity; there was a slight increase in body temperature in the hours after dosing and some loss in body weight over the same period but these were not of a magnitude to be considered adverse.

Local inflammatory reactions were observed at the intramuscular injection site. Injection site changes noted were of oedema, erythema, and induration, more severe and more frequent after the second and/or third doses compared to the first; however, these resolved prior to subsequent dosing and were fully recovered at the end of the 3-week recovery period.

Macroscopic findings at the injection sites included induration or thickening, occasionally accompanied by encrustation, which was noted for nearly all rats. This correlated microscopically with inflammation and variable fibrosis, oedema, and myofibre degeneration. Inflammation at the injection site was accompanied by elevations in circulating white blood cells and acute phase proteins (fibrinogen, alpha-2 macroglobulin, and alpha-1 acid glycoprotein).

Inflammation was occasionally evident extending into tissues adjacent to the injection site. There was enlargement of the draining (iliac) lymph nodes evident at the end of dosing. This correlated with increased cellularity of germinal centres and increased plasma cells in the draining (iliac) lymph node and is an anticipated immune response to the administered vaccine.

Enlargement of spleen and increased spleen weights correlated microscopically to increased haematopoiesis and increased haematopoiesis was also evident in the

bone marrow. These findings are likely secondary to the immune/inflammatory responses to the vaccine.

At the end of the recovery period, injection sites were normal, clinical pathology findings and macroscopic observations had resolved and there was evidence of recovery of the injection site inflammation on microscopy.

Microscopic vacuolation of portal hepatocytes was present. There were no elevations in alanine aminotransferase (ALAT). There were elevations in gamma-glutamyltransferase (GGT) in all vaccinated rats, but there were no macroscopic or microscopic findings consistent with cholestasis or hepatobiliary injury to explain the increased GGT activity, which was completely resolved at the end of the 3-week recovery period.

The vacuolation may be related to hepatic distribution of the pegylated lipid in the LNP. No changes were seen in serum cytokine concentrations. Additional ADME data has been received since this authorisation and has been reviewed as part of the ongoing assessment for this product. This data is not discussed here.

There were no effects noted on ophthalmological and auditory assessments, nor on external appearance or behaviour; in particular, gait was normal meaning that the changes seen did not affect the rats' mobility. No vaccine-related changes were seen in serum cytokine concentrations.

Testing for immunogenicity showed that COVID-19 mRNA Vaccine BNT162b2 elicited a specific IgG antibody response to SARS CoV-2 spike protein directed against the S1 fragment and the receptor binding domain. A neutralizing antibody response was also observed with the vaccine in a pseudovirus neutralization assay.

In conclusion, COVID-19 mRNA Vaccine BNT162b2 was well tolerated, and produced inflammatory changes at the injection sites and the draining lymph nodes, increased haematopoiesis in the bone marrow and spleen, and clinical pathology changes consistent with an immune response or inflammation in the injection sites. The findings in this study are typical of those expected with dosing of LNP encapsulated mRNA vaccines.

Study 20GR142 had the objective to determine toxicity in rats given COVID-19 mRNA Vaccine BNT162b2. This study was in compliance with Good Laboratory Practice. Two candidate vaccines were tested; however, results are presented here only for COVID-19 mRNA Vaccine BNT162b2.

Male and female Wistar Han rats were given BNT162b2 as an IM injection into the hind limb on three occasions, each a week apart (dosing days 1, 8 and 15). Necropsy was performed on study day 17, ~48 hours after the last dose, and after the 3-week recovery period. COVID-19 mRNA Vaccine BNT162b2 was supplied at

0.5 mg/ml, and the dose volume was 60 µL, to give 30 µg per dose. Control rats received saline. Each group contained 15 males and 15 females.

All rats given COVID-19 mRNA Vaccine BNT162b2 survived to their scheduled necropsy: there were no changes noted in clinical signs or body weight changes noted. A reduction in food intake was noted on days 4 and 11 (to 0.83x controls) and there was an increase in mean body temperature post-dose on day 1 (up to 0.54°C), day 8 (up to 0.98°C) and day 15 (up to 1.03°C) compared to controls.

At injection sites, there were instances of oedema and erythema on days 1 (maximum of slight oedema and very slight erythema), 8 (maximum of moderate oedema and very slight erythema) and 15 (maximum of moderate oedema and very slight erythema) which fully resolved and were not noted prior to dosing on days 8 and 15.

Haematological tests showed higher white blood cells (up to 2.95x controls), primarily involving neutrophils (up to 6.80x controls), monocytes (up to 3.30x controls), and large unstained cells, LUC, (up to 13.2x controls) and slightly higher eosinophils and basophils on days 4 and 17. White blood cells were higher on day 17 as compared with day 4. There were transiently lower reticulocytes on day 4 (to 0.27x controls) in both sexes and higher reticulocytes on day 17 (up to 1.31x controls) in females only. Lower red blood cell mass parameters (to 0.90x controls) were present on days 4 and 17. There were lower A:G ratios (to 0.82x) on days 4 and 17. Higher fibrinogen was noted on day 17 (up to 2.49x) compared to controls, consistent with an acute phase response. The acute phase proteins alpha-1-acid glycoprotein (up to 39x on day 17) and alpha-2 macroglobulin (up to 71x on Day 17) were elevated on days 4 and 17 with higher concentrations in males. There were no changes urinalysis parameters.

At post-mortem there were higher absolute and relative spleen weights in vaccinated rats (up to 1.42x in males and to 1.62x in females). There were no other changes in organ weights. Macroscopic findings included enlarged draining lymph nodes and pale/dark firm injection sites in a minority of vaccinated rats. The dosing is reported as tolerated without inducing any systemic toxicity and with all changes consistent with an inflammatory response and immune activation: findings are consistent with those typically associated with dosing of lipid nanoparticle-encapsulated mRNA vaccines. Since this authorisation the manufacturer has provided the final study report which has been reviewed as part of the ongoing assessment for this product and is not discussed here.

Toxicokinetics

No toxicokinetic studies have been performed with the vaccine. This is consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005).

Genotoxicity

No genotoxicity studies are planned for BNT162b2, as the components of all vaccine constructs are lipids and RNA that are not expected to have genotoxic potential (WHO, 2005).

Carcinogenicity

Carcinogenicity studies with BNT162b2 have not been conducted as the components of all vaccine constructs are lipids and RNA that are not expected to have carcinogenic or tumorigenic potential. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005).

Reproductive and developmental toxicity
Fertility and early embryonic development and embryofoetal development

In the general toxicity studies, macroscopic and microscopic evaluation of male and female reproductive tissues showed no evidence of toxicity.

A combined fertility and developmental study (including teratogenicity and postnatal investigations) in rats is ongoing.

Prenatal and postnatal development, including maternal function

No such studies have been done.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No such studies have been done.

Local tolerance

No such studies have been done. The assessments made as part of the general toxicity study should suffice and a separate study is not needed.

Other toxicity studies

No such studies have been done.

Toxicity conclusions

The Public Assessment Report summarises the initial assessment at the time of approval in December 2020. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics

(https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19) and the data about adverse reactions can be viewed in the Summary of Coronavirus Yellow Card reporting (https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting).

The absence of reproductive toxicity data is a reflection of the speed of development to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need. In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available. In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time: however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination. Women who are breastfeeding should also not be vaccinated. These judgements reflect the absence of data at the present time and do not reflect a specific finding of concern. Vaccine advice for Healthcare professional about women of childbearing potential, pregnant women and breastfeeding women (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine) and vaccine advice for women of childbearing potential, pregnant women and breastfeeding women (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-uk-recipients-on-pfizerbiontech-covid-19-vaccine) has been provided.

3.5 Ecotoxicity/Environmental Risk Assessment

It is agreed that, in accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use)" published 01 June 2006, due to their nature, vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, an environmental risk assessment is not provided in this application. This is acceptable.

3.6 Discussion and conclusion on the non-clinical aspects

The non-clinical data currently available for COVID-19 mRNA Vaccine BNT162b2 can be accepted as sufficient with specific mitigations in place. There are no scientific objections arising from this review to the authorisation for temporary supply for this product under Regulation 174.

Further information

The rest of this document, including sections on clinical aspects, user consultation, and the overall conclusion, can be found in this PDF (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/944544/COVID-19_mRNA_Vaccine_BNT162b2__UKPAR___PFIZER_BIONTECH__15Dec2020.pdf).

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Productie 41

BIOTECHNOLOGY AND HEALTH

What are the ingredients of Pfizer's covid-19 vaccine?

We asked experts to help us decode the contents.

By Antonio Regalado

December 9, 2020

MS TECH | GETTY

Facebook said on December 3 that it would remove posts with false claims or conspiracy theories about what's in the covid-19 vaccines that everyone's counting on.

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What's actually on the official ingredient list? This week an elderly UK woman became the first person outside of a trial to get the newly approved vaccine developed by Pfizer and BioNTech, and the US could greenlight the same inoculation as soon as Thursday, December 10. Along with the regulatory actions over the last week have come the most detailed disclosures yet of the new vaccine's makeup.

Here, for instance, is what the US Food and Drug Administration says is in Pfizer's vaccine:

📲 Who made the 10 Breakthrough Technologies 2024 list? Subscribe to see the exceptional innovations.

- **Active Ingredient**
  - nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2
- **Lipids**
  - (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis (ALC-3015)
  - (2- hexyldecanoate),2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
  - 1,2-distearoyl-snglycero-3-phosphocholine (DPSC)
  - cholesterol
- **Salts**
  - potassium chloride
  - monobasic potassium phosphate
  - sodium chloride
  - basic sodium phosphate dihydrate
- **Other**
  - sucrose

Reading the ingredient list is like looking at the side of a cereal box, except that you need a degree in organic chemistry to understand it. We got help from various scientists and biotech entrepreneurs to understand what each of the ingredients does and make some educated guesses about others.

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The new vaccine, delivered as a shot in the arm muscle, contains an RNA sequence taken from the virus itself; it causes cells to manufacture the big “spike” protein of the coronavirus, which the pathogen uses to glom onto a person’s cells and gain entry. On its own, without the rest of the virus, the spike is pretty harmless. But your body still reacts to it. This is what leaves you immunized and ready to repel the real virus if it turns up.

The mRNA in the vaccine, to be sure, isn’t quite the same as the stuff in your body. That’s good, because a cell is full of defenses ready to chop up RNA, especially any that doesn’t belong there. To avoid that, what’s known as “modified nucleosides” have been substituted for some of the mRNA building blocks.

But Pfizer is holding back a little. The spike gene sequence can be tweaked in small ways for better performance, by means that include swapping letters. We don’t think Pfizer has said *exactly* what sequence it is using, or what modified nucleosides. That means the content of the shot may not be 100% public.

The lipids

The Pfizer vaccine, like one from Moderna, uses lipid nanoparticles to encase the RNA. The nanoparticles are, basically, tiny greasy spheres that protect the mRNA and help it slide inside cells.

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These particles are probably around 100 nanometers across. Curiously, that’s about the same size as the coronavirus itself.

Pfizer says it uses four different lipids in a “defined ratio.” The lipid ALC-0315 is the primary ingredient in the formulation. That’s because it’s ionizable—it can be given a positive charge, and since the RNA has a negative one, they stick together. It's also a component that can cause side-effects or allergic reactions. The other lipids, one of which is the familiar molecule cholesterol, are “helpers” that give structural integrity to the nanoparticles or stop them from clumping. During manufacturing, the RNA and the lipids are stirred into a bubbly mix to form what the FDA describes as a “white to off-white” frozen liquid.

Salts

The Pfizer vaccine contains four salts, one of which is ordinary table salt. Together, these salts are better known as phosphate-buffered saline, or PBS, a very common ingredient that keeps the pH, or acidity, of the vaccine close to that of a person’s body. You’ll understand how important that is if you’ve ever squeezed lemon juice on a cut. Substances with the wrong acidity can injure cells or get quickly degraded.

Sugar

The vaccine includes plain old sugar, also called sucrose. It’s acting here as a cryoprotectant to safeguard the nanoparticles when they’re frozen and stop them from sticking together.

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Saline solution

Before injection, the vaccine is mixed with water containing sodium chloride, or ordinary salt, just as many intravenously delivered drugs are. Again, the idea is that the injection should more or less match the salt content of the blood.

No preservatives

Pfizer makes a point of saying its mixture of lipid nanoparticles and mRNA is "preservative-free." That's because a preservative that's been used in other vaccines, thimerosal (which contains mercury and is there to kill any bacteria that might contaminate a vial), has been at the center of worries around over whether vaccines cause autism. The US Centers for Disease Control says thimerosal is safe; despite that, its use is being phased out. There is no thimerosal—or any other preservative—in the Pfizer vaccine. No microchips, either.

The vaccine is still known by the code name BNT162b, but once it's authorized, expect Pfizer to give it a new, commercial name that conveys something about what's in it and what it promises for the world.

We thank the following people for explaining the vaccine ingredients: Jacob Becraft and Aalok Shah, Strand Therapeutics; Yizhou Dong, Ohio State University; Jason Underwood, Pacific Biosciences; Andrey Zarur, Greenlight Biosciences; Charles L. Cooney, MIT; and the communications staffs of Pfizer and Moderna Therapeutics.

by Antonio Regalado

Productie 42

EN
P-003980/2021
Answer given by Ms Kyriakides
on behalf of the European Commission
(26.10.2021)

The Commission confirms that there is no ferromagnetic or metallic material in all the vaccine formulations approved for use in the EU.

The composition of all authorised COVID-19 vaccines is described in section 6 of the patient information leaflet and graphene oxide is not listed in the composition of these products:
- Comirnaty[1] - mRNA
- Spikevax[2] - mRNA
- Vaxzevria, COVID-19 Vaccine (ChAdOx1-S [recombinant])[3] – adenovirus
- COVID-19 Vaccine Janssen, INN-Ad26.COV2-S, recombinant[4] - adenovirus

There are currently no approved COVID-19 DNA vaccines in the EU.

In addition to the original quality assessment, each batch of product in the EU is also released by an independent official medicines control laboratory before it may be marketed. This release involves testing of some key parameters and a comprehensive manufacturing protocol review for each batch.

The Commission, together with the European Medicines Agency, is ensuring that COVID-19 vaccines made available in the EU correspond to high standards of safety, quality and efficacy.

[1] https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
[2] https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf
[3] https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf
[4] https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf

Productie 43

EN
P-000303/2022
Answer given by Ms Kyriakides
on behalf of the European Commission
(8.3.2022)

In the EU a marketing authorisation is granted to a medicinal product only after its quality, safety and efficacy have been evaluated and a positive benefit-risk balance related to its use has been concluded. For EU authorisations of COVID-19 vaccines this assessment is carried out by the European Medicines Agency (EMA).

EMA has analysed reports describing the analysis of several vials of COVID-19 vaccines suggesting the presence of graphene and concluded that the currently available data do not show presence of graphene in the vaccines concerned. The analysis by EMA's working party for biological medicines included an input on the Raman spectroscopy from the European Directorate for Quality of Medicines and the independent national testing laboratories responsible for batch release (OMCLs).

Graphene oxide is not used in the manufacture or formulation of any of the COVID-19 vaccines or other medicines, so it would not be present at manufacturing facilities and there is no obvious way that it could get into the vaccines. Quality control testing and quality assurance review, by the vaccine manufacturers and OMCLs responsible for batch release, confirm that each batch met all quality standards prior to release. No product complaints have been received for the batches mentioned in the paper. The presence of graphene or graphene derivatives in the vaccines therefore are not plausible.

The Commission and EMA do not consider that any further actions are necessary at this stage.

Productie 44

COVID-19 vaccines do not contain graphene oxide

By Reuters Fact Check
July 23, 20214:49 PM GMT+2Updated 3 years ago

Online reports that COVID-19 vaccines contain graphene oxide are unfounded.

The allegations are based on an analysis by a professor in Spain which has been rejected by experts. He obtained what he himself described as non-conclusive results after studying one vial. He said the vial was purported to contain a dose of the Pfizer-BioNTech vaccine but said it had come to him by a messenger service and acknowledged that the vial's origin was unknown.

Pfizer told Reuters its vaccines do not contain the material. This material is also not listed in any of the widely available COVID-19 vaccines worldwide.

Social media posts and blogs with this false claim can be seen here, here , here , here . Many of the posts wrongly suggest the vaccines are therefore toxic.

Graphene oxide is a "single-atomic layered material" made through the oxidation of graphite (here). When chemically reduced (here , here), graphene oxide can create graphene which has been described as "the strongest, thinnest and most conductive material on earth" (here).

INGREDIENTS

“Graphene oxide is not used in the manufacture of the Pfizer-BioNTech COVID-19 vaccine,” Pfizer’s Senior Associate of Global Media Relations told Reuters.

According to a factsheet on the U.S. Food and Drug Administration’s website here the ingredients of the Pfizer vaccine include: mRNA, lipids, potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose. It does not list graphene oxide.

None of the other COVID-19 vaccines available worldwide, manufactured by Moderna , Janssen, AstraZeneca, CanSino, Sinovac and Sputnik V, contain graphene oxide, according to ingredients lists visible here , here , here , here , here and here .

A “SAMPLE” OF UNKNOWN ORIGIN, NO CONCLUSIVE RESULTS

The report in question (here), dated June 28, 2021 was published by Pablo Campra Madrid, a professor of the University of Almería (UAL). The author states in the report that the study was not made on behalf of the university (page 23).

In a Twitter post (here), the University of Almería described the publication as an “unofficial report by a university professor about an analysis of a sample of unknown origin with a total lack of traceability”. It added that it was a “report that this university neither subscribes to nor shares, as the report itself warns.”

As stated on page 3 and 8 of his report here, Campra Madrid analyzed samples out of a Pfizer-BioNTech vial of “unknown origin” (that goes by the brand “Cominarty” in the EU, here) with two types of microscopes. The vial was sent to him by “messenger service”. The paper does not provide further details regarding the vaccine dose’s source.

In his report, Campra Madrid said he compared images of this vaccine liquid under the microscopes with images of graphene oxide published in scientific journals (see for example, page 12 in his study and here). He concluded that they looked similar.

Experts consulted by Spanish fact-checker Maldita.es said here images could show any material.

In his study, Campra Madrid himself acknowledges that the “microscope doesn’t provide conclusive evidence” and that the analysis comes from “a single, limited sample” – one of unknown origin and traceability.

Campra Madrid also says the investigation was requested by Ricardo Delgado Martín, founder of the blog “La Quinta Columna” (see page 3 here). According to articles by

Spanish fact-checker Maldita.es and outlet La Vanguardia, Delgado has previously spread misinformation about COVID-19 (here, here).

COVID-19 VACCINES ARE TRANSPARENT

Matthew Diasio, an American Chemical Society Congressional Science & Engineering Fellow (here) took to Twitter to criticise Campra Madrid's report.

Among other arguments, Diasio said that liquids containing graphene or graphene oxide in any significant amount tend to be dark brown or black. If the shots had "even 1% graphene or graphene oxide" (the claim states it has 99.9%), the liquid would look black or at least, dark, Diasio said.

The Pfizer-BioNTech COVID-19 vaccine is a transparent or yellowish liquid (as visible here , here), as are other available COVID-19 shots in the U.S. – Moderna (here), Janssen (here) and AstraZeneca (here).

False. Pfizer said their COVID-19 vaccines do not contain graphene oxide.

This article was produced by the Reuters Fact Check team. Read more about our work to fact-check social media posts here .

Productie 45

Pfizer vaccine does not contain graphene oxide

BY ALI SWENSON

Published 8:33 PM GMT+1, July 8, 2021

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CLAIM: The Pfizer coronavirus vaccine is made up of 99.9% graphene oxide, a toxic compound.

AP'S ASSESSMENT: False. The Pfizer vaccine does not contain any graphene oxide, a Pfizer representative confirmed to The Associated Press. The study referenced in this bogus claim is not peer reviewed, nor is it supported by Spain's University of Almeria as some have claimed.

THE FACTS: Graphene oxide is not among the ingredients found in Pfizer's COVID-19 vaccine, despite alarmist claims to the contrary on social media.

Videos spreading widely on Instagram and Twitter on Thursday touted a report from Spain that allegedly claimed to find graphene oxide — a material made by oxidizing graphite — in a vial of the Pfizer shot.

"There's no other reason for this to be in here except to murder people," said a woman in one of the videos. The woman also baselessly claimed the compound would cause an inflammatory immune reaction called a cytokine storm in people who got the vaccine.

In reality, there's no graphene oxide in the Pfizer vaccine, according to the ingredient list and Kit Longley, senior manager of science media relations at Pfizer. There's also no evidence to suggest the Pfizer vaccine would cause a cytokine storm, Longley said. The coronavirus, however, has caused this type of immune response in some patients.

Chemical and medical experts who are not associated with Pfizer confirmed to The Associated Press that there is no way graphene oxide would be found in the vaccine.

"It is not in the ingredient list and there is no way it could be present," said Allen Myerson, a professor of chemical engineering at the Massachusetts Institute of Technology.

"Utter nonsense," said Dr. Paul Offit, a vaccine expert at the Children's Hospital of Philadelphia.

There has been research on potentially using graphene oxide in other vaccines, but the amounts would not be toxic to human cells, according to Johns Hopkins infectious disease specialist Dr. Amesh Adalja.

The report cited in some of the viral posts lists Spain's University of Almeria on its title page, and appears to be written by a professor at the university. The university has said it was not involved in research indicating the presence of graphene in the vaccine.

The university added in a statement that it supports vaccines and disavows the conclusions of the professor's unofficial report, which analyzed a "sample of unknown origin."

The report has not been peer reviewed and is not published in a scientific journal. It includes a disclaimer that its findings do not represent any institutional position of the university.

This is part of The Associated Press' ongoing effort to fact-check misinformation that is shared widely online, including work with Facebook to identify and reduce the circulation of false stories on the platform.

Here's more information on Facebook's fact-checking program: https://www.facebook.com/help/1952307158131536

Productie 46

Periodic safety update report

Share

A report prepared by the marketing-authorisation holder describing the worldwide safety experience with a medicine at a defined time after its authorisation. Abbreviated as PSUR.

More information can be found under 'Periodic safety update reports: questions and answers'.

Product emergency hotline
OUTSIDE WORKING HOURS

Productie 47

COMIRNATY : Periodic safety update report assessment

19 June 2022 to 18 December 2022

This document consists of:

1. The PRAC assessment report of the Comirnaty periodic safety update report (PSUR) covering the period 19th June 2022 to 18th December 2022, and;

2. The Comirnaty PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/304118/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010898/202212

Active substance(s): tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5)

Period covered by the PSUR: 19/06/2022 To: 18/12/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
COMIRNATY	BioNTech Manufacturing GmbH

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	9 March 2023	9 March 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	8 May 2023	8 May 2023
☐	MS/PRAC members and MAH comments	7 June 2023	7 June 2023
☐	PRAC Rapporteur's updated assessment report following comments	22 June 2023	22 June 2023
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	6 July 2023	6 July 2023

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Procedure resources	
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Assessor – PRAC Rapporteur	Name: Email: Name: Email: Name: Email:
EMA Procedure Lead	Name: Tel: Email:
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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for tozinameran (COMIRNATY), tozinameran/riltozinameran (COMIRNATY Original/Omicron BA.1), tozinameran/famtozinameran (COMIRNATY Original/Omicron BA.4-5).

2. Assessment conclusions and actions

The MAH submitted the 4th EU Periodic Safety Update Report (PSUR) for Comirnaty (dated 17 Feb 2023) covering the period 19 Jun 2022 to 18 Dec 2022.

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in people aged 6 months and older.

During the reporting period of the PSUR:

- A booster dose of Comirnaty 10 µg in children 5 to 11 years of age was recommended (procedure EMEA/H/C/005735/II/0129)
- The indication of Comirnaty was extended to children 6 months - 4 years old (tozinameran; Tris/Sucrose presentation 3 micrograms per dose). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose. (procedure EMEA/H/C/005735/X/0138)
- Two adapted Comirnaty vaccines became available:
    - Comirnaty Original/Omicron BA.1 that contains tozinameran and riltozinameran:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0140)
    - Comirnaty Original/Omicron BA.4-5 that contains tozinameran and famtozinameran:
        - Booster dose (15/15 micrograms per dose) for people aged 12 years and older at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/II/0143)
        - Booster dose (5/5 micrograms per dose) for people aged from 5 years to 11 years at least 3 months after primary vaccination with a COVID-19 vaccine. (procedure EMEA/H/C/005735/X/0147)

During the reporting interval, 813,783,710 doses of Comirnaty original and bivalent vaccines were shipped worldwide. Cumulatively, 4,369,782,515 doses of Comirnaty original and bivalent vaccines were shipped worldwide.

There were no marketing authorisation withdrawals for safety reasons during the reporting interval.

During the reporting interval, Dizziness (with frequency Uncommon) and Heavy menstrual bleeding (with frequency Unknown) were added as ADRs to the Comirnaty product information.

During the reporting interval, the following signals were evaluated, not to be determined risks, and no new important safety issue was identified based on the data provided in the PSUR:

- Haemophagocytic lymphohistiocytosis (HLH); Dermatomyositis; Histiocytic necrotizing lymphadenitis (HNL); Genital (e.g., vulvovaginal) ulceration.

The following were ongoing signals during the reporting interval:

- Pemphigus and Pemphigoid (EPITT 19859).

During the reporting interval, there were post-approval regulatory requests for the following topics for which no safety signal was identified based on the information provided in the PSUR:

- Multisystem inflammatory syndrome children/-adults (MIS-C/-A); Dyspnoea; Palpitations; Tachycardia/Heart Rate Increase; Subacute thyroiditis; Amenorrhea.

There was a new aspect of a previously recognised important safety issue identified, which included the clinical course (including intensive care support) and outcome (including fatal outcome) of Comirnaty associated myocarditis/pericarditis at short term follow-up (≤3 months). Therefore, the wording of the warning concerning myocarditis and pericarditis in the Comirnaty PI should be amended accordingly (please refer to section 3 Recommendations below).

During the reporting interval, the important identified risk Anaphylaxis was removed from the list of safety concerns in the Comirnaty RMP.

The important potential risk VAED/VAERD can be removed from the list of safety concerns in both RMP and PSUR, as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD should continue to monitor through routine pharmacovigilance.

Taking into account the extensive use of the vaccine and the relatively well-established safety profile, the PRAC endorses the proposal to move the PSUR cycle to 1 year. As the MAH has expressed a wish to keep the cycle aligned with the EURD, two additional 6-monthly PSURs will be submitted, followed by the yearly PSUR.

The benefit-risk balance for the use of Comirnaty (tozinameran), Comirnaty Original/Omicron BA.1 (tozinameran and riltozinameran), and Comirnaty Original/Omicron BA.4-5 (tozinameran and famtozinameran) in its authorised indications remains unchanged.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on myocarditis and pericarditis from the literature and spontaneous reports, the PRAC considers that the current warning on this risk should be amended to reflect the clinical course and outcome (including very rare fatal outcome) of Comirnaty associated myocarditis/pericarditis. The PRAC concluded that the product information of products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran should be amended accordingly.

Precise scope:

Update of section 4.4 of the SmPC to amend the warning/precaution regarding myocarditis and pericarditis and section 2 of the package leaflet accordingly.

The following changes to the product information of medicinal products containing tozinameran, tozinameran/riltozinameran, tozinameran/famtozinameran are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males **(see section 4.8)**. Available data **indicate** ~~suggest~~ that **most cases recover. Some cases required intensive care support and fatal cases have been observed.** ~~the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general (see section 4.8).~~

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Package Leaflet

- Section 2

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. **Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen.** Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

In addition, MAH should address the issue concerning the removal of the important potential risk VAED/VAERD, as detailed in section 2 of the Assessment report, in the next RMP update to be submitted within the next upcoming regulatory procedure affecting the RMP.

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM)

The MAH should also address the following issues in the next PSUR:

1. For future PSURs in the section 'Evaluation of AESI's', the AESIs in subjects with Malnutrition;

HIV infection should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.

2. For future PSURs in the section 'Evaluation of Other Risks (not categorised as important)', the reactogenicity on individuals previously exposed or not to SARS-COV-2, the systemic adverse reactions, and the age-related adverse reactions should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
3. For future PSURs in the section 'Evaluation of special situations', death (cases reporting fatal outcome) should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
4. For future PSURs in the section 'Update on special populations', the use in elderly should only be included and discussed in the PSUR if the reporting pattern changes and/or there is a safety issue/signal.
5. The MAH should present a case level analysis for all cumulative positive rechallenge cases of dyspnoea, palpitations and tachycardia/heart rate increase with a duration of the events not considered stress/anxiety-related reactions, including cases with a TTO of <2 days. The MAH should discuss whether these events should be added in section 4.8 of the Comirnaty SmPC and PIL accordingly.

5. PSUR frequency

☒ Changes of PSUR frequency are proposed.

The current frequency of submission should be changed from 6 months to 1 year at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

Noting that the MAH has expressed a wish to stay aligned with the EURD, two additional 6-monthly PSURs (DLP June 2023 and DLP December 2023 respectively) will be submitted, then a first yearly PSUR (DLP December 2024), to be followed by further yearly PSURs.

Productie 48

EMA/596333/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMEA/H/C/005735/R/0046

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Steps taken for the assessment	
Description	**Date**
Start of procedure:	19 Jul 2021
CHMP and PRAC Rapporteurs Joint Assessment Report	17 Aug 2021
CHMP and PRAC members comments	23 Aug 2021
Updated CHMP and PRAC Rapporteurs Joint Assessment Report	N/A
PRAC endorsed relevant sections of the assessment report	02 Sep 2021
Request for supplementary information	16 Sep 2021
MAH responses to (RfSI) received on	21 Sep 2021
CHMP and PRAC Rapporteurs' joint assessment report	28 Sep 2021
PRAC endorsed relevant sections of the assessment report	30 Sep 2021
CHMP and PRAC members comments	N/A
Updated CHMP and PRAC Rapporteurs joint assessment report	N/A
Opinion	14 Oct 2021

Procedure resources	
CHMP Rapporteur:	Filip Josephson
PRAC Rapporteur:	Menno van der Elst

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1. Background information on the annual renewal

The European Commission issued on 21 December 2020, a conditional marketing authorisation (MA) for Comirnaty. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH BioNTech Manufacturing GmbH, submitted to the Agency on 18 June 2021 an application for renewal of the conditional marketing authorisation for Comirnaty. The expiry date of the MA is 21 December 2021.

The period covered by this annual renewal is 21 December 2020 to 29 April 2021.

2. Specific Obligations

2.1. Specific Obligations adopted by the CHMP at time of initial marketing authorisation

Number	Description	Due date
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
SOB 003	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

2.2. Outstanding Specific Obligations – Status report for period covered

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
Specific Obligation 1 (SO1)	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021	02/08/2021		Not Fulfilled
SO1 (a)	Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into Assessment report EMA/707383/2020 Page 37/140 truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated.	July 2021	02/08/2021		Ongoing
SO1 (b)	The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail.	July 2021	02/08/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO1 (c)	Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the in vitro expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated	July 2021	02/08/2021		Ongoing
Specific Obligation 2 (SO2)	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021	02/08/2021		Not Fulfilled
SO2 (a)	The active substance and finished product specifications acceptance limits should be reassessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials.	July 2021	02/08/2021		Ongoing
SO2 (b)	Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed, and appropriate acceptance criteria should be set.	July 2021	02/08/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO2 (c)	The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes.	July 2021	02/08/2021		Ongoing
SO2 (d)	Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability.	July 2021	02/08/2021		Ongoing
SO2 (e)	Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly.	July 2021	02/08/2021		Ongoing
SO2 (f)	Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021.	July 2021	26/07/2021		Ongoing
Specific Obligation 3 (SO3)	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021	29/03/2021	20/05/2021	Fulfilled
SO3 (a)	Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities.	March 2021	29/03/2021	20/05/2021	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO3 (b)	The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment.	March 2021	29/03/2021	20/05/2021	Fulfilled
Specific Obligation 4 (SO4)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021	06/01/2021 26/07/2021		Not Fulfilled
SO4 (a)	A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO4 (b)	Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed by July 2021.	July 2021	26/07/2021		Ongoing
SO4 (c)	Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided.	July 2021	26/07/2021		Ongoing
SO4 (d)	Information and justification on critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021		Ongoing
SO4 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies.	July 2021	26/07/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO4 (f)	The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate.	July 2021	26/07/2021		Ongoing
SO4 (g)	The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product.	July 2021	26/07/2021		Ongoing
SO4 (h)	Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided.	July 2021	26/07/2021		Ongoing
SO4 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021		Ongoing
Specific Obligation 5 (SO5)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021	06/01/2021 26/07/2021		Not Fulfilled
SO5 (a)	A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO5 (b)	Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG.	July 2021	26/07/2021		Ongoing
SO5 (c)	Information and justification of critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021		Ongoing

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO5 (d)	The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product.	July 2021	26/07/2021		Ongoing
SO5 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies.	July 2021	26/07/2021		Ongoing
SO5 (f)	The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate.	July 2021	26/07/2021		Ongoing
SO5 (g)	Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis.	January 2021	06/01/2021	27/01/2021	Fulfilled
SO5 (h)	Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided.	July 2021	26/07/2021		Ongoing
SO5 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021		Ongoing
Specific Obligation 6 (SO6)	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023			Pending

SOB 1: Quality: Characterisation

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0056/G is under assessment. An interim report was submitted within a PAM-ANX procedure in March 2021 and monthly status reports submitted in January, February and May 2021.

SOB 2: Quality: Control strategy

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0056/G is under assessment. An interim report was submitted within a PAM-ANX procedure in March 2021 and monthly status reports submitted in January, February and May 2021.

SOB 4: Quality: Process and control strategy for the excipient ALC-0315

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0054/G is under assessment. Interim reports were submitted in January and April 2021.

SOB 5: Quality: Process and control strategy for the excipient ALC-0159

The due date for this SOB was July 2021 and a variation application EMEA/H/C/005735/II/0054/G is under assessment. Interim reports were submitted in January and April 2021.

SOB 6: Clinical

In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.

Interim results from study C4591001 were included in the initial Marketing Authorisation Application for Comirnaty, and the study design and results were extensively assessed during the approval procedure. The study is still ongoing according to plan, and final results are expected in December 2023.

CHMP comment:

Specific Obligations 1,2, 4, 5 and 6 are ongoing and progressing according to plan.

The CHMP issued an opinion on the 20th of May 2021 concluding that Specific Obligation 003 had been fulfilled, and therefore deleted from the Annex II.

2.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, several aspects for all quality SOBs have been addressed.

SOB 004 and SOB 005 relating to the novel excipients are partially fulfilled. The data to fulfil the remaining parts of these SOBs have been submitted in variation EMEA/H/C/005735/II/0054/G and are currently under assessment by the CHMP. A Request for Further Information has been adopted on 14

October 2021.

Similarly, data to fulfil SOB 001 (characterisation) and SOB 002 (control strategy & specifications) have been submitted in variation EMEA/H/C/005735/II/0056/G and are currently under assessment by the CHMP. A Request for Further Information has been adopted on 14 October 2021.

Therefore, overall SOB 001, SOB 002, SOB 004 and SOB 005 are not fulfilled at the time point of the present assessment report; nevertheless, the MAH has been compliant in providing the data in response to these SOBs in line with the imposed deadlines, and therefore, the overall status of compliance is satisfactory.

Regarding SOB003*: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data,* the due date for this SOB was March 2021 and the SOB was fulfilled with the variation EMEA/H/C/005735/II/0023/G (approved on 20 May 2021).

During the period covered by this annual renewal interim data on the clinical SOB 006 have been submitted that overall are compliant in terms of adherence to deadlines and in terms of acceptability of data submitted. The available clinical evidence includes a tolerable safety profile and high vaccine efficacy against COVID-19 in individuals ≥12 years of age.

3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

3.1. Quality

For several of the remaining Quality SOBs the due date was July 2021 and variations EMEA/H/C/005735/II/0054/G and EMEA/H/C/005735/II/0056/G are currently under assessment.

3.2. Clinical efficacy

Since approval of Comirnaty the MAH has submitted efficacy and safety data for children 12-15 years of age, and approval of an indication in this age group was obtained on May 31, 2021. (EMEA/H/C/005735/II/0030). For further details on the efficacy of Comirnaty, please see the initial marketing authorisation approval.

3.3. Clinical safety

The MAH submitted the Addendum to the Clinical Overview (ACO), covering the period from 21 December 2020 until 29 April 2021.

Worldwide Marketing Authorisation Status

BNT162b2 received a first temporary authorisation for emergency supply under regulation 174 in the UK on 1 December 2020 and in EEA countries on 21 December 2021. Up to the DLP (29 April 2021), it is currently conditionally approved in 42 countries (including EEA).

Actions Taken for Safety Reasons During the Period Covered Since the Initial Marketing Authorisation

Issue	Country	Action Taken	Date
Compared to the global supply of BNT162b2, an increased complaints rate for leakages was observed by the MAH in Hong Kong, with 19 vials with leakages reported from 3 different vaccination sites in the country; overall 26 vials with leakages and/or loose caps were reported. All vials were from 1 batch, the only batch in use for vaccination in Hong Kong and Macau. During the investigation, it became apparent that the root cause of the reported product quality complaints is a combination of the container closure process (crimping) at 1 single CMO and of the specific transport conditions on dry ice that are required for BNT162b2. Vaccination in Hong Kong and Macau was stopped as soon as the issue became apparent (24 March 2021). A total of 2 batches have been affected (including the one being used and another one already shipped to Hong Kong, but still in storage) and were quarantined. The root cause of the reported product quality complaints was clearly identified through analysis of the data generated and collected as of 31 March 2021. According to the data, the crimping process used for batches at the CMO fill and finish site requires optimization to ensure the container integrity during storage and shipment with dry ice. Under the ultra-cold conditions created by storing and shipping on dry ice, the stopper loses flexibility and, if not optimally crimped, allows the ingress of ambient gas into the vial. During thawing the flexibility of the stopper is regained and the stopper reseals the vial. This can result in increased pressure in the vial and presence of elevated CO2 levels. Due to the identified root cause the MAH could exclude any influence on batches that are on the market anywhere outside of Hong Kong and Macau. The CMO in question has not manufactured any batch that was released for any market other than Hong Kong and Macau. Vaccinations in Hong Kong and Macau were resumed with a vaccine batch from a different CMO on 3 April 2021; discussions to address the issue and resume supplies with the previous CMO are ongoing, no batches from this CMO are currently distributed.	Hong Kong and Macau	Vaccination in Hong Kong and Macau was stopped on 24 March 2021 and was resumed with a vaccine batch from a different CMO on 3 April 2021	24 March 2021
On 5 February 2021 Health Canada requested to issue a joint Pfizer-Health Canada Health Product Risk Communication to communicate revisions to Product Monograph (addition of 6-dose vial information and text on anaphylaxis). Final HPRC was approved on 8 February 2021.	Canada	Health Product Risk Communication to inform about the revisions to Product	8 February 2021

Issue	Country	Action Taken	Date
		Monograph (addition of 6-dose vial information and text on anaphylaxis).	
On 15 January 2021, following fatal events involving elderly patients vaccinated with BNT162b2 in Norway, the Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.	Norway	Norwegian Agency updated their guidance for vaccination, advising that caution and case-by-case judgement should be used when vaccinating frail, elderly subjects.	15 January 2021

Significant Changes to the Reference Safety Information

The Reference Safety Information (RSI) for this ACO is the BNT162b2 CDS (Company Data Sheet) Version 3.0, dated 20 April 2021, in effect at the end of the reporting period.

The previous CDS version 2.0 (dated 2 March 2021) and CDS version 1.0 (dated 12 February 2021) were also in effect during the reporting period. The safety related changes made in CDSs is as follows:

CDS version 3.0 (dated 20 April 2021)		
Section Number	Revision Type	Revision
4.8	Addition	A summary of the safety profile in the adolescents 12 through 15 years of age was added in Section 4.8 Undesirable effects, based on the planned data analysis from the ongoing multi-country clinical trial, C4591001, on adolescent study participants 12 through 15 years of age.
CDS version 2.0 (dated 2 March 2021)		
4.8	Addition	Diarrhoea, Pain in extremity (arm) and Vomiting were added as adverse reactions from post-authorisation experience in Section 4.8 Undesirable effects

The MAH also reported that **after the DLP of this ACO**, the CDS has been further updated (CDS ver. 4.0 dated 19 May 2021) with the following:

- a warning on stress-related responses associated with the process of vaccination was added in section 4.4 Special warnings and precautions for use
- data from studies in section 4.8 Undesirable effects was updated to add available data in 12 to 15-year-old subjects and in stable HIV-infected subjects
- Decreased appetite, Lethargy, Hyperhidrosis, Night sweating and Asthenia were added as Adverse Drug Reactions in section 4.8 Undesirable effects.

Respectively on 5 May 2021, on 10 May 2021 and on 28 May 2021, BNT162b2 was authorized for use in individuals 12 years of age and older in Canada, in US and in Japan.

Variation 0030 (EMEA/H/C/005735/II/0030) was also submitted to EMA on 30 April 2021 to seek expansion of the indication to subjects 12 to 15 years of age; on 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 years and the European Commission adopted a decision accordingly on 31 May 2021.

PRAC comment:

The SmPC is in line with the core data sheet (CDS).

Furthermore, the CHMP adopted an Opinion on the 16th September 2021 to add asthenia, lethargy, decreased appetite, hyperhidrosis, and night sweats as side effects to the product information. In addition, following the PRAC meeting in July, myocarditis and pericarditis were added to sections 4.4. and 4.8 of the SmPC, and the package leaflet was updated accordingly.

Patient exposure

Clinical studies

Cumulatively up to 21 April 2021, the MAH estimated that 49,315 subjects have participated in the Pfizer-managed studies of the COVID-19 vaccine clinical development program: 195 subjects received BNT162b1 (modRNA which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain); 41,368 subjects received BNT162b2 (modRNA which encodes a membrane-anchored SARS-CoV-2 full-length spike) of which, 20,291 subjects, who had received Placebo, were offered BNT162b2 post-unblinding and 758 subjects received BNT162b2 and the Blinded boost; 329 received BNT162S017, 6,370 subjects received blinded-therapy; and 1,053 subjects received placebo.

Additionally, 1,691 subjects have participated in 2 studies managed by BioNTech (BNT162-01 and BNT162-04) and in 2 studies (BNT162-03 and BNT162-06) managed by Shanghai Fosun Pharmaceutical in China.

PRAC comment:

The MAH was requested to explain what "BNT162S017" is, compared to BNT162b1 and BNT162b2. (**Request for Supplementary Information**)

Post-marketing experience worldwide

This estimation is based on the proportion of doses administered out of those shipped upon review of data currently available for the EU countries and the US.

The MAH estimated that approximately 415,922,715 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 1 December 2020 through 29 April 2021, corresponding to 332,738,172 estimated administered doses.

The estimated cumulative number of shipped and administered doses of BNT162b2 by region based on data provided in the shipment tracker (Order Book), from the receipt of the first temporary authorisation for emergency supply on 1 December 2020 through 29 April 2021, are summarized in Table 1 below.

Table 1. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	**37.1%**	**154,251,240**	**123,400,992**
European Union[a] (27)	28.9%	120,356,925	96,285,540
Commonwealth of Independent States[d]	**0.0%**	**170,820**	**136,656**
North America[e]	**41.8%**	**173,708,925**	**138,967,140**
Central and South America[f]	**5.1%**	**21,330,270**	**17,064,216**
Asia	**15.3%**	**63,627,720**	**50,902,176**
Oceania	**0.6%**	**2,377,440**	**1,901,952**
Africa[h]	**0.2%**	**627,120**	**501,696**
Total	**100.0%**	**415,922,715**	**332,738,172**

a. In this Region BNT162b2 was conditionally approved;
b. Includes Georgia, Moldova and Ukraine; in these countries BNT162b2 was shipped for COVAX;
c. In this Region BNT162b2 received authorization for emergency supply;
d. Includes Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru and Uruguay where BNT162b2 received authorisation for emergency supply (some doses in Colombia and Peru were also shipped for COVAX), Brazil where BNT162b2 was conditionally approved, and Bolivia and El Salvador where BNT162b2 was shipped for COVAX;
e. Includes Cape Verde, Rwanda and Tunisia where BNT162b2 was shipped for COVAX and South Africa where BNT162b2 received authorization for emergency supply.

Post-marketing exposure data in the EU

The MAH estimated that approximately 121,880,460 doses of BNT162b2 were shipped in the EU-EEA countries from the receipt of the first conditional marketing authorisation approval on 21 December 2020 through 29 April 2021, corresponding to 97,504,368 estimated administered doses.

Table 2 provide the cumulative estimated number of persons who received 1 dose or 2 doses of BNT162b2, in total, and by age group where available, in the EU-EEA countries.

Table 2. Cumulative Administered 1&2 doses of BNT162b2 by Age Group in EU-EEA Countries[a]

Countries	18-24 years		25-49 years		50-59 years		60-69 years		70-79 years		≥80 years		Age Unknown		All	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Austria	32601	18144	239207	130993	219059	90021	318379	75014	326639	140700	335807	293603	4546	2246	1476238	750721
Belgium	52593	35800	293119	213871	244493	116179	509734	90760	521985	95815	379603	200561	2596	2161	2004123	755147
Bulgaria	6159	2994	91073	53735	62270	40928	68639	39715	45433	21092	13544	6110	230	114	287348	164688
Croatia	4569	1560	66321	29122	57981	20840	104365	27281	95611	32417	54000	28683	82	34	382929	139937
Cyprus	67	132	24777	1459	17825	1449	7243	5255	112	877	19812	7812	58343	47244	128179	64228
Czech Rep	24298	14744	300516	182307	186681	102898	411983	75205	462712	285166	233366	213979	1024	415	1620580	874714
Denmark	12172	11349	100433	95272	70155	64869	215219	79996	489102	148799	234027	216113	807	0	1121915	616398
Estonia	3900	1995	35929	15436	29141	9623	39210	10497	51796	18286	38854	24687	96	25	198926	80549
Finland	20009	5211	164266	52763	163750	27400	211291	16390	432259	13109	249309	50709	0	0	1240884	165582
France													10678144	5870393	10678144	5870393
Germany													16302110	6165751	16302110	6165751
Greece	8657	5508	178846	131191	123573	76311	174906	40155	478077	215987	463446	402532	3193	77	1430698	871761
Hungary	68071	19492	532097	164815	234138	84751	323113	159588	287650	208967	197264	170584	4142	928	1646475	809125
Iceland	1510	515	12660	4461	8658	1911	12582	4204	8571	8268	12357	12290	131	63	56469	31712
Ireland	14443	9893	121182	83267	73386	35093	48177	20871	297164	119213	163486	151163	2070	610	719908	420110
Italy	152389	107855	1179042	1023120	914562	659910	1258996	558357	1603504	535098	3295757	2773399	515532	2289	8919782	5660028
Latvia	1701	831	12069	2349	7009	1394	8473	1285	3894	1714	1595	776	15986	13069	50727	21418
Liechtenstein													4617	2152	4617	2152
Lithuania	17322	6725	86710	42364	72027	36875	109972	60902	89537	66043	52024	37840	752	292	428344	251041
Luxembourg	999	647	8506	5009	23442	2410	28819	1773	12309	11142	18133	17509	5221	4796	97429	43286
Malta	3715	2544	34966	18553	16833	9036	17636	10225	35820	32940	21394	19093	500	1	130864	92392
Netherlands													2867626	1059516	2867626	1059516
Norway													666707	77265	666707	77265
Poland	85825	60529	987763	418915	926701	235199	1332294	267273	1748066	896698	899037	738724	5781	3406	5985467	2620744
Portugal	19908	10838	248888	132357	143630	61761	248335	49080	400468	76875	557181	498668	365	232	1618775	829811
Romania													2626409	1655770	2626409	1655770
Slovakia													610591	451720	610591	451720
Slovenia	1710	1419	21019	18350	16002	11063	69804	30038	85139	70616	61059	56730	227	132	254960	188348
Spain	74690	66594	780878	720572	437097	401459	411832	270351	3037645	697953	2640774	2434770	1744	1209	7384660	4592908
Sweden	22699	12657	154168	96111	158728	61720	498361	63157	526616	125817	418347	323265	0	8	1778919	682735
Total	**630007**	**397976**	**5674435**	**3636392**	**4207141**	**2153100**	**6429363**	**1957372**	**11040109**	**3823592**	**10360176**	**8679600**	**34379572**	**15361918**	**72720803**	**36009950**

a. Source is https://covid19-vaccine-report.ecdc.europa.eu/ (point 6, cumulative period as of week 17, 02 May 2021).

PRAC comment:

Up to 29 April 2021, it is estimated that over 332 Mio doses of BNT162b2 were administered worldwide.

During the reporting period of this renewal, it is estimated that over 97 Mio doses of Comirnaty were administered in the EU and EEA countries.

Data in Summary Tabulations

Cumulatively, there have been 882 clinical trial cases (1072 SAEs) reported.

Cumulatively[1] up to 29 April 2021, there have been 109,692 post-marketing cases (414,594 unique PTs) reported. During the reporting interval, there have been 108,980 post-marketing cases (412,318 unique PTs) reported.

Significant Findings from Clinical Trials and Non-Interventional Studies

Completed Clinical Trials

No clinical trials were completed up to 21 April 2021.

Ongoing[2] Clinical Trials

There were 10 ongoing clinical trials up to 21 April 2021 (sponsored by BioNTech SE), out of which 2 studies (BNT162-03 and BNT162-04) for study vaccines BNT162b1 and BNT162b3.

Six studies were conducted by Pfizer: C4591001, C4591005, C4591007, C4591015, C4591017, C4591020.

Four studies were conducted by BioNTech, including 2 studies in China managed by Shanghai Fosun Pharmaceutical Development (BNT162-03 and BNT162-06).

Clinically important emerging efficacy and/or safety findings were identified for Study C4591001/BNT162-02[3] and C4591005 and are summarized below.

- **Study C4591001/BNT162-02**

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
Countries: Argentina, Brazil, Germany, South Africa, Turkey, US

This study is a Specific Obligation in the context of BNT162b2's conditional marketing authorisation and it is being conducted in order to confirm the efficacy and safety of the vaccine; the MAH should submit the final Clinical Study Report, including a 2-year follow up of the studied population.

Study C4591001/BNT162-02 is an ongoing, randomized, placebo-controlled, observer-blind, dose-finding Phase 1/2/3 registration study evaluating the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.
Study C4591001/BNT162-02 was started as a Phase 1/2 study in adults in the US and was then amended to expand the study to a global Phase 2/3 study to accrue sufficient COVID-19 cases to conduct an efficacy assessment. The protocol was initiated in adults 18 years of age and older and subsequently amended to include adolescents as young as 12 years of age. The study has

[1] Collected since 01 December 2021, the date of the first temporary authorisation for emergency supply under regulation 174 in the UK.
[2] Includes ongoing studies as well as studies in which patient enrolment and follow-up have been completed, but the analysis and CSR are in-progress.
[3] Pfizer-conducted clinical trial C4591001/BNT162-02 has an interim study report that is available upon request.

enrolled approximately 46,000 participants, including 2,260 young adolescents 12 to 15 years of age. Data from the Phase 1 part of the study was the basis for selection of the vaccine candidate and dose level for Phase 2/3. The Phase 2/3 part of the study evaluated the safety, immunogenicity, and efficacy of the selected vaccine candidate, BNT162b2, and is intended to support licensure globally.

The available clinical evidence for BNT162b2 includes a tolerable safety profile and high VE against COVID-19 in individuals ≥12 years of age.

The potential risks are based on the observed safety profile to date, which shows mostly mild to moderate reactogenicity, an acceptable incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19, as defined by the FDA Guidance for Industry (June 2020)[4], in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of vaccine-associated enhanced disease.

Vaccine efficacy was ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those irrespective of prior infections. Observed VE was >93% when data were stratified by age, sex, race/ethnicity, and country with the exception of the "all others" race group (89.3% VE) and Brazil (87.7% VE).

Severe cases evaluated for efficacy were confined predominantly to the placebo group; only 1 severe case was reported in the BNT162b2 group in the final analysis. The efficacy data suggest high efficacy against COVID-19 in a broad population of individuals.

- **Study C4591005**

Title: A Phase 1/2, Placebo-Controlled, Randomized, and Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate Against Covid-19 In Healthy Japanese Adults
Country: Japan

Study C4591005 is a Phase 1/2, randomized, placebo-controlled, and observer-blind study in healthy Japanese adults. The study will evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 mRNA vaccine candidate (BNT162b2) against COVID-19 administered as two 30-µg doses, 21 days apart, in Japanese adults 20 to 85 years of age.

Clinical laboratory tests were performed for the first 24 participants (12 participants 20 to 64 years of age and 12 participants 65 to 85 years of age) (clinical laboratory subset). Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain), and use of antipyretic medication were collected by all participants in an e-diary from Day 1 through Day 7 after each administration of study intervention. AEs were collected from the time the participant provided informed consent through 1 month after Dose 2. SAEs will be collected from the signing of the ICD to approximately 12 months after Dose 2.

In this study, 160 Japanese participants (including 130 participants 20 to 64 years of age [younger age group] and 30 participants 65 to 85 years of age [older age group]) were randomized in an approximate 3:1 ratio of BNT162b2 to placebo. Interim data show BNT162b2 was well tolerated, with local reactions and systemic events mostly mild or moderate in severity, and no immediate AEs within 30 minutes reported. An acceptable safety profile was observed in both younger and older Japanese adults with no SAEs reported through 1 month after Dose 2. Immune responses elicited by BNT162b2 were robust 1 month after Dose 2, consistent with data from the global program. These

[4] Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry June 2020.

encouraging results led to the marketing authorization of BNT162b2 in Japan. This study has since been converted to a post-marketing study.

PRAC comment:

This small study does not add to the current knowledge on the safety profile of Comirnaty.

Non-Interventional Studies

There were 3 ongoing non-interventional studies (C4591008, C4591012 and C4591006) up to 21 April 2021, which are presented below:

Study No.	Study Title and Country
C4591008 Voluntary PASS	**Study Title**: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers. **Country**: United States **Primary study objectives**: • Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization. **Secondary objectives:** • Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post vaccination. • Estimate the incidence rates of safety events of interest and other clinically significant events among sub cohorts of interest such as individuals who are pregnant, individuals who are immunocompromised, and stratified by age.
C4591012 Committed PASS (post-authorisation commitment)	**Study Title**: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine **Country**: United States **Primary study objectives:** • To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. • To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. **Secondary study objective**: • To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA, including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.
C4591006	**Study Title**: General Investigation of Comirnaty Intramuscular Injection (Follow-up study for Subjects [Healthcare Professionals] Who are Vaccinated at an Early post- Approval Stage) **Country**: Japan **Study objective**: The healthcare professionals who are vaccinated with this product early after the marketing approval of this product (participants in the Investigation of Health Status of Recipients Vaccinated First conducted by the Science Research Group of the Ministry of Health, Labour and Welfare) will be followed for 11 months from the day following 28 days after the final vaccination of this product (end date of observation period in Investigation of Health Status of Recipients Vaccinated First) to 12 months after the final vaccination of this product, information on serious adverse events and COVID-19

Study No.	Study Title and Country
	observed during the follow-up period will be collected, and the long-term safety of this product will be assessed (to be conducted as 11-month follow-up investigation after completion of Investigation of Health Status of Recipients Vaccinated First).

According to the MAH, there was no new safety information reported regarding these ongoing non-interventional studies.

PRAC comment:

Within the first interim report of the PASS study C4591012, which is listed in the RMP of Comirnaty, (procedure EMEA/H/C/005735/MEA/010), only demographic and clinical characteristics of the two cohorts (Pfizer-BioNTech COVID-19 vaccine recipients and seasonal influenza vaccines recipients) were provided. No safety information was provided in the first interim report of study C4591012. Studies C4591008 and C4591006 are not part of the EU RMP.

Medication Errors

During the reporting interval, there were no serious clinical trial cases contained in the Global safety database that reported medication errors.

From post-authorisation sources, 4,591 cases potentially indicative of medication errors were retrieved from the global safety database worldwide up to 29 April 2021. Upon review, 447 cases were determined to be non-contributory and are not included in the discussion for the following reasons:

- Off-label use or misuse rather than medication error was reported in 95 cases;
- Questions about the scheduling of the 2 doses of BNT162b2 and/or information that the second dose may be administered (but it was not administered yet at the time of reporting) or was scheduled outside the prescribed dosing window were reported in 169 cases;
- No error or intercepted/potential error with BNT162b2 were identified in 183 cases, including 55 cases where the callers asked for information other than the scheduling of the 2 doses of BNT162b2.

Among the 4,144 relevant medication error cases, the following scenarios, were described:

- Medication errors associated with harm [i.e., resulting in adverse reaction(s)] were reported in 154 cases (3.7% of relevant medication error cases);
- Medication errors without harm [i.e. not resulting in adverse reaction(s)] were reported in 3,814 cases (92.0% of relevant medication error cases), of which 2,043 cases involved co-reported AEs;
- Potential medication errors were reported in 172 cases (4.1% of relevant medication error cases).
- Intercepted medication errors were reported in 4 cases (0.1% of relevant medication error cases).

The analysis of the relevant cases indicative of medication error did not lead to any change in the RSI with regard to the instructions for preparation, administration or storage of BNT162b2.

PRAC comment:

No new safety signal was identified from the cases reporting medication errors.

Medication errors are also analysed in the MSSRs for Comirnaty. From the MSSR assessments covering the period from 21 December 2020 to 29 April 2021, no safety issues were identified that required mitigation activity.

The MAH stated that further analysis of cases indicative of medication errors will be provided in the PSUR with DLP of 18 June 2021. This is accepted.

Non-clinical Data

No new non-clinical safety findings were identified in the period from 21 December 2020 to 21 April 2021.

Literature

Nonclinical (Published)

According to the MAH, a search of the Medline and Embase databases did not identify non-clinical studies that presented important new safety findings for Comirnaty up to 21 April 2021.

Clinical (Published)

From a search of the Medline and Embase databases up to 21 April 2021, the MAH identified 4 clinical trials that presented important new safety/efficacy findings for Comirnaty when administered in at risk patients (i.e., patients on haemodialysis) or special population, including elderly and pregnant/lactating women. The abstracts are presented in table 3 below.

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	At Risk Patients
1.	***Grupper A, Sharon N, Finn T, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol. 2021. doi: 10.2215/CJN.03500321.*** **Background and objectives:** Coronavirus disease 2019 (COVID-19) is associated with higher morbidity and mortality in patients on maintenance hemodialysis. Patients on dialysis tend to have a reduced immune response to infection or vaccination. We aimed to assess, for the first time to the best of our knowledge, the humoral response following vaccination with the BNT162b2 vaccine in patients on maintenance hemodialysis and the factors associated with it. **Design, setting, participants, & measurements:** The study included 56 patients on maintenance hemodialysis (dialysis group) and a control group composed of 95 health care workers. All participants had received two doses of the BNT162b2 (Pfizer-BioNTech) vaccine. The serology testing was done using Quant II IgG anti-Spike severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) assay by Abbott a median of 30 days after receipt of the second dose of the vaccine. **Results:** All subjects in the control group developed an antibody response compared with 96% (54 of 56) positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; interquartile range, 1128–5651) were significantly lower than in the control group (median, 7401; interquartile range, 3687–15,471). A Mann–Whitney U test indicated that this difference was statistically significant (U=1238; P<0.001). There was a significant inverse correlation of age and IgG levels in both groups. The odds of being in the lower quartile were significantly higher for older individuals (odds ratio, 1.11 per year of age; 95% confidence interval, 1.08 to 1.20; P=0.004) and for the dialysis group compared with the control group (odds ratio, 2.7; 95% confidence interval, 1.13 to 7.51; P=0.05). Within the dialysis group, older age and lower lymphocyte count were associated with antibody response in the lower quartile (odds ratio, 1.22 per 1-year older; 95%

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	confidence interval, 1.13 to 1.68; P=0.03 and odds ratio, 0.83 per 10-e3/µl-higher lymphocyte count; 95% confidence interval, 0.58 to 0.97; P=0.05). **Conclusions**: Although most patients on maintenance hemodialysis developed a substantial humoral response following the BNT162b2 vaccine, it was significantly lower than controls. Age was an important factor in the humoral response, regardless of chronic medical conditions.
	Special Patient Population(s)
2.	***Abu Jabal K, Ben-Amram H, Beiruti K, et al. Impact of age, ethnicity, sex and prior infection status on immunogenicity following a single dose of the BNT162b2 mRNA COVID-19 vaccine: Real-world evidence from healthcare workers, Israel, December 2020 to January 2021. Euro Surveill. 2021; 26(6):2100096. doi: 10.2807/1560-7917.ES.2021.26.6.2100096*** The BNT162b2 mRNA COVID-19 vaccine showed high efficacy in clinical trials but observational data from populations not included in trials are needed. We describe immunogenicity 21 days post-dose 1 among 514 Israeli healthcare workers by age, ethnicity, sex and prior COVID-19 infection. Immunogenicity was similar by ethnicity and sex but decreased with age. Those with prior infection had antibody titres one magnitude order higher than naïve individuals regardless of the presence of detectable IgG antibodies pre-vaccination.
3.	***Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Efficient maternofetal transplacental transfer of anti- SARS-CoV-2 spike antibodies after antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Clin Infect Dis. 2021: ciab266. doi: 10.1093/cid/ciab266. (Accepted manuscript).*** Maternal and cord blood sera were collected from 20 parturients who received the BNT162b2 vaccine. All women and infants were positive for anti S- and anti-RBD-specific IgG. Cord blood antibody concentrations were correlated to maternal levels and to time since vaccination. Antenatal SARS-CoV-2 vaccination may provide maternal and neonatal protection.
4.	***Kelly JC, Carter EB, Raghuraman N, et al. Anti-SARS-CoV-2 antibodies induced in breast milk after Pfizer-BioNTech/BNT162b2 vaccination: SARS-CoV-2 antibodies in breast milk after vaccination. Am J Obstet Gynecol. 2021: S0002-9378(21)00211-8. doi: 10.1016/j.ajog.2021.03.031.*** **Objective:** In December 2020, 2 lipid nanoparticle-formulated, nucleoside-modified messenger RNA–based vaccines received emergency use authorization by the US Food and Drug Administration, after their trials demonstrated 94% to 95% efficacy in preventing coronavirus disease 2019 (COVID-19). Although no lactating people were included in the vaccine trials, national organizations support vaccination of this population, suggesting potential infant protection by passive transfer of maternal antibodies. The authors sought to characterize breast milk levels of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in lactating people undergoing COVID-19 vaccination. **Study Design:** Participants were prospectively recruited during phase IA rollout of the COVID-19 vaccine at a tertiary care center, after institutional review board approval. Inclusion criteria included lactation and planned vaccination with the Pfizer-BioNTech BNT162b2 vaccine. After obtaining informed consent, participants provided frozen breast milk samples at the following time points of vaccination: before, within the first 24 hours, and the following week. Samples were assessed for SARS-CoV-2 RNA by quantitative real-time polymerase chain reaction and antispike immunoglobulin (Ig) G and IgA by an enzyme-linked immunosorbent assay. **Results:** A total of 5 subjects and 29 human milk samples were included in the analysis. All prevaccine milk samples tested negative for SARS-CoV-2 RNA, as defined by the cycle threshold value of >40 for the N1 target. Antispike IgG and IgA levels were significantly elevated relative to the prevaccine baseline at all time points. Antispike protein IgG remained sustained at a significant elevation beginning at 20 days after the first dose compared with the prevaccine baseline (P=.0061), through the final milk sample (day 30–39 P=.0095, >40 days P=.0040. Levels of antispike protein IgA were significantly elevated from baseline, starting 2 weeks after the first dose (P=.0286) through to the final sample (day 20–29 P=.0121, day 30–39 P=.0095, >40 days P=.0040); however, individual level data suggest a possible gradual decline in antispike IgA in human milk over time after the second dose.

Table 3. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

No.	Citation/Abstract
	Conclusion. The Authors characterized longitudinal breast milk levels of antispike IgG/A following Pfizer-BioNTech BNT162b2 vaccination, demonstrating sustained elevation of IgG/IgA levels. This response is similar to previous studies on maternal vaccination, which have shown high levels of breast milk IgA/G production for up to 6 months after vaccination for influenza and pertussis. A concurrent decrease in infant respiratory illness rates suggest that maternal vaccination confers protection against infection in breastfed infants. Thus, the Pfizer-BioNTech/BNT162b2 vaccination may also confer protection against COVID-19 to breastfed infants as well. Our study is limited by a small number of participants, but we report data that suggest a potential immune benefit to infants of lactating people up to 80 days after COVID-19 vaccination. Further studies are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates after maternal COVID-19 vaccination.

PRAC comment:

It is agreed with the authors that further investigation regarding vaccination with BNT162b2 in subjects at higher risk of COVID-19 (e.g., patients on hemodialysis) or special populations, including elderly and pregnant/lactating women, is needed. From the literature provided by the MAH, no new safety issues were identified. No changes to the product information are considered warranted at this moment.

Overview of Signals: New, Ongoing, or Closed

Tabular Summary of Safety Signals Evaluated During the Reporting Period (21 December 2020 – 29 April 2021)

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Open Signals							
Myocarditis and Pericarditis	15 Feb 2021 Re-opened 19 April 2021 and closed as no risk on 05 May 2021. Re-opened 24 May 2021	Ongoing	-	Ongoing discussions with a health authority (Israel MoH) Requests from health authorities	To determine if myocarditis or pericarditis is a risk.	Clinical study and post-authorization safety database review	The available data has not supported a causal association with BNT162b2. The signal remains open as further data accrues, and independent health authority evaluations are in progress.
Dizziness	Initially opened on 18 Jan 2021 and closed on 31 March 2021 as risk not important) Re-opened after DLP of ACO (10 May 2021)	Ongoing	-	Post-authorization spontaneous reports and inquiry from a competent authority Re-opened due to inquiry from a competent authority	Dizziness is a frequently reported AE; EMA PRAC request for safety evaluation.	Clinical study and safety database case series review	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021). Dizziness was re-opened for evaluation after the DLP of this ACO.
Signal determined to be Important identified risk							
Anaphylaxis	08 Dec 2020	Closed	30 Dec 2020	Post-authorization reports of anaphylaxis; EMA request to include as an Important identified	Post-authorization reports of anaphylaxis	Review of unblinded clinical study data; review of post-authorization data	Anaphylaxis was included in the EU-RMP and US-PVP as an Important Identified Risk and was included as an adverse reaction in

				risk in EU-RMP and as an adverse reaction in EU SmPC at time of conditional approval; FDA request to include it as an Important Identified Risk in the US PVP			the Section 4.8 of the CDS and EU SmPC.
Signals Determined to be Risks							
Hypersensitivity reactions (other than anaphylaxis)	19 Dec 2020	Closed	13 Jan 2021	EMA request to include "Hypersensitivity" as an adverse reaction in EU SmPC at time of conditional approval	Potential hypersensitivity events (other than anaphylaxis) were assessed to determine if product labeling information needed to be updated for completeness.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Hypersensitivity was added as an adverse reaction (not important) to Section 4.8 of the EU SmPC per EMA request. Core Position: "Hypersensitivity (e.g. rash, pruritus, urticaria, angioedema)" was added to the CDS as an adverse reaction.
Pain in extremity	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether pain in extremity is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, pain in extremity was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Pain in extremity has been added to the CDS as an adverse reaction.
Paraesthesia	29 Dec 2020	Closed	31 Mar 2021	Post authorization spontaneous reports and inquiry from a competent authority	Inquiries from Israel MOH and PRAC request for review.	Post-authorization reports and clinical study cases were reviewed. Reported events	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).

						that were reviewed included dizziness, paraesthesias and tachycardia among others	
Vomiting	16 Nov 2020 (before starting period of this ACO, ie., 21 December 2020) Re-opened 18 Jan 2021 following receipt of the 1st SMSR PRAC assessment report	Closed	Initially closed on 07 December 2020 (before starting period of this ACO) After re-evaluation, closed on 10 Feb 2021	Initially reviewed as a potential reactogenicity event in using unblinded clinical study data (DLP 14 Nov 2020) Re-opened due to inquiry from a competent authority	In review of unblinded clinical study data (data lock date 14 Nov 2020), vomiting was not found to occur at an increased frequency in vaccine group compared to placebo group following vaccination.	Review of unblinded clinical study data Review of post-authorization safety data	Based on evaluation of the post-authorization data, Vomiting has been added to the CDS as adverse reaction.
Diarrhoea	16 Nov 2020 (before starting period of this ACO, ie., 21 December 2020) Re-opened 18 Jan 2021 following receipt of	Closed	Initially closed on 07 December 2020 (before starting period of this ACO) After re-evaluation, closed on 10 Feb 2021	Initially reviewed as a potential reactogenicity event in using unblinded clinical study data (DLP 14 Nov 2020) Re-opened due to inquiry from a competent authority	In review of unblinded clinical study data (data lock date 14 Nov 2020), diarrhoea was not found to occur at an increased frequency in vaccine group compared to placebo group following vaccination.	Review of unblinded clinical study data Review of post-authorization safety data	Based on evaluation of the post-authorization data, Diarrhea has been added to the CDS and local labels as an adverse reaction.

	the 1st SMSR PRAC assessment report						
Tachycardia	28 Jan 2021	Closed	31 Mar 2021	Board of Health PV report	Noted as potential signal in PV Report from France (Marseille PV Regional Centre) for period 17 Dec 2020 to 15 Jan 2021.	Post-authorization reports and clinical study cases were reviewed. Reported events that were reviewed included dizziness, paraesthesias and tachycardia among others	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).
Vaccine stress-related responses	10 Feb 2021	Closed	31 Mar 2021	Post authorization reports	To determine if data is supportive of including the concept in the CDS and local labels.	Post-authorization reports and clinical study cases were reviewed. Reported events that were reviewed included dizziness, paraesthesias and tachycardia among other	A warning about stress-related responses associated with the process of vaccination has been added in the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).
Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats	27 Apr 2021	Closed	27 Apr 2021	Clinical Trial Data	Based on review of unblinded clinical study C4591001 safety data (data lock date 13 Mar 2021), and supported by post-authorization AE reports, the following AEs were determined to be causally	Review of unblinded clinical study data; review of post-authorization data	Decreased appetite, Lethargy, Asthenia, Night sweats, and Hyperhidrosis has been added as ADRs to the CDS after DLP of this ACO (CDS ver. 4.0 dated 19 May 2021).

					associated adverse reactions for BNT162b2.		
Signals determined not to be a risk							
Facial nerve palsy	03 Dec 2020 (before starting period of this ACO, ie., 21 December 2020) opened as safety topic. 19 Dec 2020 reopened	Closed	10 March 2020	Clinical Trial Data Enquiry from competent authority Post-authorization reports	Initially opened and closed following review of unblinded clinical study data (C4591001) (DLP 14 Nov 2020). Re-opened due to EMA request to include as adverse reaction in EU SmPC at time of conditional approval. Signal closed on 10 March 2021.	Review of unblinded clinical study data; review of post-authorization and epidemiological safety data (Observed vs Expected analyses)	At the time of conditional approval by the EMA, facial paralysis was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core position: Based on the results of the evaluation to date, a causal association with BNT162b2 has not been established. However, causality assessment will be further informed by additional safety data from clinical study C4591001, and from non-interventional post-authorization safety studies which are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy after vaccination through formal comparative analyses. Facial nerve paralysis, an adverse reaction as presented in the SmPC, but not in the CDS, was re-reviewed and closed on 10 March 2021; there was not sufficient evidence to conclude a causal association to the vaccine. This signal will be re-opened for re-evaluation if appropriate when non-interventional study safety data is available.

Insomnia	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether insomnia is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Insomnia was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Insomnia is determined not to be a risk and no further action is warranted at this time.
Injection site pruritus	19 Dec 2020	Closed	20 Jan 2021	EMA request to include as an adverse reaction in EU SmPC at time of conditional approval	To determine the company position on whether injection site pruritus is an adverse reaction for the vaccine.	Review of unblinded clinical study data; review of post-authorization data	At the time of conditional approval by EMA, Injection site pruritus was added as an adverse reaction to Section 4.8 of the EU SmPC per EMA request. Core Position: Based on review of clinical study and post-authorization data, Injection site pruritis is determined not to be a risk and no further action is warranted at this time.
Overdose	27 Dec 2020	Closed	20 Jan 2021	Post-authorization cases received of full-vial dosing per patient.	Review occurred to determine if there was further useful information with which to update Overdose section of labeling.	Post-authorization medication errors of full vial dosing and co-reported adverse events were reviewed	No significant new safety information was associated with these cases of overdose therefore it was determined that no updates to Overdose section of labeling was warranted.
Eye Pain & Eye Swelling	22 Jan 2021	Closed	03 Feb 2021	Inquiry from a competent authority	The 1st SMSR (with reporting period 01 December 2020 – 31 December 2020) PRAC	Review of post-marketing safety data	Based on review of post-authorization data, Eye pain and Eye swelling was determined not to be a risk for the vaccine.

					Assessment Report request prompted a review of the topic.		
Deaths including in elderly or frail individuals	18 Jan 2021	Closed	20 Jan 2021	Inquiry from a competent authority	Due to cluster of deaths in elderly and frail adults in Norway, as assessment of the cases was undertaken.	Review of post-authorization data and epidemiological safety data	Based on review of post-authorization data and epidemiology background data, death was determined not to be a risk for the vaccine.
Delayed Syncope	04 Feb 2021	Closed	24 Feb 2021	Competent authority (US-FDA) request for assessment	To determine if delayed syncope is a risk following the US-FDA request to provide an assessment of syncope occurring at least 1 day after vaccination.	Clinical study and safety database case review	Delayed syncope and loss of consciousness were evaluated, and it was determined that there is insufficient evidence to support a causal relationship to vaccine. The topic will continue to be monitored.
Hearing Loss and Tinnitus	08 Feb 2021	Closed	17 Feb 2021	Post-authorization reports and clinical safety data review. Note: Following internal review of hearing loss, the 2nd SMSR (with reporting period 01 January 2021 – 31 January 2021) EMA/PRAC final assessment requested review of hearing loss and tinnitus (Competent authority [EMA] request for assessment)	Cases of hearing loss were noted in clinical study C4591001 and in post-authorization reports.	Clinical study and safety database case series review Epidemiology observed vs expected analyses Note: Following receipt of the 2nd SMSR PRAC Final assessment report, Hearing loss was re-evaluated, and Tinnitus was evaluated	Following evaluation of reports and vaccine literature, it was determined that that the available data did not support a causal association with vaccine. The topic will continue to be monitored.

Immune Thrombocytopenia	21 Jan 2021 Re-opened 25 Feb 2021	Closed	Initially closed on 26 January 2021 After re-evaluation, closed on 08 Mar 2021	Inquiry from multiple competent authorities Signal re-opened following receipt of EMA/PRAC final assessment report of the 2nd SMSR (with reporting period 01 January 2021 – 31 January 2021) requesting a review of immune thrombocytopenia	To determine if thrombocytopenia is a risk of vaccination.	Review of clinical and non-clinical study data and review of post-authorization and epidemiological safety data	Following evaluation, it was determined that that the available data did not support a causal association with vaccine. The topic will continue to be closely monitored.
Seizure	01 Mar 2021	Ongoing at DLP of this ACO; closed on 06 May 2021	06 May 2021	Routine review of post-authorization neurological events Request from a health authority (Saudi Arabia)	To determine if seizure is a risk.	Clinical study and post-authorization safety database review	The available data do not support a causal association with the vaccine. The topic will continue to be monitored.
Reaction associated with dermal fillers[a]	02 Mar 2021	Closed	24 Mar 2021	Medical literature and enquiry from health authority (EMA/PRAC)	To determine if this use of BNT162b2 causes reactions in individuals who have had dermal fillers injected.	Literature, clinical study cases and post-authorization safety database case series review	The available data do not support a causal association with BNT162b2 at this time. This topic will continue to be monitored.
Delayed skin reactions	08 Mar 2021	Closed	24 Mar 2021	Medical literature and enquiry from health authority (UK MHRA)	To determine if delayed skin reactions are a risk of BNT162b2.	Literature and post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. This topic will continue to be monitored.
Thrombo-embolic events, including	12 Mar 2021	Closed	31 Mar 2021	Reports for other COVID-19 vaccines and request for	To determine if thromboembolic events, including those associated	Post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. The topic will continue to be closely monitored.

those associated with thrombocytopenia				evaluation from health authorities	with thrombocytopenia, are a risk of BNT162b2.		
Extensive swelling of vaccinated limb[a]	18 Mar 2021	Closed	06 Apr 2021	Request from health authority (The Netherlands, Lareb and EMA PRAC)	To determine if extensive limb swelling following vaccination is a risk of BNT162b2.	Post-authorization safety database case series review	The available data do not support a causal association with BNT162b2. This topic will continue to be closely monitored.
Herpes Zoster, including Ophthalmic herpes zoster	05 Oct 2020 as safety topic. Reopened 21 Feb 2021 Re-opened 26 Apr 2021	Ongoing at DLP of this ACO; closed on 30 April 2021	30 Apr 2021	Reports of herpes zoster in clinical studies and post-authorization AE reports on non-statistical line listing review	Initially opened as safety topic and closed as no risk following review of clinical study data (C4591001). To determine if herpes zoster including ophthalmic herpes zoster is a risk.	05 Oct 2020: Review of clinical study data 21 Feb 2021: Review of post-authorization safety and O/E analyses 30 Apr 2021: Review of post-authorization, clinical study and O/E data	The available data do not support a causal association with BNT162b2. The topic will continue to be monitored. The re-evaluation of this signal in April 2021 confirmed the above assessment.

ACO= Addendum to the Clinical Overview; ADR= Adverse Drug Reaction; AE= Adverse Event; CDS= Core Data Sheet; DLP= Data Lock Point; EMA= European Medicine Agency; EU= European Union; FDA= Food and Drug Administration; MHRA= Medicines and Healthcare Products Regulatory Agency ; MOH= Minister of Health; O/E= Observed vs Expected; PRAC= Pharmacovigilance Risk Assessment Committee ; PV= Pharmacovigilance; PVP= Pharmacovigilance Plan; RMP= Risk Management Plan; SmPC= Summary of Product Characteristics; SMSR= Summary Monthly Safety Report; US= United States

a. Variation (EMEA/H/C/005735/II/0038/G) has been submitted after DLP (on 19 May 2021) to add "Vaccine stress-related responses" to section 4.4 (Special warnings and precautions for use) and to add "Extensive swelling of the vaccinated limb" and "Facial swelling" to the EU SmPC section 4.8 (Undesirable effects).

PRAC comment:

Regarding the **ongoing signals** '*Myocarditis and Pericarditis*' and '*Dizziness*':

After the DLP of the ACO, section 4.4 of the SmPC has been updated with a warning for myocarditis and pericarditis (procedure IAIN/0050). Dizziness was included as part of 'stress-related responses associated with the process of vaccination' in section 4.4 of the SmPC. Myocarditis and Pericarditis were also added as ADRs in section 4.8 of the SmPC.

With regards to the **closed signals** for which signal closed is **accepted**:

Anaphylaxis: included as ADR in section 4.8 of the SmPC and added as important identified risk in the RMP. Signal closed is accepted.

Hypersensitivity reactions (other than anaphylaxis): included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G).
Signal closed is accepted.

Pain in extremity: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Vomiting: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Diarrhoea: included as ADR in section 4.8 of the SmPC (procedure Type II/0016/G). Signal closed is accepted.

Tachycardia: as part of a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. Signal closed is accepted.

Vaccine stress-related responses: a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. Signal closed is accepted.

Facial nerve palsy: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Insomnia: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Injection site pruritus: included as ADR in section 4.8 of the SmPC. Signal closed is accepted.

Overdose: based on review of post-authorisation medication errors of full vial dosing and co-reported adverse event in the 2nd MSSR, no significant new safety information was identified and no updates to the Overdose section of labelling was warranted. Signal closed is accepted.

Eye pain & Eye swelling: review of the cases reporting eye pain and/or eye swelling in the 2nd MSSR did not suggest a causal association with the Comirnaty vaccine. No update of the included ADRs in the Comirnaty SmPC was considered needed regarding eye pain and eye swelling. Closure of the signal concerning "Eye pain" and "Eye swelling" is accepted.

Hearing loss and Tinnitus: In the 3rd MSSR AR (covering 1 February until 28 February 2021), based on a cumulative review of the cases reporting hearing loss and/or tinnitus it was concluded that a causal association with Comirnaty exposure was not suggested and the signal was closed.

Seizure: under close monitoring as part of Neurological AESIs in the MSSRs. At the moment no new safety signal of seizure identified. Signal closed is accepted.

Reaction associated with dermal fillers: after the DLP of the ACO, Facial swelling (in vaccine recipients with a history of injection of dermatological fillers) has been added to section 4.8 of the SmPC (EMEA/H/C/005735/II/0038/G). Signal closed is accepted.

Delayed skin reactions: based on a review by the MAH of literature and cases reporting delayed skin reactions, a causal association was not supported. Signal closed is accepted.

Delayed syncope: following US-FDA request, delayed syncope and loss of consciousness were evaluated by the MAH. It was concluded that there is insufficient evidence to support a causal relationship to the vaccine. Signal closed is accepted.

Extensive swelling of vaccinated limb: after the DLP of the ACO, Extensive swelling of the vaccinated limb has been added to section 4.8 of the SmPC (EMEA/H/C/005735/II/0038/G). Signal closed is accepted.

The closed signals for which however further evaluation is **ongoing or requested in MSSR/PSUR** and therefore **cannot be considered closed** are the following:

Paraesthesia: as part of a warning about stress-related responses with the process of vaccination added to section 4.4. of the SmPC. This signal is closed, however, for the 8th MSSR (covering 1 July-31 July 2021) the MAH has been requested to provide an analysis of hypoaesthesia and paraesthesia and to discuss whether paraesthesia and hypoaesthesia are sufficiently covered in the product information in the context of stress-related reactions or these should be included in the product information as separate ADRs.

As an outcome of the review provided by the MAH in the 9th MSSR, PRAC did not agree that hypoesthesia/paraesthesia is sufficiently covered in the product information by the currently included text regarding stress-related reactions and requested the MAH to add hypoesthesia and paraesthesia to the product information (SmPC section 4.8 and PIL section 4) and to propose a frequency, via an appropriate variation procedure.

Asthenia, Lethargy, Decreased appetite, Hyperhidrosis, Night sweats: the CHMP adopted an Opinion on the 16th September 2021 to add as side effects to the product information of Comirnaty.

Deaths including elderly or frail individuals: no new safety information was identified based on review of the fatal cases (EMEA/H/C/005735/LEG/019). Death/fatal cases are reviewed in the MSSRs as a Special Situation.

Immune thrombocytopenia: a re-review of this signal is provided in the PSUR submitted in August 2021.

Thromboembolic events, including those associated with thrombocytopenia: at the moment, there is insufficient evidence to support a causal association. However, TTS (Thrombosis with Thrombocytopenia Syndrome) is an ongoing signal of the MSSR for Comirnaty. In addition, thromboembolic events are reviewed in the MSSRs as AESIs.

Herpes zoster, including ophthalmic herpes zoster: it should be noted that following assessment of the 7th MSSR, the MAH was requested to provide an analysis of herpes zoster and discuss possible mechanisms that could underpin herpes zoster reactivation following vaccination, in the PSUR submitted in August 2021.

Risk Evaluation

Summary of Safety Concerns

Safety Concerns at the beginning of the reporting period

Important Identified Risk	Anaphylaxis[a]
Important Potential Risk	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)[a,b]
Missing Information	Use in Pregnancy and While Breast Feeding[a,b]
	Use in Immunocompromised Patients[a]
	Use in Frail Patients With Co-Morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular disorders)[a]
	Use in Patients With Autoimmune or Inflammatory Disorders[a]
	Interaction With Other Vaccines[a]
	Long-Term Safety Data[a]
	Use in Paediatric Individuals <16 Years of Age[b]
	Vaccine Effectiveness[b]

a. As per EU RMP ver. 1.0 (dated 21 December 2020).
b. As per the EUA PVP ver. 0.2 (dated 05 December 2021).

During the reporting period, the EU RMP has been updated as follows:

- EU RMP version 1.0 (dated 21 December 2021, when the initial marketing authorization was granted) was updated during the reporting period (EU RMP version 1.1, dated 17 March 2021 and approved on 15 April 2021), to revise the post-authorization vaccine effectiveness study C4591014 included in the RMP (Category 3) as a commitment and to add 2 vaccine effectiveness epidemiology studies (WI235284 and WI255886) not sponsored by Pfizer.
- After DLP of this ACO, on 4 May 2021 and on 14 May 2021, EU RMP version 2.0 (dated 29 April 2021) and version 2.1 (dated 14 May 2021) were submitted.

  EU RMP version 2.0 was submitted on 30 April 2021 with Variation 0030 to seek for extension of the indication to individuals aged 12-15 years of age; on 28 May 2021, EMA CHMP recommended granting the extension of indication for use in children aged 12-15 years and the European Commission adopted a decision accordingly on 31 May 2021.

  EU RMP version 2.1 has been submitted in the context of Variation 0036.

No changes to the list of the safety concerns were implemented in the above stated EU RMPs during and after the reporting period of this ACO.

PRAC comment:

Based on the data submitted with the renewal application, no changes are warranted for the RMP.

At the end of the interval period, the missing information "*Use in pediatric individuals <16 years of age*" was re-worded to "*Use in paediatric individuals <12 years of age",* which is only applicable for the EUA US PVP.

Furthermore, the CHMP adopted an Opinion on the 16th September 2021 for the EMEA/H/C/005735/II/0036 variation in which the RMP version 2.2 was approved.

3.4. Pharmacovigilance inspections

During the renewal period, the following inspection of MAH's pharmacovigilance system was conducted:

Inspecting Authority	Site Inspected	Inspection Start Date	Inspection End Date	Type of Inspection	Impact of findings on benefit/risk balance of BNT162b2
Swissmedic	Pfizer Switzerland Office (Virtual)	8 March 2021	9 March 2021	Routine Pharmacovigilance Inspection	None of the findings impacts the B/R of BNT162b2

PRAC comment:

The MAH was requested to provide the findings of the inspection performed by Swissmedic. (**Request for Supplementary Information**)

4. Risk management plan

The MAH has confirmed the current approved RMP remains unchanged and applicable.

Since the granting of the marketing authorisation, the following changes have been implemented in the RMP:

- Revision of the Pharmacovigilance Plan, including updates on milestones, objectives, study rationale and design;
- Revision of the post-authorization vaccine effectiveness study C4591014 and addition of 2 new vaccine effectiveness epidemiology studies;
- Update of the indication to include individuals aged 12-15 years, with supporting epidemiology and exposure data;
- Inclusion of myocarditis and pericarditis as important identified risks, with supporting data from clinical trials and safety databases and update of the information on planned/ongoing post-authorization safety studies with inclusion of 2 new studies, and the circulation of a DHPC;
- Inclusion of a new formulation and update on potential medication errors.

5. Changes to the Product Information

No changes to the Product Information (PI) are introduced with this renewal procedure.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Comirnaty (COVID-19 mRNA vaccine

(nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

The summary of product characteristics and the package leaflet therefore includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle

6. Request for Supplementary Information - RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI:

6.1. Other concerns

Clinical aspects

1. The MAH is requested to provide the findings of the inspection performed on 8-9 March 2021 by Swissmedic.
2. The MAH is requested to explain what "BNT162S017" is compared to BNT162b1 and BNT162b2.

7. Assessment of the MAH responses to the RfSI

7.1. Other concerns

Clinical aspects

Question 1

The MAH is requested to provide the findings of the inspection performed on 8-9 March 2021 by Swissmedic.

Summary of the MAH's response

The findings of the inspection performed on 8-9 March 2021 by Swissmedic can be found in the audit report herewith submitted as attachment to the cover letter. The audit report is a redacted copy of the final Pfizer response (redacted inspector names and Pfizer names for privacy), also you will notice there are track changes in the report as Swissmedic had asked for updated responses to be tracked in the final response as accepted by Swissmedic. Additionally, please note that this audit report contains information that is considered confidential by Pfizer..

Assessment of the MAH's response

As requested, the MAH provided the findings of the inspection performed by Swissmedic on 8-9 March 2021. It is acknowledged that the content of the audit report is confidential and therefore is not

presented in this assessment report. In the context of the MSSR assessment, several comments have been made regarding the handling and presentation of data. The inspection from Swissmedic did not raise additional issues relevant for the EU.

Conclusion

Issue is solved.

Question 2

The MAH is requested to explain what "BNT162S017" is compared to BNT162b1 and BNT162b2.

Summary of the MAH's response

The code BNT162S017 reported on page 12 of the Addendum to the Clinical Overview submitted in the renewal application results from a typo and should be read as BNT162b2s01.

The figure 7 at the end of the code refers to the footnote 7 where it is stated that BNT162S01 is also named BNT162SA. In the same footnote (footnote 7, Page 12) BNT162SA should read as BNT162b2SA.

Both these codes (BNT162b2s01 and BNT162b2SA, in the submitted ACO erroneously reported as BNT162S01 and BNT162SA) refer to the same clinical candidate, a new construct based on BNT162b2 and modified to address the B.1.351 lineage, first identified in South Africa. This clinical vaccine candidate has been introduced in study C4591001 / BNT162-02 as part of the global program to address emerging variants.

Assessment of the MAH's response

The code "BNT162S017" was a typo and should be BNT162b2s01, also named BNT162b2SA , which is explained as a new construct based on BNT162b2 and modified to address the B.1.351 lineage, first identified in South Africa. This is noted.

Conclusion

Issue is solved.

8. Overall conclusions and benefit-risk balance

8.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal, data on the Quality Specific Obligations (SOBs) have been submitted. Interim reports and monthly updates have been provided as requested.

Regarding the Quality SOB 003: *In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data,* on the 20th May 2021, following the assessment of additional validation data (provided in variation EMEA/H/C/005735/II/0023/G), the CHMP was of the opinion that the obligation had been fulfilled, and therefore recommended its deletion from the Annex II.

For the Quality SOB 001, SOB 002, SOB 004 and SOB 005 the due date was July 2021. On 27 July and 2 August 2021 respectively, the MAH submitted two variations (EMEA/H/C/005735/II/0054/G and EMEA/H/C/005735/II/0056/G) to provide the additional data requested to fulfil these SOBs. These variations are currently under assessment by CHMP and Requests for Further Information have been adopted on 14 October 2021.

During the period covered by this annual renewal interim data on the clinical SOB 006 have been submitted that overall are compliant in terms of adherence to deadlines and in terms of acceptability of data submitted. The available clinical evidence includes a tolerable safety profile and high vaccine efficacy against COVID-19 in individuals ≥12 years of age.

Updated list of specific obligations (SOBs)

In the framework of a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Number	Description	Due date
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

8.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the established benefit-risk balance of Comirnaty in the approved indication.

The data collected as part of the specific obligations for Comirnaty during the period covered by this annual renewal support its positive benefit-risk balance in the approved indication.

Favourable effects

The favourable effects were demonstrated in the initial marketing authorisation for persons 16 years of age and older and updated in a type II variation to also include adolescents 12-15 years of age. No additional efficacy data have been submitted during this renewal procedure. The most important favourable effects are briefly summarised below.

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

The efficacy of the vaccine (BNT162b2, 2 doses of 30 µg, separated by 21 days) to prevent COVID-19 in the adolescents aged 12- 15 years either without or with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 100.0% (CI95% 75.3, 100).

In addition, Comirnaty was shown to elicit non-inferior immune responses in subjects 12-15 years of age without previous Covid-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2.

Uncertainties and limitations about favourable effects

The uncertainties and limitations of favourable effects are similar to those at the time of the initial assessment and were updated in variation EMEA/H/C/005735/II/0030 (12-15-year-old subjects). The principal uncertainties remain on duration of protection and efficacy in risk groups, e.g. pregnant women and immunocompromised subjects. Since the initial approval, uncertainty regarding the vaccine efficacy against upcoming virus variants of concern has arisen with variants of concern (VOC) emergence.

Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty in the initial approval application. Overall, the safety profile of Comirnaty is considered acceptable. The product information has been updated since approval as new data has emerged. All data have been assessed in other procedures such as monthly safety updates, signal assessments and variations.

Uncertainties and limitations about unfavourable effects

The uncertainties and limitations of unfavourable effects have been discussed in other procedures. The principal uncertainties are related to long-term effects, and effects in specific risk groups.

Benefit-risk assessment and discussion

The benefits of Comirnaty in terms of protection against COVID-19 clearly outweigh the identified risks, and no new information has emerged during this renewal period that has changed the balance. The clinical SOBs are currently ongoing, according to plan. The quality related SOBs are also considered either fulfilled or ongoing according to plan.

Importance of favourable and unfavourable effects

Not Applicable.

Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk balance of Comirnaty remains positive.

9. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the marketing authorisation holder has complied with the specific obligations and the benefit-risk balance for Comirnaty in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable, and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

The renewal requires no amendments to the terms of the marketing authorisation.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific obligations to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

10. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional marketing authorisation for Comirnaty, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

Please refer to Scientific Discussion 'Comirnaty/H/C/005735/R/0046'

Productie 49

Pages of suspected side effects released about Pfizer's COVID-19 vaccine 'may not have any causal relationship' to the jab, company says

By Reuters Fact Check
March 17, 20222:59 PM GMT+1Updated 2 years ago

Nine pages of adverse event reports from Pfizer-BioNTech in relation to its COVID-19 vaccine are not confirmed adverse events to the shot. They "may not have any causal relationship" to each other, the pharmaceutical company has told Reuters. The statement comes in response to claims online that the list is definitive.

The document was submitted by Pfizer as part of its Biological License Application (BLA) to the United States Federal Drug Administration (FDA) (here).

It compiled data from 63 countries such as the U.S., UK, Italy, Germany and France received between Dec. 1, 2020 and Feb. 28, 2021 – and includes nine pages of "adverse events of special interest".

Examples of such events are difficult breathing, déjà vu and myocardial infarction, as well as 1,223 events with a fatal outcome (here).

Some people on social media have since concluded that every entry is definitively caused by Pfizer's COVID-19 vaccine.

One post, which includes screenshots of all nine pages (here) and has been shared hundreds of times, reads: "Amongst these newly released pages are 9 PAGES OF ADVERSE SIDE-EFFECTS! The list includes auto-immune conditions, multitudinous heart issues, hemorrhaging, kidney disease, many syndromes relayed to other viruses, and even anti-sperm antibodies! Safe and effective, right...?"

Similar posts can be seen on Facebook (here, here, here, here and here)) and Twitter (here and here).

However, the list was compiled using voluntary reports through various national reporting systems, such as the U.S. Vaccine Adverse Event Reporting System (VAERS), the UK's Yellow Card reporting scheme and the EU's EudraVigilance database.

Reuters has produced numerous fact checks on these systems (VAERS: here and here; Yellow Card: here and here); EudraVigilance here and here) - all of which explain that reports of potential side-effects are not definitively linked to vaccines.

A Pfizer spokesperson told Reuters that reported side effects "may not have any causal relationship to the vaccine", adding that all reports are taken "very seriously".

"Rather, the event may be due to an underlying disease or some other factor such as past medical history or concomitant medication or the AEs (adverse events) may be coincidental," they said.

AEs are collected for all Pfizer's products – including its COVID-19 vaccine – to monitor safety issues that might not have been flagged in clinical studies.

The spokesperson explained that the company has "robust processes" in place to assess the potential safety risks of every product and to ensure post-authorisation responsibilities are met.

"In addition to our pharmacovigilance efforts and compliance with various regulatory requirements related to quality and safety, we also cooperate with the FDA and regulatory authorities around the world as they independently monitor the safety profile of our vaccine," they said.

A spokesperson for the FDA told Reuters that reports to VAERS post-vaccination "do not necessarily mean that a vaccine caused a health problem" – and anyone can submit a report, regardless of plausibility.

The FDA spokesperson added: "In fact, reviews by FDA and CDC have determined that the vast majority of the deaths reported are not directly attributable to the vaccines. FDA requires healthcare providers to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause."

They also explained that VAERS is an "early warning system" that is used to establish any issues with vaccines or medicines that may have been missed before they were licenced. This means, Pfizer would not have known about the suspected AEs prior to licensure.

Likewise, a spokesperson for the European Medicines Agency (EMA) told Reuters that reports of suspected side effects from COVID-19 vaccines by patients and healthcare professionals "are not necessarily related to or caused by the vaccine".

"Spontaneous case reports of suspected adverse reactions alone are rarely sufficient to prove that a certain suspected reaction has indeed been caused by a specific medicine. This could be a symptom of another illness, or it could be associated with another medicinal product taken by the patient at the same time. Hence, a case report should be seen as a piece of a jigsaw puzzle."

They added: "For most medicines, the vast majority of suspected side effects are not eventually confirmed as side effects."

Missing context. The nine pages of "adverse events of special interest" are not confirmed side effects from Pfizer's COVID-19 vaccine.

This article was produced by the Reuters Fact Check team. Read more about our fact-checking work here.

Productie 50

Bourla-50
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Parliamentary question - E-001537/2023(ASW)

European Parliament

Answer given by Ms Kyriakides on behalf of the European Commission

3.7.2023

Written question

As for any other medicinal products authorised in the EU, once a COVID-19 vaccine has received approval, each vaccine batch can only be released following quality control testing to confirm that the product is in line with the specifications that were approved as part of the respective marketing authorisation.

This control is carried out by the manufacturer. However, for most centrally authorised vaccines, the EU legislation requires that a Member State Official Medicines Control Laboratory performs an additional independent control for each batch before it is put on the EU market.

This independent control is referred to as Official Control Authority Batch Release testing and includes testing of agreed quality parameters and a compliance check of the manufacturer's own test results.

The Danish study looked at a potential link between serious adverse events cases and vaccine batch labels reported to the Danish Medicines Agency.

As highlighted by the authors themselves, there are several limitations when carrying out a study on data from passive surveillance such as this one.

Pharmacovigilance systems are in place to monitor the suspected adverse reactions (AR), which include medical literature monitoring and a product quality issue detection algorithm to detect safety issues potentially related to quality.

As regards literature monitoring, if various sources of information point to a potential issue more in-depth review is initiated. This was not the case for the mentioned Danish study.

In addition to the limitations mentioned in the study, analyses performed by the European Medicines Agency on the batches reported in suspected AR cases did not reveal an increased risk of side effects for specific batches.

Productie 51

COVID-19 vaccines: development, evaluation, approval and monitoring

Share

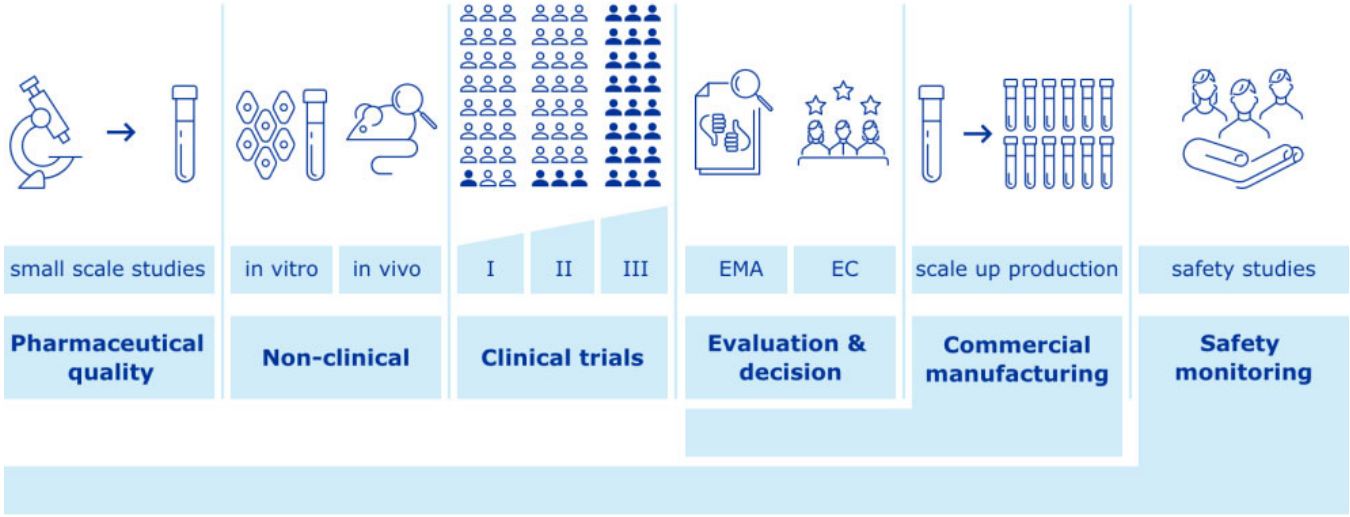
The European Medicines Agency (EMA) plays an important role in enabling the development, scientific evaluation, approval and monitoring of COVID-19 vaccines in the European Union (EU).

Human COVID-19 Vaccines

EMA published the information on this page for use during the COVID-19 public health emergency. EMA is no longer updating this page.

Vaccines for COVID-19 are developed, evaluated and approved according to current scientific knowledge and applicable regulatory guidelines and legal requirements.

Figure 1: Overview of vaccine development and approval stages



Development

Like all medicines, COVID-19 vaccines are first tested in the **laboratory** (e.g. studies on their pharmaceutical quality and studies to check first the effects in laboratory tests and animals).

Vaccines are then tested in human **volunteers** in studies called clinical trials. These tests help confirm how the vaccines work and, importantly, to evaluate their **safety** and protective **efficacy**.

Standard vaccine development

Standard vaccine development is a long process and studies are done in sequential steps.

Companies first make **small batches** and do small scale studies to characterise and optimise the production process. They perform studies to determinate a suitable formulation that can keep vaccine components **stable** to the end of its shelf life.

Then the company decides whether to continue development and scale up production. To assure that the vaccine meets its intended quality profile and complies with regulatory standards, the company develops a suitable and effective **quality control** strategy.

Studies on pharmaceutical quality look at the individual vaccine components, the final formulation to be used and at the whole **manufacturing process** in detail.

The vaccine developer conducts more studies in laboratory models, using **in vitro** studies (e.g. cells in culture) or animal models (**in vivo** studies), to show how the vaccine triggers an immune response and works to prevent infection.

Finally, the vaccine developer studies the vaccine in three phases of **clinical trials**, with larger numbers of volunteers in each phase.

For approval, companies must also show that large scale **commercial manufacturing** consistently produces vaccines of the required quality.

Scaling up production and adaptations to commercial manufacturing can continue in the post-authorisation phase.

Did you know..?

Clinical trials in human medicines, including those for COVID-19 vaccines, are authorised and managed at national level in the EU. National competent

authorities and **ethics committees** ensure that studies are scientifically sound and conducted in an ethical manner.

Human pharmacology studies (phase I trials) generally involve between 20 and 100 healthy volunteers to confirm if the medicine behaves as expected based on laboratory tests. This can establish:

- if the vaccine triggers the expected immune response;
- if the vaccine is safe to move into larger studies;
- which doses can be adequate.

Therapeutic exploratory studies (phase II trials) involve several hundred volunteers. The purpose of this phase is to study the best **doses** to use, the most common **side effects** and how many doses are needed.

These studies also check that the vaccine triggers a good immune response in a broader population. In certain cases, it could also provide some preliminary indications of how well the vaccine will work (efficacy).

Clinical efficacy and safety studies (phase III trials) include thousands of volunteers. This phase shows how **efficacious** the vaccine is at protecting against the infection compared with placebo (dummy) or alternative treatment and what are the less common side effects in those receiving the investigational vaccine.

The reduction in number of people with symptoms, severe disease or diagnosed with the infection can help to measure the efficacy of the vaccine.

For information on **ongoing COVID-19 clinical trials** in the European Economic Area (EEA), see:

- Clinical trials in human medicines
- Approval of vaccines in the European Union: European Vaccination Information Portal

- Authorisation of medicines

Fast-track vaccine development in a public health emergency

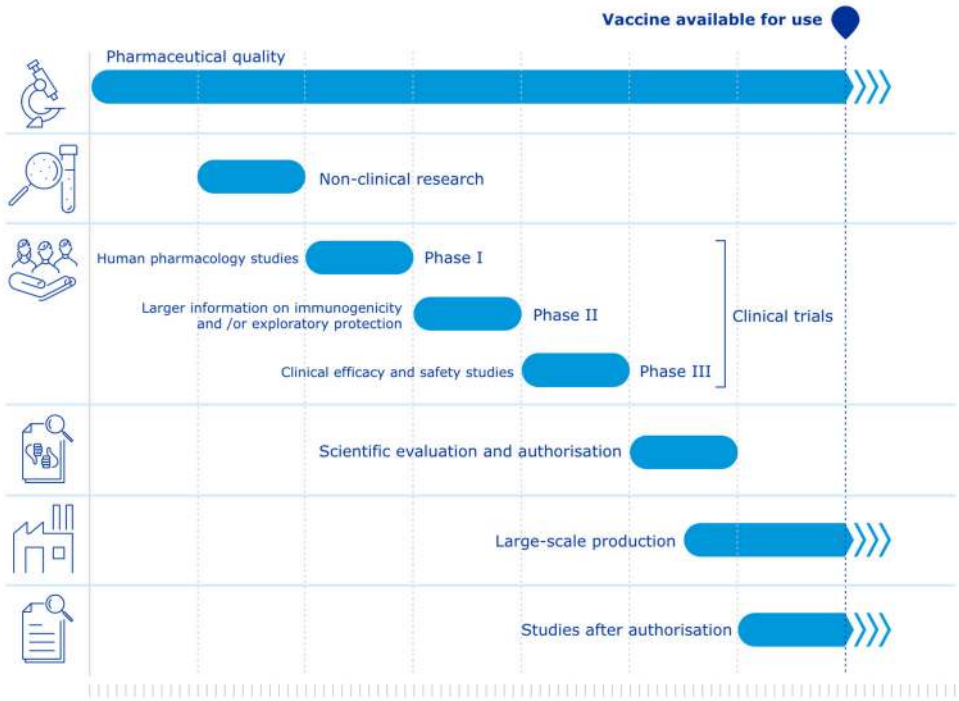
Vaccine development for COVID-19 vaccines continues to be fast-tracked globally. Development is compressed in time, applying the extensive knowledge on vaccine production gained with existing vaccines.

Early **scientific advice** from regulators helps speed up development. EMA additionally offers informal consultation with its COVID-19 Task Force (ETF) and rapid scientific advice. COVID-19 vaccine developers can receive prompt guidance and direction on the best methods and **study designs** to generate robust **data**. For more information, see:

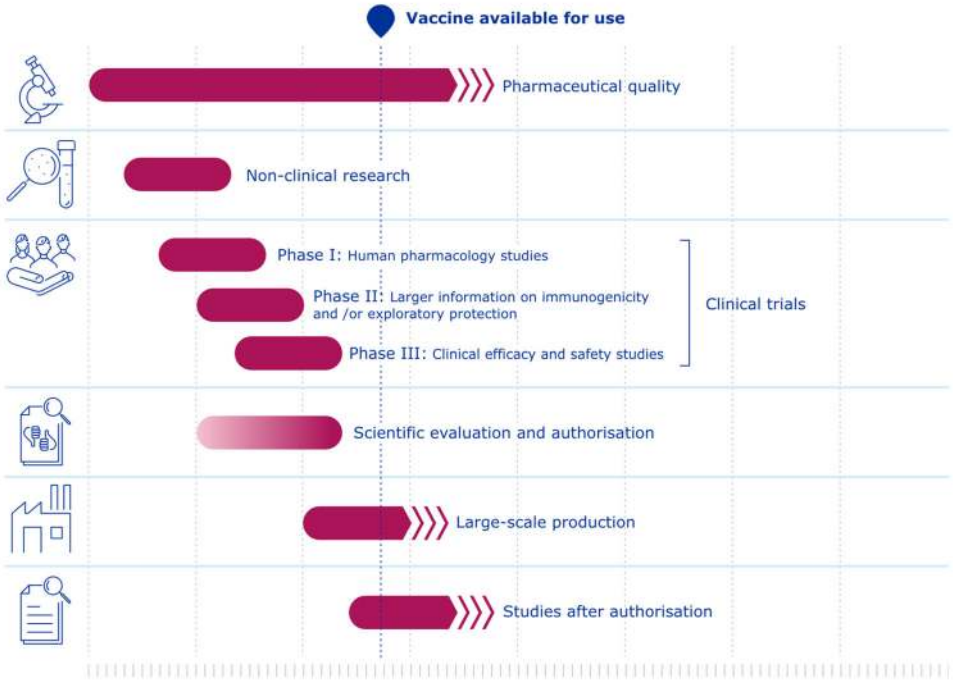
- Early support for medicine and vaccine developers
- COVID-19 medicines that have received EMA advice

Advising companies on regulatory requirements helps ensure that standards of **quality**, **safety** and **efficacy** are embedded early in the process and are taken into consideration when planning fast track development. Channeling resources and efforts at various levels ensures that high standards are maintained in the development and in the assessment of the dossiers.

Figure 2: Indicative timelines for COVID-19 vaccines compared with standard vaccines



Standard vaccines



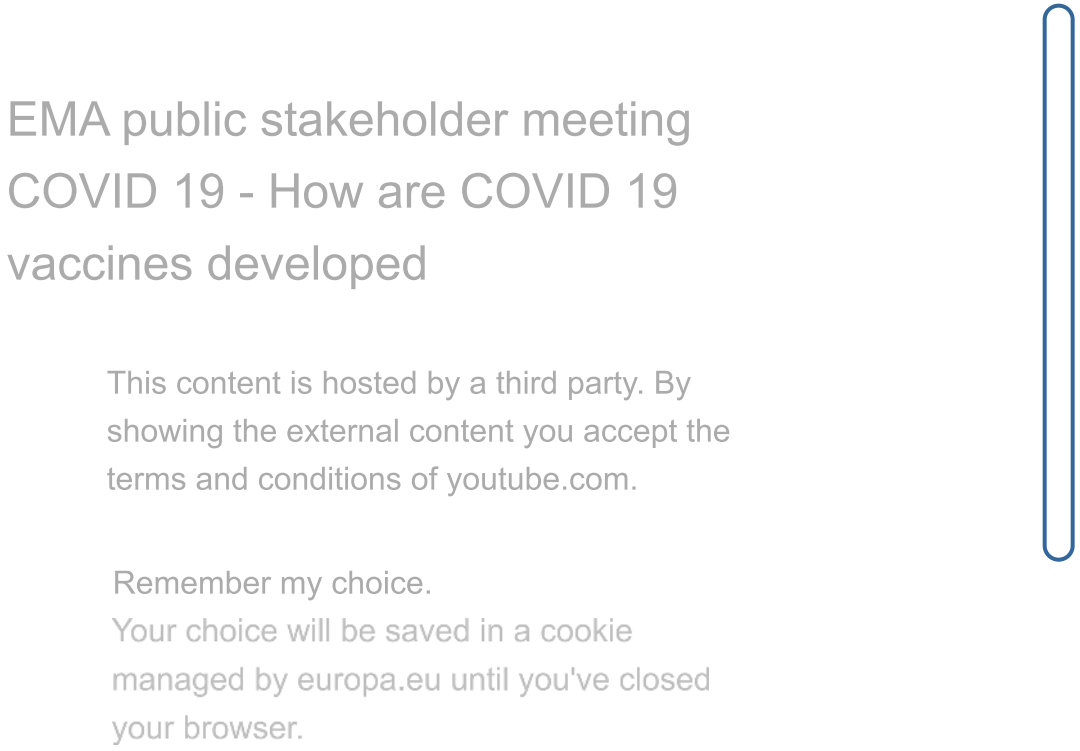
COVID-19 vaccines

Vaccine manufacturers and academics use established **production systems** already used for **safe and effective vaccines**. In addition, they continuously research novel approaches to producing and developing vaccines, and some of the advances made to date are also applied to developing vaccines for COVID-19.

Some vaccines for COVID-19 are developed using **novel methods** intended to increase the **volume** and **speed of production** compared to other types of vaccines, enhance product stability and bring about strong immune responses.

Other vaccines are developed using existing methods used for vaccines for other diseases, making it easier to use **existing production facilities** to produce

COVID-19 vaccines at a large scale.



Companies may use various approaches to reduce **development timelines while ensuring high standards and adherence to legal requirements**, such as:

- mobilising more human resources simultaneously to analyse results from earlier studies more quickly and map out next steps in terms of resources, funding and regulatory strategy;
- combining clinical trial phases or conducting some studies in parallel where safe to do so.

Companies have also expanded **manufacturingcapacity** and large-scale production to facilitate **vaccine deployment** without delay once approved. In the

EU, the European Commission has provided support to facilitate vaccine development and deployment as quickly as possible.

Some vaccine developers started **manufacturing** their COVID-19 vaccine before obtaining an EU marketing authorisation. This allowed them to be ready to **distribute** doses rapidly enough to meet demand once they were authorised.

Developers must still uphold the same **good manufacturing practice** (GMP) standards that apply in the EU to all vaccines.

All pharmaceutical manufacturers need a **manufacturing licence** from the national competent authority where they operate. National competent authorities carry out **GMP inspections** to check that manufacturers comply with EU standards, the conditions of their licence and the marketing authorisation if obtained.

The European medicines regulatory network has sped up the approval of new **manufacturing lines** and **manufacturing sites** for COVID-19 vaccines. The EU's labelling and packaging requirements are also more flexible for COVID-19 vaccines to enable rapid roll-out.

For more information, see:

- COVID-19 medicines
- Good manufacturing practice
- COVID-19 guidance: assessment and marketing authorisation - Labelling flexibilities for COVID-19 vaccines
- European Commission - HERA Incubator to anticipate the threat of coronavirus variants

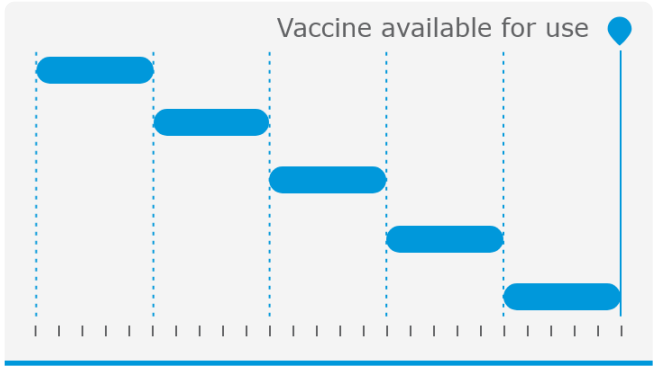
Figure 3: Key components of vaccine development - standard vaccines compared with COVID-19 vaccines

Regulatory standards

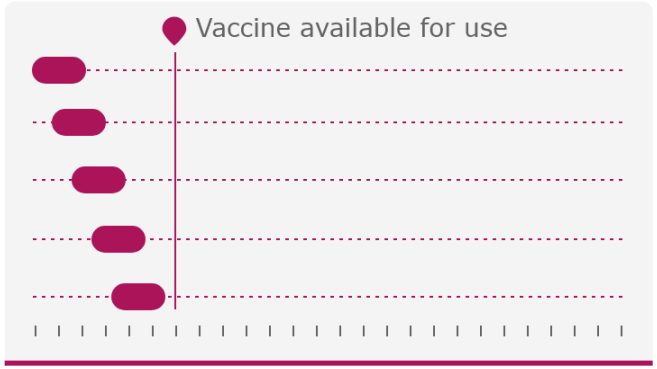
COVID-19 vaccines must be approved according to the same standards that apply to all medicines in the EU

Development

COVID-19 vaccine development is compressed in time, applying the extensive current knowledge on vaccine development.



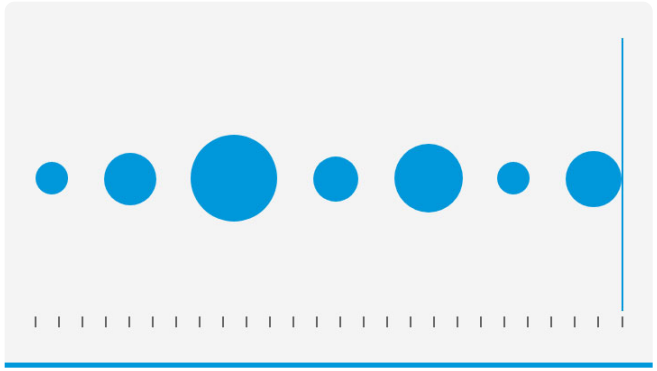
Standard vaccines



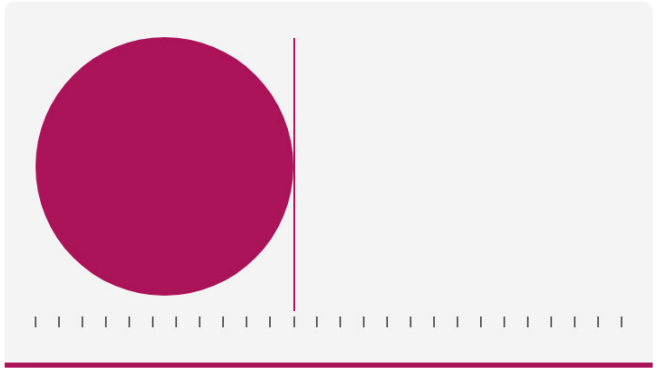
COVID-19 vaccines

Resources

COVID-19 vaccine development mobilises more resources simultaneously.



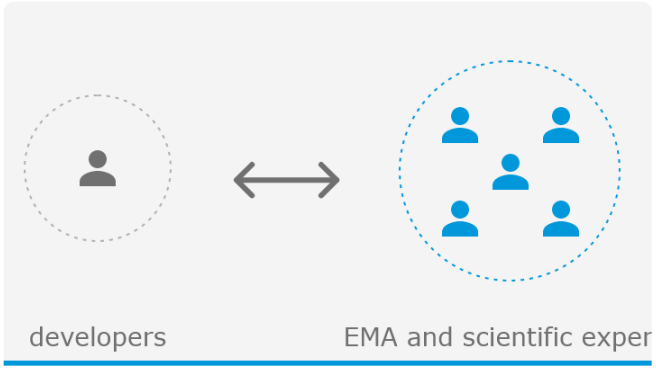
Standard vaccines



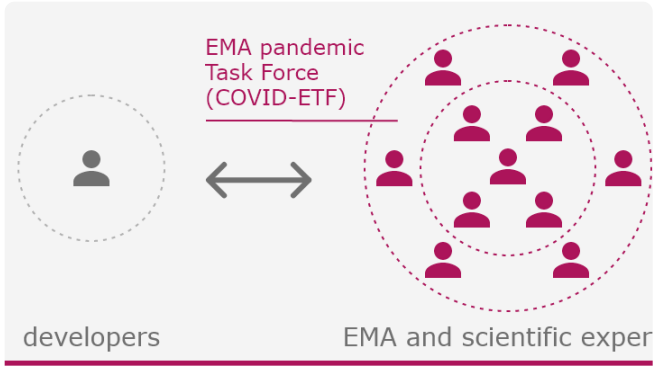
COVID-19 vaccines

Continuous dialogue

COVID-19 vaccine development is supported by early, continuous dialogue between developers and a dedicated group of regulatory experts.



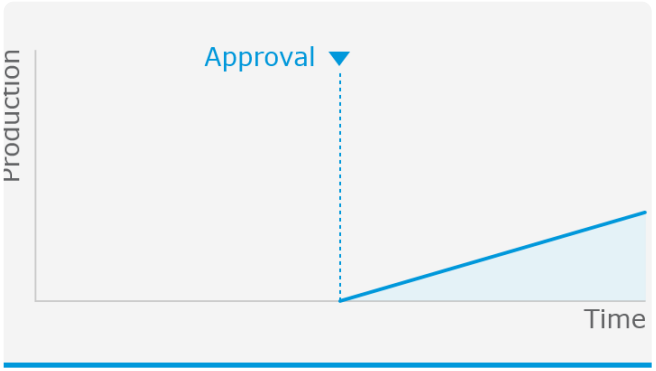
Standard vaccines



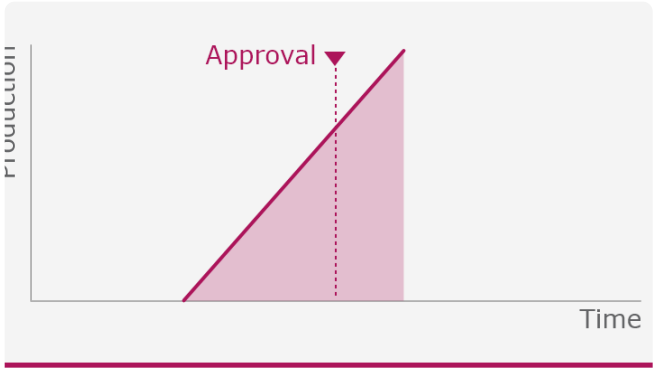
COVID-19 vaccines

Manufacturing

Companies are expanding manufacturing and production capacity to ensure efficient vaccine deployment.



Standard vaccines



COVID-19 vaccines

Did you know..?

EMA is not involved in providing **incentives** to developers of COVID-19 vaccines, other than enabling access to regulatory procedures, such as providing free scientific advice for vaccine development. EMA also has no role in negotiating potential **vaccine availability**, funding or deployment at EU or national level.

For more information on these topics, see:

- European Commission: Safe COVID-19 vaccines for Europeans
- Decisions on vaccines in use in different European countries: European Vaccination Information Portal

Scientific evaluation and approval

COVID-19 vaccines can only be approved and used if they comply with all the requirements of **quality**, **safety** and **efficacy** set out in the EU pharmaceutical legislation. For more information, see Authorisation of medicines.

In view of the pandemic, EMA and regulatory agencies in Europe are diverting **resources** to speed up processes and reduce **timelines** for the evaluation and authorisation of COVID-19 vaccines.

EMA public stakeholder meeting COVID 19 - EU’s regulatory process for evaluation and approval

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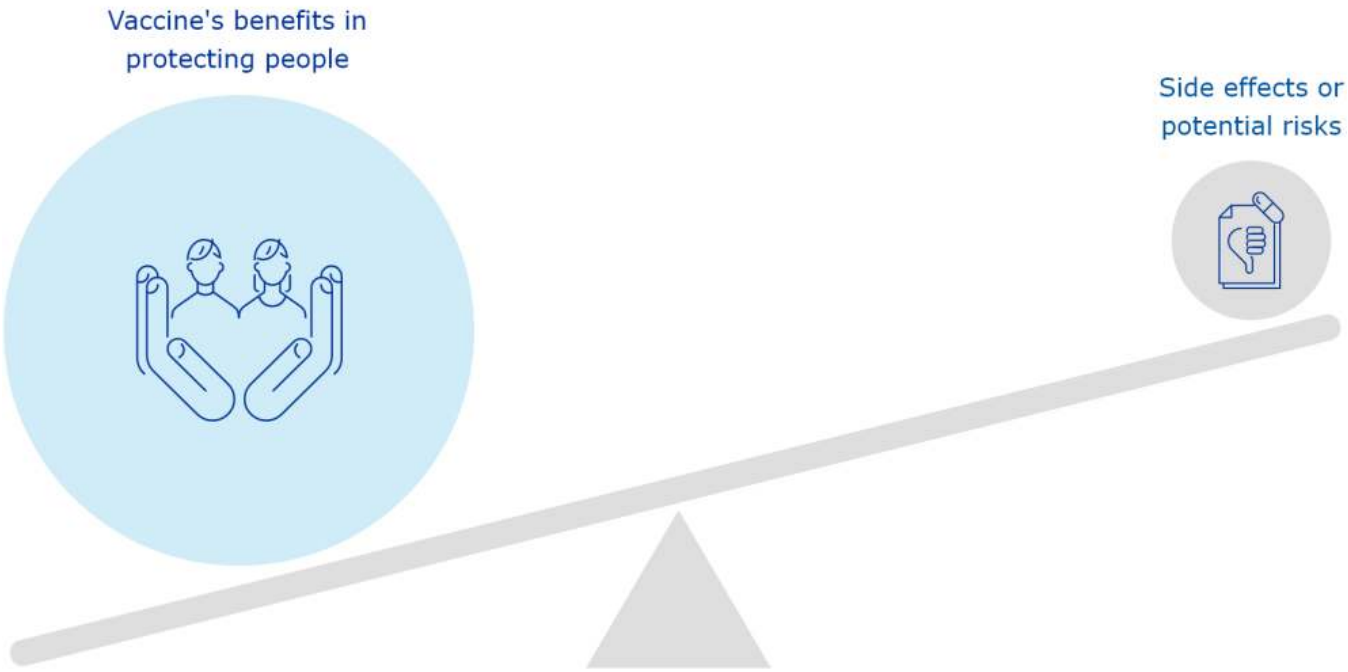
Robust regulatory framework and scientific expertise in the EU

The EU’s pharmaceutical legislation ensures that vaccines are only approved after scientific evaluation has demonstrated that their overall benefits outweigh their risks.

A vaccine's benefits in protecting people against COVID-19 must be far greater than any **side effect** or potential risks.



EMA ensures that scientific **experts** evaluating medicines do not have any financial or other interests that could affect their impartiality. For more information see Handling competing interests.

A high level of transparency, which opens EMA's scientific evaluation work to public scrutiny, safeguards the **independence** of EMA's scientific evaluations. For more information, see Transparency: exceptional measures for COVID-19 medicines.

Scientific evaluation and approval processes

To gain approval for a vaccine in the EU, the vaccine developer submits the results of all testing / investigations to the medicines regulatory authorities in Europe. This is part of a marketing authorisation application.

Figure 4: Evaluation and approval steps for COVID-19 vaccines

Approval steps:	Who is involved:	
Marketing authorisation application	**Vaccine developers**	Submit the results of all testing to the medicines regulatory authorities in Europe
EMA's evaluation and scientific opinion	**EMA scientific experts (CHMP, PRAC)**	Carry out scientific evaluation of vaccines
	EMA pandemic Task Force (COVID-ETF)	Enables EU Member States and the European Commission to take quick and coordinated regulatory action on the development, authorisation and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19
European Commission review and authorisation	**European Commission**	Reviews EMA's scientific opinion and grants an EU-wide marketing authorisation in case of a positive outcome
Vaccine adoption in national healthcare systems	**National authorities**	Decide on introduction of the newly approved vaccine and vaccination policies

Most COVID-19 vaccines in the EU will be evaluated by EMA via the centralised procedure (which is mandatory for any vaccine using **biotechnology**).

EMA's expert scientific committees on human medicines (CHMP and PRAC) carry out EMA's evaluations. EMA has set up the multidisciplinary COVID-19 EMA pandemic Task Force (COVID-ETF) bringing together key experts from across the European medicines regulatory network to ensure a fast and coordinated response to the pandemic.

EMA also collaborates with international experts during the review of COVID-19 vaccines through the OPEN initiative, launched in December 2020. OPEN allows non-EU regulators from Australia, Canada, Japan, Switzerland, as well as WHO, to take part as observers in the scientific evaluation of EMA's ETF and CHMP, while maintaining their scientific and regulatory independence.

For more information see:

- The evaluation of medicines, step-by-step
- Authorisation of medicines
- From laboratory to patient: the journey of a centrally authorised medicine
- Committees, working parties and other groups
- EMA COVID-19 assessments 'OPEN' to non-EU regulators (04/02/2021)
- World Health Organization (WHO)

Did you know..?

A vaccine is introduced into national healthcare systems only after regulatory approval and thorough quality control. The details differ for each EU Member State but each batch released onto the EU market is always tested prior to release.

Stringent **testing** is done by the company holding the marketing authorisation and batches must meet the specifications approved by authorities.

For vaccines used in public health **immunisation programmes**, an official medicines control laboratory performs an additional independent control for each batch of vaccine. This independent control is referred to as Official Control Authority Batch Release (OCABR) and includes testing of agreed quality parameters and compliance check of the manufacturer's own test results.

For more information, see:

- European Directorate for the Quality of Medicines
- European Vaccination Information Portal

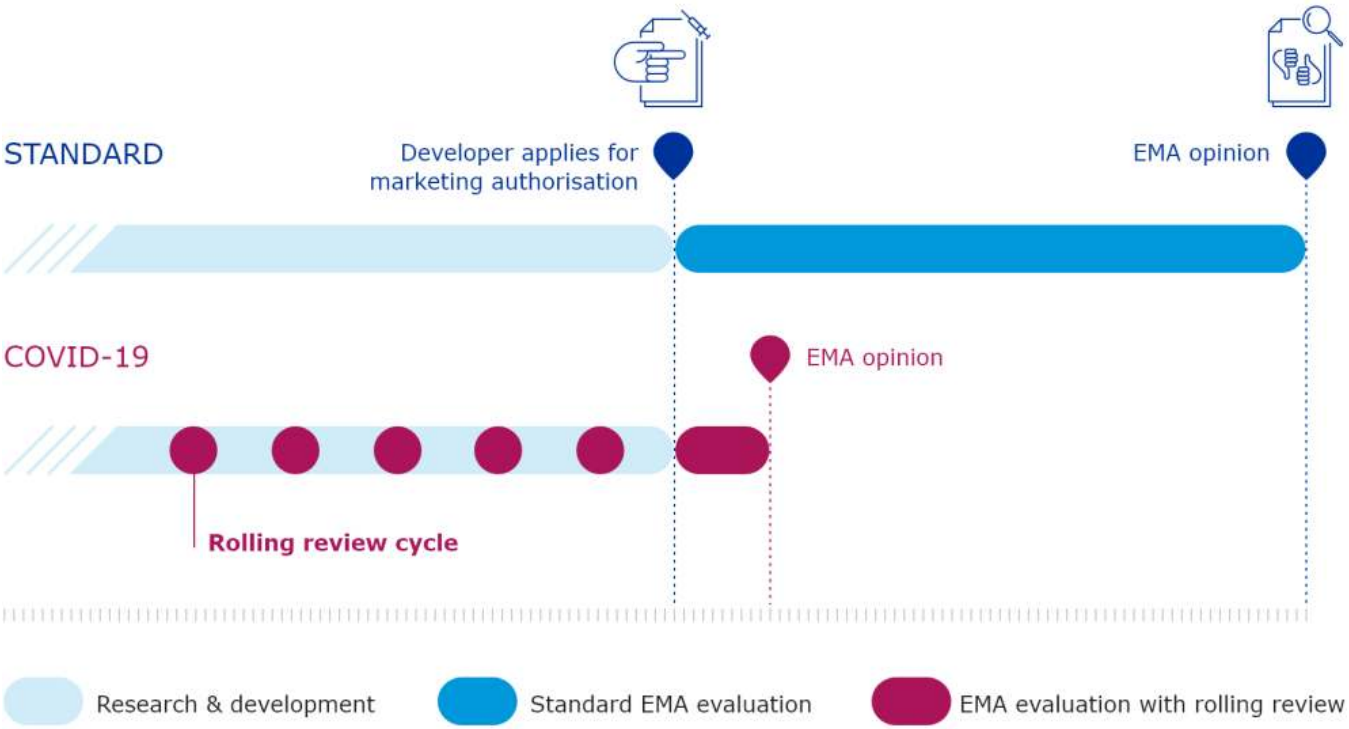
Accelerated evaluation

According to the EU pharmaceutical legislation, the standard timeline for the evaluation of a medicine is a maximum of 210 active days.

However, EMA treats marketing authorisation applications for COVID-19 products in an expedited manner. This allows the timeline for evaluation to be reduced to less than 150 working days.

For this scope, EMA can use its rolling review procedure for promising medicines for COVID-19. This allows EMA to begin assessing data as they become available during the development process, to expedite the subsequent formal marketing authorisation application assessment even further.

Figure 5: Standard evaluation process compared with rolling review of COVID-19 vaccines



When an evaluation is complete, EMA has the option of recommending a conditional marketing authorisation, a type of approval for medicines addressing unmet medical needs, and in particular those to be used in emergency situations in response to public health threats recognised by the WHO or the EU.

For more information, see Accelerated procedures for COVID-19 treatments and vaccines.

Did you know..?

A **conditional marketing authorisation** guarantees that the approved vaccine:

- meets rigorous EU standards for safety, efficacy and quality

- is manufactured and controlled in approved, certified facilities in line with high pharmaceutical standards that are compatible with large-scale commercialisation.

Conditional marketing authorisation is a tool that allows regulators to approve a medicine quickly and in a pragmatic manner when there is an urgent need.

A conditional marketing authorisation is different from an **emergency use authorisation**, which some countries use to permit the temporary use of an unauthorised medicine in an emergency situation. An emergency use authorisation is not a marketing authorisation.

EU legislation foresees that conditional marketing authorisation is used as the fast-track authorisation procedure during public health emergencies to speed up approval and save lives.

It is the most appropriate tool to grant access to a vaccine to all EU citizens at the same time and to underpin mass vaccination campaigns.

Monitoring vaccine effectiveness, safety and real-life use

The scientific evaluation needs to show that a vaccine's benefits in protecting people against a specific disease, like COVID-19, are far greater than any potential risk.

Like any medicine, vaccines have benefits and risks. Even highly effective vaccines are not one hundred per cent effective in preventing disease or one hundred per cent safe in all vaccinated people.

At the time of approval, the main body of **evidence** for vaccine safety and efficacy comes from large, controlled, randomised clinical trials. As part of such trials, selected volunteers are randomly given either the vaccine being tested or a placebo injection. They are then monitored under controlled conditions, in line with strict protocols.

After approval, many people will be vaccinated. Certain rare or very rare **side effects** may only emerge when millions of people are vaccinated. EU law requires that the safety of vaccines is monitored while they are in use in routine clinical practice.

Safety information on COVID-19 vaccines is available:

- Safety of COVID-19 vaccines

Standard monitoring

The EU has a comprehensive **safety monitoring** and **risk management** (pharmacovigilance) system, which ensures measures are in place for:

- providing advice to minimise risk;
- reporting suspected side effects;
- conducting studies after authorisation;
- detecting any potential side effects;
- conducting rigorous scientific assessments of all safety data;
- introducing any necessary mitigating actions early on.

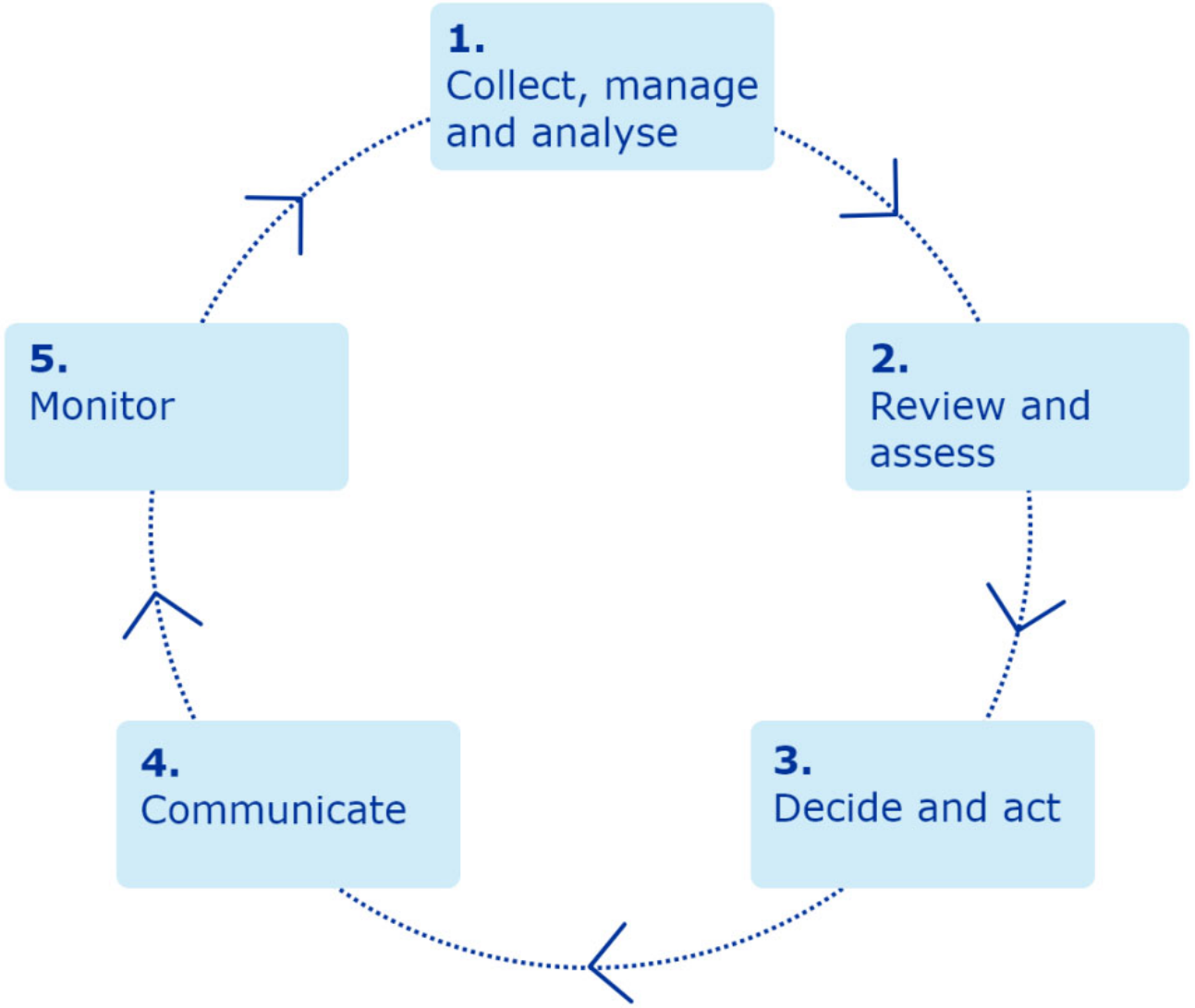
Competent authorities may carry out safety and efficacy studies after authorisation and can also require a marketing authorisation holder to carry out such studies as an obligation of the authorisation. Public health authorities responsible for vaccination programmes will also conduct other studies.

Studies collecting effectiveness data give additional information, for example, on **long-term protection,** on the need for and timing of **booster** doses, or on the effectiveness of a vaccine against new variants, to complement the 'efficacy' data obtained in clinical trials before the vaccine was authorised.

For more information, see:

- Pharmacovigilance: Overview.
- Monitoring vaccine safety and reporting side effects: European Vaccination Information Portal

Figure 6: Pharmacovigilance cycle

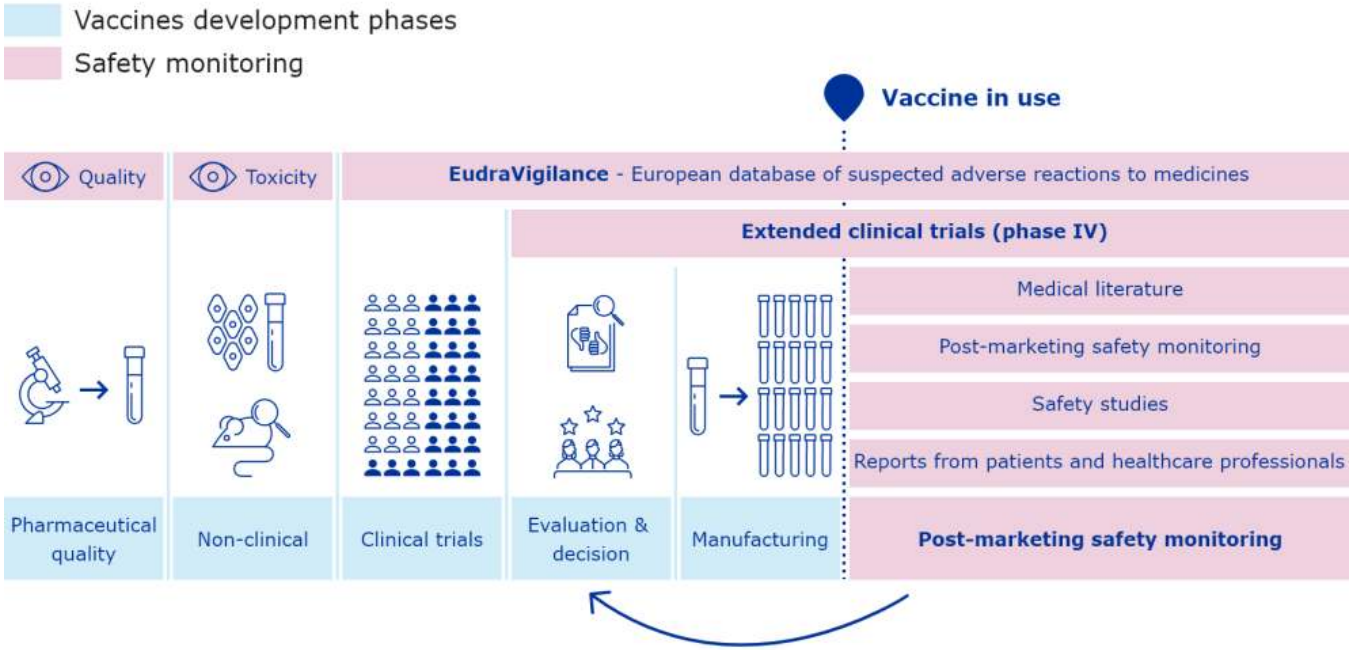


Large scale monitoring activities in the pandemic context

Regulators and vaccine developers are also mobilising extra resources to **monitor safety** and manage risk during the **pandemic**. This is important because exceptionally large numbers of people receive COVID-19 vaccines once they are

authorised; many more than the large numbers who have been receiving the vaccines in clinical trials. In addition, people vaccinated as part of mass vaccination campaigns are more diverse than those selected to take part in trials.

Figure 7: How vaccine safety is studied



The pharmacovigilance plan for COVID-19 vaccines sets out how EMA and the national competent authorities in the EU Member States identify and evaluate any new information that arises promptly, including any safety signals that are relevant for the benefit-risk balance of these vaccines:

- Pharmacovigilance plan of the EU Regulatory Network for COVID-19 vaccines

This plan also ensures that regulators can take any appropriate regulatory actions and communicate these to the public as quickly as possible.

The **monitoring** activities in the plan apply to all vaccines, but they take place on a larger scale during this pandemic:

- Collecting exposure data to COVID-19 vaccines
- Adopting specific safety signal detection and management measures
- Setting up a European infrastructure for monitoring COVID-19 treatments and vaccines
- Using real-world data from clinical practice
- Applying exceptional transparency measures

EMA's guidance on preparing risk management plans for COVID-19 vaccines helps marketing authorisation applicants develop risk management plans for COVID-19 vaccines:

- Risk management for COVID-19 vaccines

These risk management plans set out how the company will monitor and report on safety and how it will characterise and manage risks following authorisation of a COVID-19 vaccine.

For a period of at least six months after authorisation, companies responsible for COVID-19 vaccines need to submit monthly safety summaries for COVID-19 vaccines, in addition to periodic safety update reports. They also need to put processes in place to manage a high volume of safety reports. They need to carry out further studies on COVID-19 vaccines that receive a conditional marketing authorisation.

Additional considerations in this guidance address traceability tools that can help record who has received which vaccine and from which batch.

EMA publishes the full body of the risk management plans for all authorised COVID-19 vaccines, in line with its exceptional transparency measures for COVID-19 medicines.

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LETTER TO THE EDITOR

Inaccurate representation of shipped vaccines as administered

Dear Editor,

I am writing in response to your recently published letter https://onlinelibrary.wiley.com/doi/10.1111/eci.13998 by Schmeling et al. The authors have not described the data that they have used correctly. They report that they have received batch-specific information on adverse event reports from the Danish Medicines Agency and administered vaccines from Statens Serum Institut (SSI). This is not correct. The information they have obtained from SSI is on shipped vaccine vials by batch number. From SSI, vaccines were shipped to regional distribution centres (with −90 degree celsius storage capacity). The dates of data retrieval for both sources of data used in the letter are 18 January 2022 (shipment volumes) and 11 January 2022 (adverse event reports). Thus, batches shipped late in 2021 or very early in 2022 will not have any or very few adverse event reports, because they have not been used or only a small proportion have been used. This is also clearly seen in the figure in the letter, where the so-called 'yellow' batches have zero or close to zero reports. Understanding this is critical for the interpretation of these results. This is a particularly serious issue as the crux of the letter hinges on the idea that different vaccine batches have drastically different safety profiles which is not supported at all when you understand that it is not administered vaccines as they claim. There are many other issues with respect to these data. For example, that the very first batches were small, administered during the introduction period where clinical practitioners were instructed to report everything including local reactions, fever, transient headache, etc. These cannot be compared to later only partially used batches, where the authorities urged that mild and transient events should no longer be reported. It is also well-known that in the early part of the vaccination deployment, those vaccinating were urged to attempt to get seven doses out of the vials instead of six due to supply concerns. Again, as the authors do not have data on administered doses but only on shipped vials, the comparisons are further skewed.

I note the statement 'Reporting of the study conforms to broad EQUATOR guidelines'. There are no EQUATOR guidelines. EQUATOR is a network for reporting guidelines and currently houses 573 different reporting guidelines—https://www.equator-network.org/reporting-guidelines/.

Finally, the 'main finding' of three distinct types of safety profiles is based on a so-called non-hierarchical cluster analysis of log-transformed counts. There is no reference to the method, and no further details. Thus, the validity of the method in this context is very difficult to validate.

In summary, the research letter is presenting the study data inaccurately and has a number of reporting inconsistencies that should also be corrected and even so the study data cannot be used to provide any meaningful insights into batch variability with respect to safety.

CONFLICT OF INTEREST STATEMENT

I declare no conflicts of interest.

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Special report

EU COVID-19 vaccine procurement

Sufficient doses secured after initial challenges, but performance of the process not sufficiently assessed

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COURT
OF AUDITORS

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Executive summary

I The EU identified vaccines as a priority in the response to COVID-19 early on in the pandemic, and started focusing on the development of a safe and efficient vaccine as a solution to ending the health crisis. It took measures to help compress the development timeline for vaccines from 10-15 years to 12-24 months. By November 2021, the Commission had signed €71 billion worth of contracts on behalf of the Member States to purchase up to 4.6 billion COVID-19 vaccine doses. Most of these contracts are advance purchase agreements, in which the Commission shares the development risk of a vaccine with the vaccine manufacturers and supports the preparation of at-scale production capacity through upfront payments from the EU budget.

II The EU experienced some supply shortfalls in the first half of 2021, but by the end of that year, nearly 952 million vaccine doses had been delivered to EU Member States and 80 % of the EU's adult population had been fully vaccinated.

III This report examines whether the Commission and Member States procured COVID-19 vaccines up to the end of 2021 effectively. We looked at the framework the EU set up, its negotiation strategy and how the Commission followed up contract implementation. We chose this topic given the central role that vaccines played in the response to the COVID-19 pandemic, the unprecedented nature of the EU's involvement in vaccine procurement and the expenditure involved. Our findings aim to contribute to the ongoing development of the EU's pandemic preparedness and response capabilities.

IV We found that the EU created a tailor-made centralised system for vaccine procurement, which succeeded in creating an initial portfolio of vaccine candidates including different companies and technologies, but it started procurement later than the UK and the US. The EU had to act ahead of clear scientific data on vaccine candidates' safety and efficacy, and therefore chose to back a range of candidates to create an initial portfolio with a range of different vaccine technologies and manufacturers. The Pfizer/BioNTech vaccine dominates the portfolio in 2022-2023 because of, according to the Commission, the company's ability to reliably supply the EU.

V Negotiations followed a procurement process laid down in the EU's Financial Regulation, while the heart of the process were the preliminary negotiations that took place before a tender invitation was sent out. The EU's negotiators were better able to

secure the EU's procurement objectives in the later contracts it signed with vaccine manufacturers. The terms of the contracts evolved over time and those signed in 2021 have stronger provisions on key issues such as delivery schedules and production location than those signed in 2020. The terms negotiated are different for each contract, except for adherence to the principles of the Product Liability Directive which regulates third party liability for adverse effects.

VI After contract signature, the Commission supported contract implementation by acting as a facilitator between the Member States and the manufacturers. However, the Commission had limited leverage to overcome supply challenges. When the EU was confronted with severe supply shortfalls in the first half of 2021, it became clear that most contracts did not include specific provisions to address supply disruptions. As such, the Commission could, and in one case did, take manufacturers to court. The Commission had also not fully analysed the production and supply chain challenges of vaccine production until after signing most of the contracts. The Commission only set up a task force to support manufacturing and supply chains in February 2021 and while it did help resolve bottlenecks, the size of its impact on the ramp-up of vaccine production was unclear.

VII The Commission has not yet scrutinised or benchmarked its procurement process to learn lessons for future improvements, nor does it currently plan to test its pandemic procurement system through stress-tests or simulations.

VIII Based on our findings, we recommend that the Commission:

- produce pandemic procurement guidelines and/or lessons learnt for future negotiating teams;
- carry out a risk assessment of the EU's procurement approach and propose appropriate measures;
- run exercises to test all parts of its updated pandemic procurement framework, including information and intelligence gathering, to identify any weaknesses and areas for improvement and publish the results.

Introduction

01 The World Health Organisation (WHO) declared the COVID-19 outbreak a global pandemic on 11 March 2020[1]. The Joint (European Council and Commission Presidents') European Roadmap towards lifting COVID-19 containment measures of 26 March 2020 stressed that "the development of a safe and effective vaccine is crucial to help put an end to the COVID-19 pandemic"[2]. The Commission published its COVID-19 vaccines strategy on 17 June 2020, presenting the rationale for a centralised EU procurement process. The Commission argued that a centralised approach "allows better hedging of bets, sharing of risks and pooling investments to achieve economies of scale, scope and speed"[3]. The strategy rests on two pillars:

- securing sufficient production of vaccines in the EU and thereby sufficient supplies for its Member States; and
- adapting the EU's regulatory framework to the current urgency and making use of existing regulatory flexibility.

The development of COVID-19 vaccines

02 Developing a successful vaccine takes an average of 10 to 15 years[4] (see ***Figure 1***). When the EU's procurement process started in mid-2020, it was not known if or when a COVID-19 vaccine would reach the market. The Commission therefore supported different vaccine candidates and technologies to promote a fast response from the market and spread the risk of failure and delay.

---

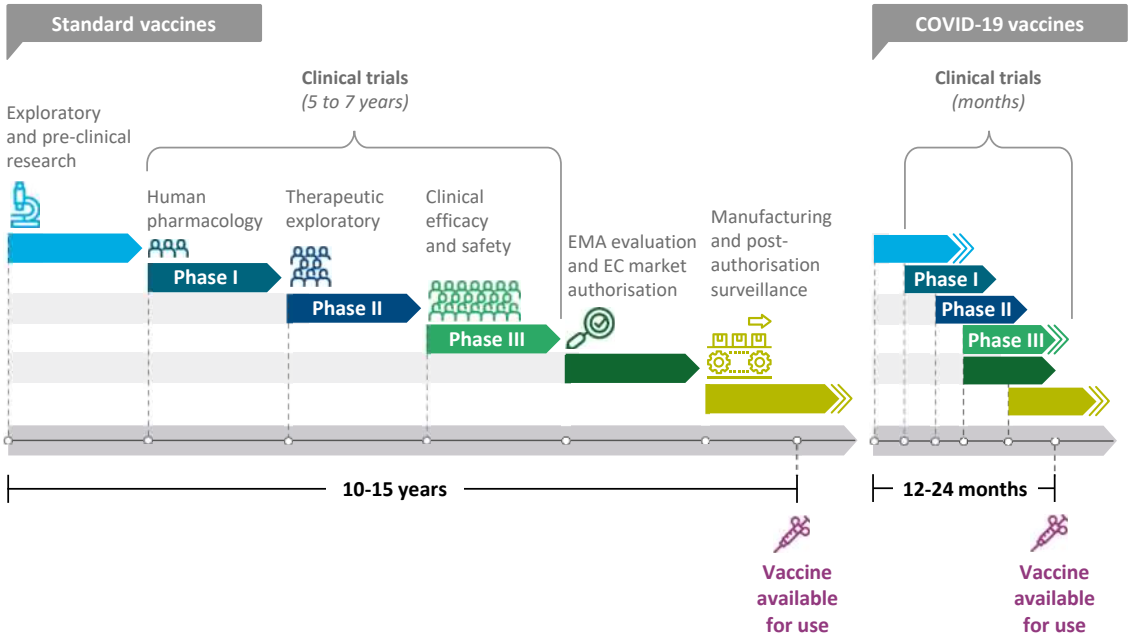
1 WHO Director-General's opening remarks at the media briefing on COVID-19, 11.3.2020.

2 Joint European Roadmap towards lifting COVID-19 containment measures, 26.3.2020.

3 EU strategy for COVID-19 vaccines, COM(2020) 245.

4 International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), "The complex journey of a vaccine. The steps behind developing a new vaccine".

Figure 1 – Standard vaccine development process and timeline vs COVID-19 vaccine development



Source: ECA, based on EMA and IFPMA information.

03 The EU took a number of measures to support efforts to compress the COVID-19 vaccine development timeline to as little as 12-24 months[5] (see ***Figure 1***). The European Medicines Agency (EMA) provided rapid guidance to developers on clinical study designs, advised companies on regulatory requirements, undertook rolling reviews of clinical trial data as it became available and sped up the approval of new production lines[6]. The Council and the European Parliament adopted a temporary derogation from the legislation on genetically modified organisms, allowing their inclusion in vaccines[7]. The heads of the Member States' Medicines Agencies adopted a Memorandum of Understanding allowing more flexible labelling and packaging requirements for COVID-19 vaccines. The EMA recommended granting conditional marketing authorisation for the first COVID-19 vaccine on 21 December 2020, nine months after the WHO had declared the coronavirus outbreak a global pandemic.

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5 EU strategy for COVID-19 vaccines, COM(2020) 245.

6 EMA, "COVID-19 vaccines: development, evaluation, approval and monitoring".

7 Regulation (EU) 2020/1043.

Contracts to procure COVID-19 vaccines

04 In parallel with the publication of its COVID-19 vaccine strategy, the Commission signed an agreement with the 27 Member States, allowing it to conclude Advance Purchase Agreements (APAs) with COVID-19 vaccine manufacturers on their behalf[8]. APAs are contracts in which the Commission secures Member States' right to buy a specified number of vaccine doses in a given timeframe and at a given price. In return for securing future vaccine supplies, part of the development costs faced by vaccine producers was financed by down payments from the EU budget. The Commission and Member States took this novel risk-sharing approach to secure sufficient quantities of vaccines. If the EMA recommends a vaccine for authorisation, the down payments are used against purchases of the vaccine by the Member States. However, these payments may not always be fully recovered in the event that a vaccine candidate is not authorised.

05 Funding for the APAs came from the Emergency Support Instrument (ESI)[9], a financing instrument directly managed by the Commission that allows it to provide support within the EU in case of disasters. It is used to intervene on top of, and in coordination with, efforts made under other national and EU initiatives. The Commission allocated €2.15 billion to the ESI budget to fund vaccine APAs, which the Member States topped up with a further €750 million to create a total budget of €2.9 billion. By the end of 2021, the Commission had paid more than €2.55 billion in down payments to vaccine manufacturers.

The Commission signed contracts worth €71 billion for deliveries of up to 4.6 billion COVID-19 vaccine doses

06 Between August 2020 and November 2021, the Commission signed 11 contracts with eight vaccine manufacturers providing access to up to 4.6 billion vaccine doses (see ***Table 1***) at an expected total cost of close to €71 billion. The weighted average cost per dose is approximately €15. This figure is calculated on the basis of doses actually ordered (delivered and yet to be delivered). Options not exercised are not included. The Curevac doses ordered are excluded, but the Curevac down payment is included as a cost.

---

[8] Commission Decision of 18 June 2020, C(2020) 4192 and its subsequent approval by each Member State.

[9] EU strategy for COVID-19 vaccines, COM(2020) 245.

Table 1 – Potential COVID-19 vaccine doses secured up to the end of 2021

Vaccine developed by	Number of contracted doses (million)	Number of optional/ additional doses (million)	Total number of doses (million)	Contract signature
AstraZeneca	300	100	400	August 2020
Sanofi/GSK		300*	300	September 2020
Janssen**	200	200	400	October 2020
Curevac	225	180	405	November 2020
Pfizer/BioNTech	200	100	300	November 2020
	200	100	300	February 2021
	900	900	1 800	May 2021
Moderna	80	80	160	December 2020
	150	150	300	February 2021
Novavax	100	100	200	August 2021
Valneva	24	36	60	November 2021
Total	***2 379***	***2 246***	***4 625***	

* The Sanofi/GSK contract is an options contract with no obligation on the MS to purchase any doses. Sanofi/GSK received a down payment.

** Janssen Pharmaceutica NV is an affiliate of Johnson & Johnson.

Source: ECA based on contracts.

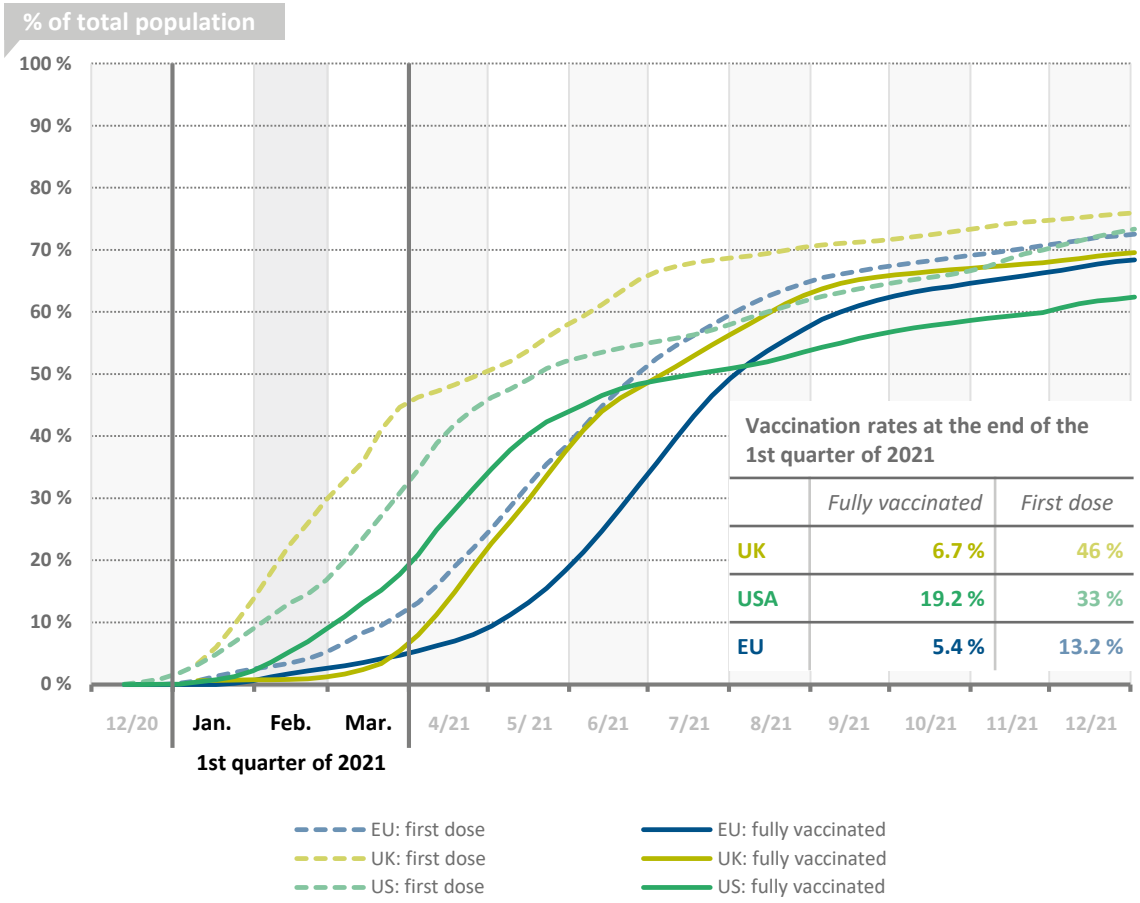
07 Eight of the contracts are APAs, concluded before the vaccines received a recommendation for a conditional marketing authorisation from the EMA. Three contracts are purchase agreements (PAs), signed with Pfizer/BioNTech and Moderna after their vaccines had received an EU conditional marketing authorisation. These do not include any down payment from the EU budget, though Moderna required a down payment from the Member States.

08 By the end of 2021, almost 952 million doses had been delivered to EU Member States (the majority from Pfizer/BioNTech) and over 739 million doses administered[10]. 80 % of the EU's adult population had been fully vaccinated. The EU had secured sufficient doses to vaccinate at least 70 % of the adult population by the end of the

[10] ECDC vaccine tracker.

summer of 2021 (see ***Figure 2***), although it experienced challenging supply shortfalls from two manufacturers in the first half of 2021.

Figure 2 – Vaccination rates in the EU, UK and USA in 2021



Source: Our world in data for UK and USA, ECDC for the EU.

Liability and indemnification

09 The Commission and Member States considered early introduction of the vaccine to be in the interest of public health. Member States were therefore willing to reduce manufacturers' risks linked to liability for adverse effects. This was intended as a risk-sharing principle in the vaccine strategy. While respecting the general principle of liability under the Product Liability Directive (see ***Box 1***), the provisions in the contracts concluded with COVID-19 vaccine manufacturers differ from the pre-pandemic practice (see ***Box 1***) as Member States have taken over some of the financial risks normally assumed by the vaccine manufacturers.

Box 1

The EU Product Liability Directive

Under the Product Liability Directive, producers are liable for damage caused by a defect in their product, even in the absence of negligence or fault on their part. A producer can be exempt from such liability if the state of scientific and technical knowledge at the time when the producer put the product into circulation was not such as to enable the defect to be discovered.

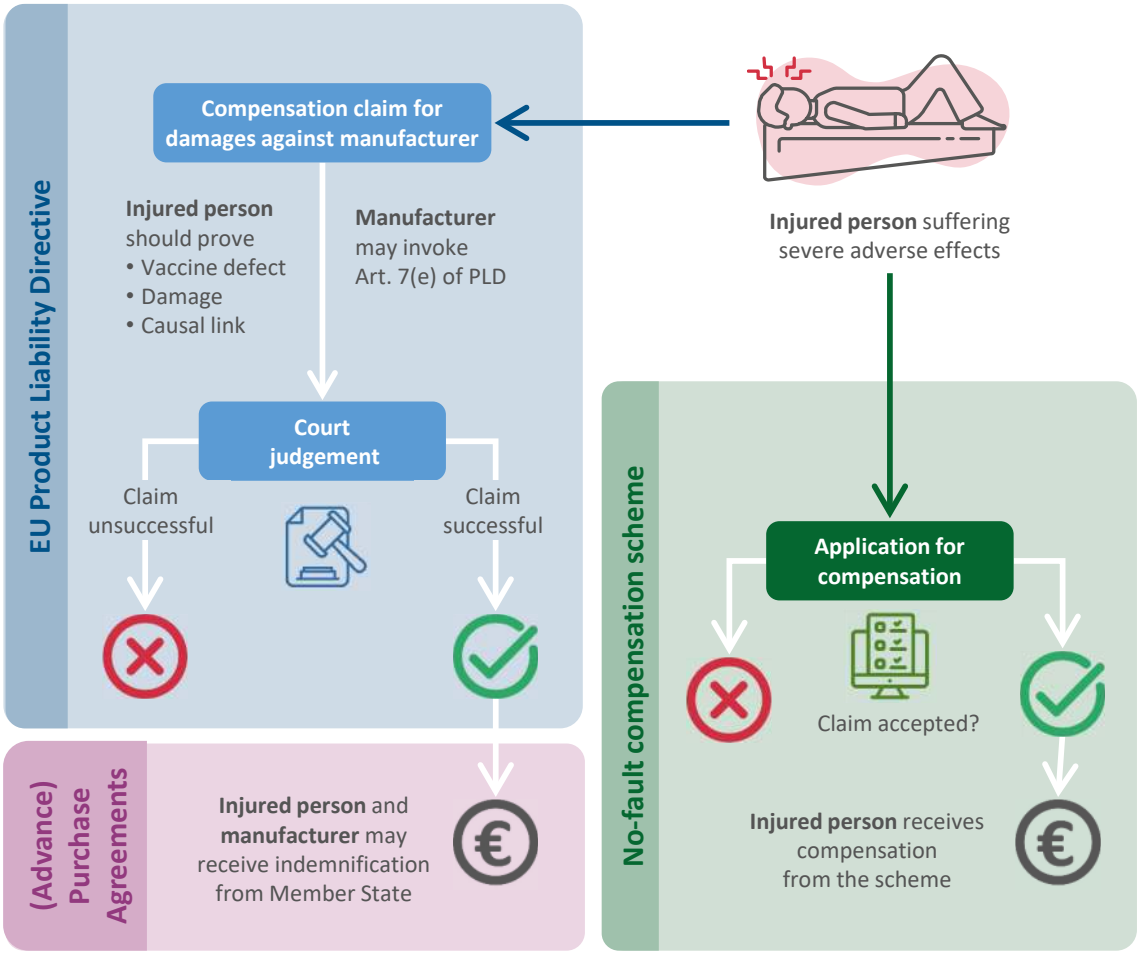
An EU citizen who suffers serious adverse effects from a medicine can file a compensation claim for damages against the manufacturer under the Directive, which has been enacted in Member States' legislation.

10 A citizen who has suffered adverse effects from one of the COVID-19 vaccines purchased under the contracts can claim damages against the manufacturer of the vaccine. If the claim is successful, the Member State that administered the vaccine will be responsible for compensating the injured party and paying the vaccine manufacturer's legal costs (indemnification) (see ***Figure 3***). This is not the case if the damages or losses result from wilful misconduct, gross negligence or failure to comply with EU good manufacturing practices.

11 In addition to claims under the Product Liability Directive, according to a recent study[11], 11 Member States have national "no fault" compensation schemes in place to indemnify injured persons for harm suffered as a result of side effects caused by a vaccination. Such schemes do not require the injured person to prove a causal link between the side effect and the vaccine. A person that chooses to receive such compensation foregoes the right to file a case against the pharmaceutical company.

[11] House of the Oireachtas, Library and Research Service, "Vaccine Injury Compensation Programmes: An Overview", 20.4.2021.

Figure 3 – Liability and indemnification in case a person suffers serious adverse effects from a COVID-19 vaccine



Source: ECA.

Audit scope and approach

12 This report examines whether the Commission and Member States procured COVID-19 vaccines up to the end of 2021 effectively. We looked at this topic because of the importance of timely access to vaccines in sufficient quantities in the EU's response to the COVID-19 pandemic as well as the expenditure at stake, and interest in the Commission's role. We examined whether:

(a) the EU's preparations for the procurement of COVID 19 vaccines were effective;

(b) the EU's negotiators were able to secure the EU's procurement objectives in the contracts it signed with vaccine manufacturers; and

(c) the Commission addressed any issues impacting the supply of vaccines.

13 We benchmarked the EU's performance with that of the UK and the US to understand what lessons could be learnt from a comparison with other procurement systems. We chose these countries as both have domestic pharmaceutical research and production capacity, were among the first countries to start vaccine procurement procedures and procured from some of the same companies as the EU. We took account of the differing competences for public health in the three jurisdictions and therefore limited our benchmarking to comparable factors: timing of procurement launch, contractual terms and support for production.

14 We held meetings with Commission officials from the Directorate General for Health and Food Safety (DG SANTE), the lead DG in this matter, and had direct access to their databases. We also had meetings with staff from the Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW), the Commission's legal service and the Secretariat General who had been involved in the procurement process. We had access to the relevant Commission documents, with the exception of those related to the President of the Commission's involvement in preliminary negotiations with Pfizer/BioNTech. We examined meeting minutes, internal Commission reports, email correspondence and the (A)PAs (hereafter known as contracts).

15 We held meetings with auditors from the UK and US supreme audit institutions to benefit from their work on their governments' COVID-19 vaccine procurement efforts. We interviewed the representatives of three Member States who had a leading role in the procurement process. We carried out a survey of the Member States' representatives on the COVID-19 vaccine procurement steering board to obtain their

opinion on the EU's vaccine procurement, to which 14 out of 27 Member States responded.

16 The results of this audit are relevant to the ongoing development of the EU's pandemic preparedness and response capacity, including the European Health Emergency Preparedness and Response Authority (HERA).

Observations

The EU created a tailor-made procurement system for COVID-19 vaccines

17 In response to the COVID-19 pandemic, the Commission took a number of steps to be able to procure vaccines for EU citizens. We assessed whether the EU set up an appropriate framework for this vaccine procurement process, leading to timely contract negotiations.

The EU identified vaccines as a priority in the response to COVID-19 early on, but started procurement later than the UK and the US

18 On 20 February 2020[12], less than three weeks after the WHO had declared COVID-19 a Public Health Emergency of International Concern[13], the Council urged Member States and the Commission to cooperate on the development of a vaccine (see ***Figure 4*** for a timeline of the key events). On 10 March[14] and again on 26 March 2020[15], the Members of the European Council stressed the importance of developing a vaccine and committed to increasing support for vaccine research.

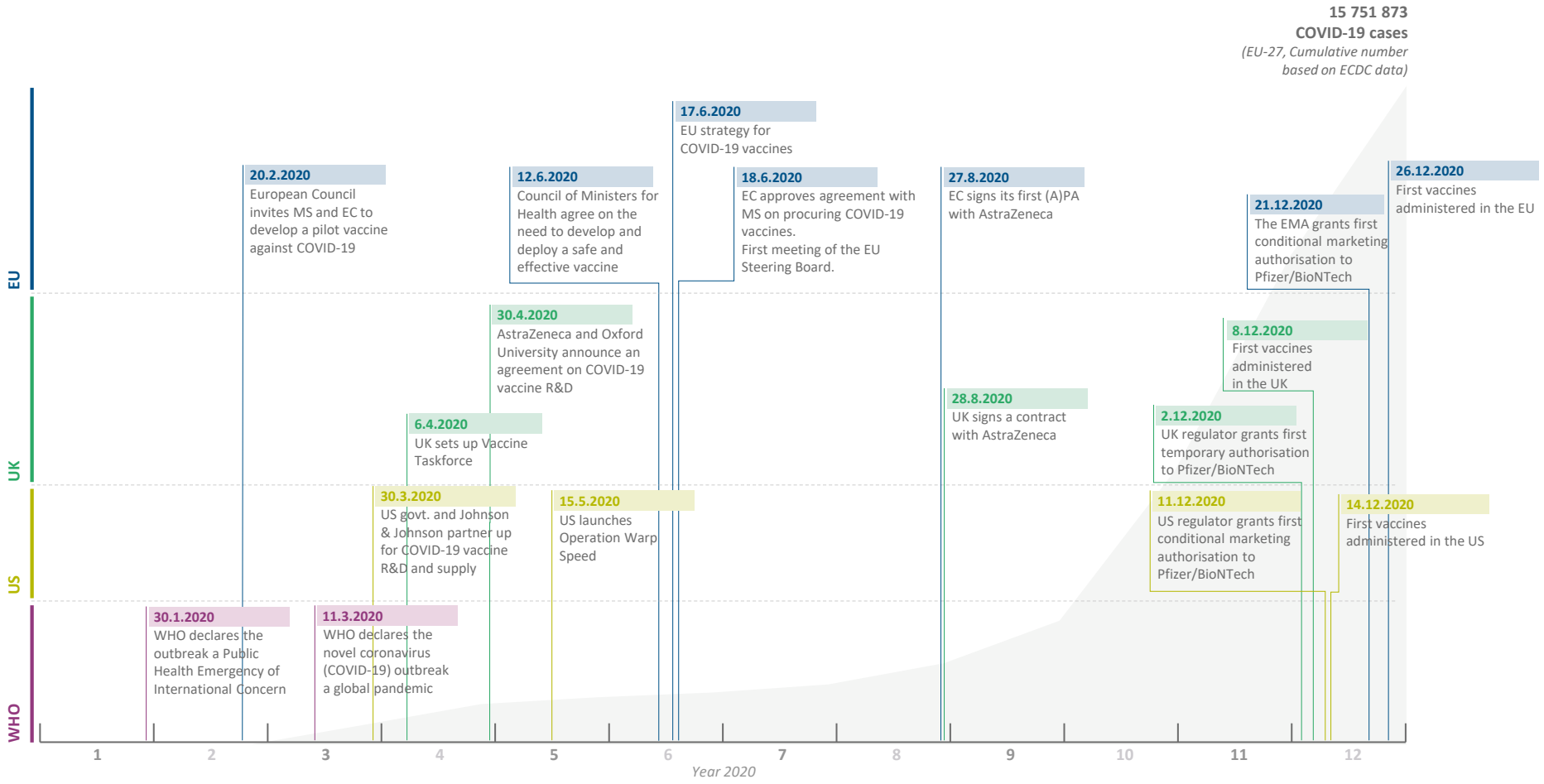
[12] Council conclusions on COVID-19 (2020/C 57/04).

[13] WHO, Statement regarding the outbreak of novel coronavirus, 30.1.2020.

[14] Conclusions by the President of the European Council, 10.3.2020.

[15] Joint statement of the Members of the European Council, 26.3.2020.

Figure 4 – Timeline of key COVID-19 procurement actions in 2020



Source: ECA.

19 On 17 April 2020, the joint Council-Commission roadmap towards lifting COVID-19 containment measures[16] stressed for the first time that joint procurement and equal access would guide the Commission's actions on vaccines. The Commission started investigating vaccine candidates in late April[17]. At this time, it did not have a mandate from the Member States, nor a final objective or strategy. It established these initial contacts without consulting or coordinating with the Member States.

20 Germany, France, Italy and the Netherlands had been working together as the Inclusive Vaccine Alliance (IVA) since May 2020 to secure vaccine supplies for their citizens. On 13 June, AstraZeneca announced a deal with the IVA for up to 400 million doses. Upon the launch of the EU's COVID-19 vaccine procurement on 18 June, the Commission and Member State negotiators took over the IVA agreement and negotiated with AstraZeneca on behalf of all 27 Member States.

21 The EU noted the importance of vaccine development early on in the pandemic, but started its procurement process (as measured by the establishment of the procurement steering board on 18 June 2020) later than the UK and USA. The UK launched its vaccine taskforce on 17 April 2020. The US government announced the creation of "Operation Warp Speed" for vaccine development and procurement on 15 May 2020, although it had started funding vaccine candidates' research in March (see ***Figure 4***).

---

[16] Joint European Roadmap towards lifting COVID-19 containment measures 2020/C 126/01.

[17] Ibid.

The EU set-up a novel centralised system to procure COVID-19 vaccines

22 The 2013 Decision[18] on serious cross-border threats to health provides an EU-level pandemic preparedness and response framework. The Commission has been supporting preparedness and response projects at EU and Member State level since 2003[19], in line with the WHO recommendations that such exercises (including at cross-border level) be an integral part of pandemic preparedness activities[20]. Nevertheless, the Council noted in April 2020 that "existing EU instruments are limited in scale and therefore do not allow a sufficient response or make it possible to address effectively the large-scale consequences of the COVID-19 crisis within the Union"[21]. These limitations included the absence of a system to procure an as yet non-existent vaccine:

- emergency support rules within the Union[22] did not allow the Commission to purchase supplies, such as vaccines, on behalf of Member States;
- the Decision[23] allows for the joint procurement of medical countermeasures by Member States, but this instrument was designed as a preparedness instrument and does not provide the flexibility and speed required to respond to the extreme urgency of the COVID-19 pandemic.

23 An April 2020 amendment to the Council Regulation on emergency support within the Union addressed these issues by allowing the Commission to negotiate contracts on behalf of the Member States for the first time. The Commission informed us that there was no vaccine strategy to implement this provision at the time the amendment was adopted.

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[18] Decision 1082/2013 on serious cross-border threats to health.

[19] European Commission website: "preparedness and response planning", accessed 22.2.2022.

[20] WHO, Recommendation for good practice in pandemic preparedness, 2010.

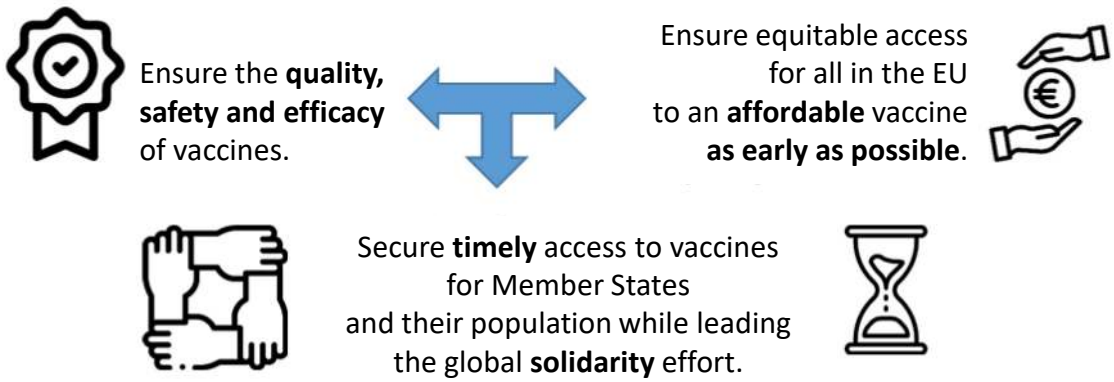
[21] Council Regulation (EU) 2020/521, recital 4.

[22] Council Regulation (EU) 2016/369 on the provision of emergency support within the Union.

[23] Article 5 of Decision 1082/2013 on serious cross-border threats to health.

24 The Council of Ministers for Health agreed on 12 June 2020[24] on "the need for joint action to support the development and deployment of a safe and effective vaccine against COVID-19 by securing rapid, sufficient and equitable supplies for Member States" and "favouring a broad portfolio and a top-up of ESI funding". The Commission published its COVID-19 vaccine strategy[25] on 17 June 2020 (see ***Figure 5***), presenting the rationale for a centralised EU procurement process. The Council adopted a financing decision on 18 June 2020 to fund vaccine procurement[26].

Figure 5 – The objectives of the EU COVID-19 strategy



Source: EU strategy for COVID-19 vaccines.

25 This centralised approach was implemented through an agreement signed by the Commission and the Member States, which made the Commission responsible for the procurement process and the conclusion of contracts. The agreements between the Commission and the Member States[27] set up a tailor-made system for the vaccine procurement (see ***Figure 6***), centred around two bodies:

- A steering board overseeing negotiations and validating contracts before signature, made up of one representative per Member State and co-chaired by the European Commission and a Member State representative. Representatives appointed to the steering board were not subject to any prerequisites or

[24] Commission Decision approving the agreement with Member States on procuring Covid-19 vaccines, C(2020) 4192.

[25] EU strategy for COVID-19 vaccines, COM(2020) 245.

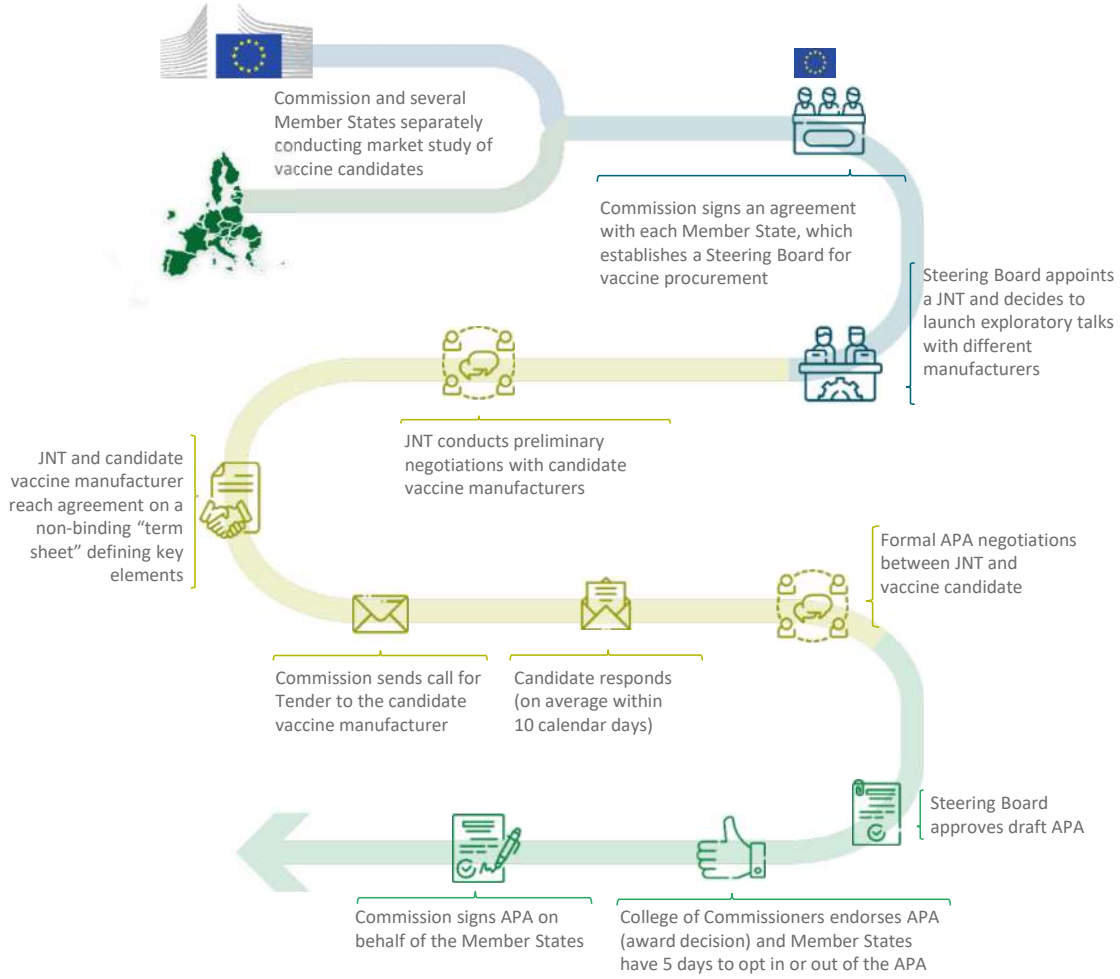
[26] Draft Amending Budget No 8 to the General Budget, C(2020) 900 final.

[27] Annex to the Commission Decision approving the agreement with Member States on procuring COVID-19 vaccines and its subsequent approval by each Member State.

requirements for specific expertise. This entailed the risk that the body overseeing vaccine procurement lacked the knowledge and experience to deal with the complexity of vaccine procurement.

- A joint negotiation team (JNT) in charge of negotiating the contracts, comprising representatives from seven Member States (Germany, Spain, France, Italy, the Netherlands, Poland and Sweden), chosen from the members of the steering board, and Commission officials from various DGs. In practice the JNT split into sub-groups of representatives from two Member States and Commission officials, each negotiating with a specific vaccine candidate manufacturer.

Figure 6 – Flowchart of the contract procurement process



Source: ECA.

26 The steering board and JNT were made up of people with a variety of profiles including members of the EMA Committee for Medicinal Products for Human Use and heads of Member States' national medicines agencies. The US and UK procurement taskforces included experts in supply chain and logistics. The Commission had not

considered which skills it needed in the JNT before the launch of the procurement process.

EU negotiators adopted a flexible approach to negotiations in the face of a high level of uncertainty

27 The Commission and Member States adopted a flexible approach to secure a broad vaccine portfolio at short notice, leaving the steering board to oversee the negotiations and validate their outcome. The steering board did not develop detailed objectives or mandates for the EU's negotiators. However, in its Decision approving the agreements with the Member States for vaccine procurement[28], the Commission did commit to considering specific elements when deciding to finance individual contracts, notably:

- available data on the quality, safety and efficacy of the vaccine at the time of negotiation of the contract;
- speed of delivery at scale;
- cost;
- diversification of technologies; and
- capacity to supply through the development of production capacity within the EU.

28 The JNT reported frequently to the steering board on the state of play of negotiations with the various vaccine candidates, but the steering board's meeting minutes make no mention of defined objectives or targets. They reflect the JNT's own assessment of the negotiations and record the steering board's occasional case-by-case instructions. The minutes rarely detail the matters the JNT was negotiating. The Commission informed us that, due to the urgency of the negotiations and the importance of avoiding leaks, these minutes do not exhaustively cover the discussions held within the steering board.

29 The steering board received input from Member States' experts on the scientific merit and potential of the various vaccine candidates. It chose to negotiate with established firms with track records in the field of vaccine development. The maturity of the vaccine candidates' technologies was also an important factor in the steering board's selection.

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[28] Ibid.

30 The agreement between the Commission and Member States (see paragraph ***25***) stipulated that the Commission would seek independent scientific advice on both the progress and on the available data on the quality, safety and efficacy of vaccine candidates before making any final decisions. The Commission did ask scientific experts for advice but, in the absence of robust data, the steering board had to make decisions before clear scientific evidence was available.

Negotiations secured a diversified vaccine portfolio for Member States

31 Between spring 2020 and autumn 2021, the EU concluded 11 contracts with COVID-19 vaccine manufacturers. We assessed whether:

- the Commission mobilised the appropriate tools and knowledge to conduct the negotiations; and
- the contracts reflect the priorities and objectives defined for the negotiations.

The negotiations followed a three-step approach

32 The priorities of the COVID-19 vaccine procurement negotiations were to obtain a safe and effective vaccine quickly and in sufficient quantity for all EU Member States. The procurement process was conducted using a negotiated procedure without prior publication of a contract notice, in accordance with the Financial Regulation[29].

33 The negotiation process consisted of three stages, each of differing duration for each candidate manufacturer (see ***Figure 7***):

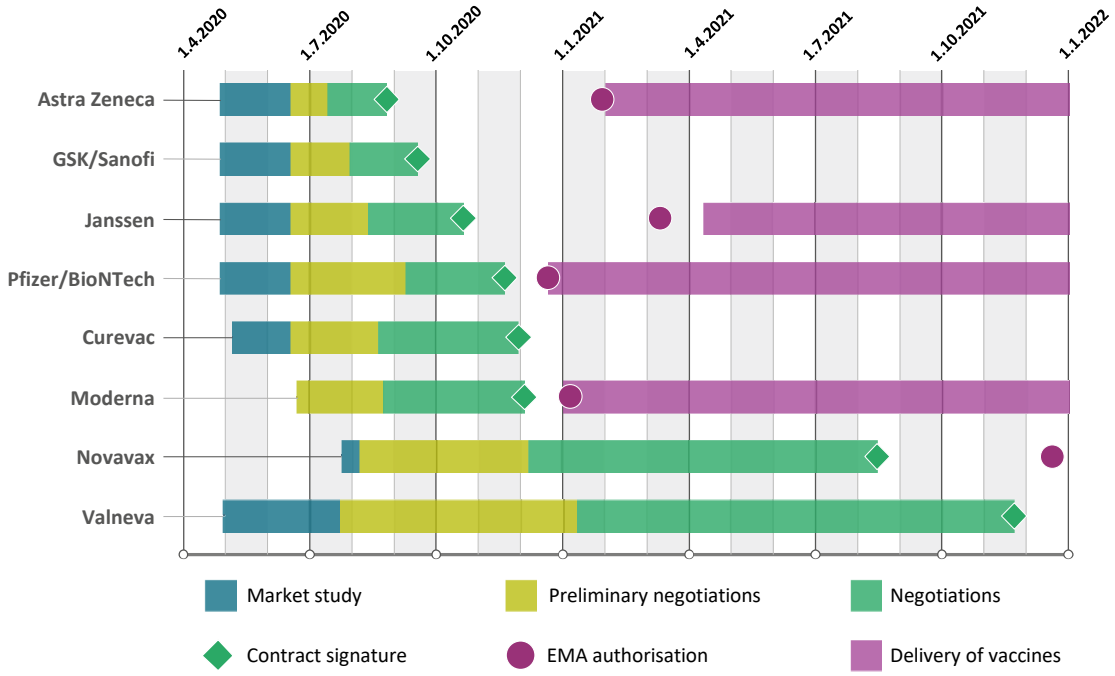
- *Market study*: the Commission sent questionnaires to candidate vaccine manufacturers and held meetings with some of them (this took place before the steering board was set up).
- *Preliminary negotiations* between the JNT and a candidate vaccine manufacturer started when the steering board gave its approval to start discussions and ended once the major elements of the agreement (price, volume, third party liability and indemnification, delivery and payment schedule) were provisionally agreed upon in non-binding "term sheets". When the steering board was satisfied with the

[29] Article 164(1)(d) and (4) and point 11(1)(c) of Annex I to Regulation 2018/1046.

outcome of the preliminary negotiations, the Commission could launch a call for tender.

- *Negotiations* between the JNT and a candidate vaccine manufacturer started when the company submitted a tender document and ended with the signature of an agreement by both parties (Commission, on behalf of the Member States, and manufacturer).

Figure 7 – Timeline of the negotiation process for each of the contracts



Source: ECA.

34 The EU followed a similar process to activate options for extra doses provided for in the contracts and to conclude two of the PAs. The steering board expressed interest in additional doses from a manufacturer and mandated the JNT to negotiate conditions.

Major elements were agreed in preliminary negotiations before the tender process

35 We analysed the tender process to determine its impact on the content of the contracts. An evaluation committee consisting of between five and 23 people from the Commission and the steering board produced evaluation reports on the files submitted by manufacturers in response to the call for tenders. We found that, for the first nine

contracts, the call for tenders did not add to what had been agreed informally on major elements in the term sheets.

36 Firstly, the vaccine candidate manufacturers and the JNT agreed major elements (notably price, volume and third party liability) of future contracts during the preliminary negotiations. Only then were the calls for tender launched. This is reflected in the short time between the tender invitation and the deadline for submitting tender documents (10 days).

37 Secondly, we found that one of the evaluation criteria was not updated to take account of the evolving situation. Criterion 1.1 "Roadmap towards starting clinical trials plans in 2020" was designed in mid-2020 to judge the reliability of candidates' plans to start clinical trials quickly. The tender invitations sent in December 2020 and January 2021 still included this criterion despite the fact that the evaluators were judging companies past performance rather than their expected output.

38 Thirdly, the evaluation of offers did not identify risks to the supply chain and manufacturing process that might lead to delivery problems. There is a weak correlation between the marks awarded and subsequent delivery performance. Approximately 40 % of the points that could be awarded to manufacturers under the tender were related directly to their production capacity (see ***Table 2***). All six companies that signed contracts with the Commission in 2020 received at least half marks for each criterion and four received maximum points for the criterion regarding production capacity in the EU.

Table 2 – Production-related criteria in the EU call for tenders for COVID-19 vaccines

The capacity to produce at scale the required volumes for the EU
Response capacity (to what extent and at what speed the company is capable of delivering proposed quantities)
Production capacity in the EU (linked to vaccines)

Source: EU calls for tenders for the development, production, priority-purchasing options and supply of COVID-19 vaccines for EU Member States.

39 Price, third party liability and delivery schedules were priority topics during the preliminary negotiations. The JNT did not assess companies' supply and production networks during preliminary negotiations and, despite the focus on this issue within the call for tender, it could not remedy this limitation in the short timeframe allowed

for tender evaluation. The Commission has recognised this weakness in the procurement process as it stated in February 2021 that manufacturers will have to submit "a detailed and credible plan showing capability to produce vaccines in the EU and deliver on a reliable timescale" as a prerequisite for negotiations[30].

Later contracts provided the EU with better guarantees for delivery and security of supply

40 We analysed the contracts with regard to: (i) enforcement of delivery schedules; (ii) guaranteeing EU access to the vaccines; (iii) the obligation to manufacture the vaccine in the EU; and (iv) respect for the EU's liability and indemnification legal framework. We found that the first three elements had weaker provisions in the early contracts.

Delivery schedules

41 Enforceable delivery schedules are one way to secure timely access to vaccines. However, the delivery schedules set out in most of the vaccine contracts are provisional and the parties acknowledge that delays may occur. Four of the 11 contracts explicitly state that the contractor is not liable for late deliveries. Five contracts mention the right to terminate the contract if any or all of the doses are not delivered by a fixed date or give the Commission the right to cancel orders if the delay exceeds a certain threshold. Four of the more recent contracts provide for discounts on the contractual price per dose for late deliveries.

42 According to the tender specifications the Commission sent to the manufacturers, the contracts may be terminated with contractors that do not have the capacity to produce a minimum number of doses as agreed in the contract. However, three of the contracts do not specify the condition for such termination, namely by when the contractor should have delivered the requisite number of doses.

EU access to vaccines

43 Another way to seek to secure timely supply of the vaccines is to ensure the order is prioritised and not overtaken by other orders. The UK negotiated provisions for priority access in four of its five contracts[31] (see ***Box 2***). Vaccine manufacturers in

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[30] Commission Communication on the HERA incubator, COM(2021) 78.

[31] UK National Audit Office, "Investigation into preparations for potential COVID-19 vaccines", 16.12.2020.

the US benefited from the government's ability to create "priority-rated contracts". This rating ensured that orders these manufacturers placed with their suppliers took precedence over those of any other clients (see ***Box 3***).

Box 2

The UK approach to vaccine procurement

The UK government established a vaccine taskforce in April 2020, bringing together up to 200 people from the civil service, army, industry and academia. Its objectives included securing access to COVID-19 vaccines and supporting the UK's industrial strategy to prepare for future pandemics[32]. In order to obtain a diversified portfolio of vaccine candidates at speed, administrative procedures, such as investment proposal and approval, were simplified.

The UK signed five APAs by November 2020, making down payments of £914 million in total[33]. Four of these APAs included priority delivery clauses and three contained provisions for partial or total reimbursement of upfront payments in case of failure. The terms of this priority delivery differ between contracts. For example, in one contract the priority supply is limited to the initial number of doses ordered. Another contract states that the UK has priority access to doses manufactured within the UK, any shortfall made up from outside the UK would not be on a priority basis. However, none of the contracts included penalties for late delivery.

All the contracts included indemnity cover to the companies by the UK government. By September 2021, the UK had secured access to 417 million doses from seven manufacturers[34], at an average price of approximately £10 per dose.

In addition to purchasing future vaccines, the taskforce also worked on the development of an industrial capacity to support vaccine production. By November 2020, it had committed £302 million in government funding in support of this aim, mostly to build or secure ever-ready vaccine production and fill and finish capacity.

44 None of the eight APAs provides explicitly for priority access to vaccines for the EU in the event of global demand exceeding supply. All EU contracts provide for a warranty from the company that they do not have any contracts conflicting with the

[32] UK Vaccine Taskforce 2020, Achievements and Future Strategy, December 2020.

[33] UK National Audit Office, "Investigation into preparations for potential COVID-19 vaccines", 16.12.2020.

[34] UK Department of Health and social care, press release, 28.4.2021.

EU contract. Three of the later contracts do state that the contractor must not enter into any agreements or commitments that would impede its ability to meet its obligations under the contract. Two of the contracts signed in 2021 include reinforced contractual clauses, along with penalties, to prioritise supplies to the EU from 2022 onward. These provisions improved the protection afforded to the EU's interests in securing vaccine supplies for the Member States.

Box 3

The US approach to vaccine procurement

As of 30 September 2021, the United States had committed at least $28.2 billion to purchase 1.7 billion vaccine doses from six vaccine manufacturers[35]. Most of the contracts the US concluded with manufacturers were flexible agreements with short award times and the possibility to negotiate specific terms and conditions.

The Department of Defence and the Department of Health and Human Services together called on staff with relevant experience and expertise (e.g. supply chain, drug development) to organise the US government's vaccine procurement. In addition, five of the six agreements provide for government officials being embedded in manufacturers' facilities. This gave the government insight into vaccine manufacturers' production capabilities and the challenges they faced[36].

During the COVID-19 pandemic, the US government frequently invoked the Defense Production Act (DPA) under which the government can conclude priority-rated contracts or place orders that take precedence over any others if a contractor is unable to make all of the contracted deliveries on time. All six vaccine manufacturers benefited from priority ratings, which helped provide them with timely access to raw materials and supplies[37]. The US government can also use the DPA to prevent companies from exporting certain goods.

The Public Readiness and Emergency Preparedness Act gives manufacturers of COVID-19 vaccines immunity from legal liability for losses related to the administration or use of their vaccines (i.e. they cannot be sued for damages in court).

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[35] US Government Accountability Office report, GAO-22-104453 of January 2022.

[36] US Government Accountability Office report, GAO-21-443 of April 2021.

[37] US Government Accountability Office report, GAO-21-387 of March 2021.

Manufacturing in the EU

45 The Commission strategy aimed at a sufficient production of vaccines in the EU for reasons of security of supply, but the structure of the global supply and production chains meant that the contracts allowed production steps to take place in non-EU locations. All 11 contracts include a clause on the location of vaccine production, although the earlier contracts have less strict requirements to manufacture in the EU. Six contracts allow the contractors to use facilities in the US, Switzerland, the UK or the EEA identified in the contract. Four contracts specify that the contractor needs to inform the Commission if it intends to use additional facilities located outside the EU. In four other cases, the contractor needs to obtain the Commission's prior consent to use facilities outside the EU, UK, EEA or Switzerland.

Liability and indemnification

46 According to the Commission, the JNT was under pressure from the pharmaceutical industry to follow the example of the US, which had released companies from their liability for COVID-19 vaccines[38] (see ***Box 3***). However, with the support of the steering board, the JNT set a red line for the negotiations, namely that the EU Product Liability Directive, the legal framework on liability for defective medicinal products, must be respected (see ***Box 1***).

47 Two contracts state that the indemnification clause may be re-discussed if additional doses are ordered or if vaccine doses are supplied during an extension of the contract. At a steering board meeting in July 2020, the Commission acknowledged that the indemnification clause currently in force should be limited in time and may not be necessary once a standard marketing authorisation has been granted. Our survey of steering board members confirms that many Member States share this view. Three-quarters of the respondents are of the opinion that the liability/indemnification regime currently provided for in the contracts should be amended once a vaccine receives a standard marketing authorisation, so that Member States carry less financial risk.

[38] US Health and Human Services Department, Declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures, 17.3.2020.

We did not receive any information on the preliminary negotiations for the EU's biggest contract

48 In mid-March 2021, the steering board agreed to plan a meeting with EU and national scientific advisors on the scientific aspects of the vaccine strategy for 2022. Such a meeting never took place. During March 2021, the President of the Commission conducted preliminary negotiations for a contract with Pfizer/BioNTech. This was the only contract for which the JNT was not involved in this stage of negotiations, contrary to the Commission decision on procuring COVID-19 vaccines[39]. On 9 April 2021, the Commission presented to the steering board the conditions negotiated between the President of the Commission and Pfizer/BioNTech, and the steering board agreed to launch a call for tender. The contract was signed on 19 May 2021 (see ***Table 1***) and covers 900 million vaccine doses to be delivered in 2022 and 2023, with the option of ordering another 900 million doses. It is the biggest COVID-19 vaccine contract signed by the Commission and will dominate the EU's vaccine portfolio until the end of 2023.

49 We asked the Commission to provide us with information on the preliminary negotiations for this agreement (scientific experts consulted and advice received, timing of the talks, records of the discussions, and details of the agreed terms and conditions). However, none was forthcoming.

50 Furthermore, the European Ombudsman opened a case on 16 September 2021 on the separate matter of the European Commission's refusal to grant public access to text messages exchanged between the Commission President and the CEO of Pfizer at the time of the preliminary negotiations. Her report of 26 January 2022 finds that the way the Commission dealt with this request constituted maladministration. The report recommends[40] that the Commission "search again for relevant text messages" and "assess whether public access can be granted to them in line with Regulation 1049/2001".

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[39] Commission Decision, C(2020) 4192 final.

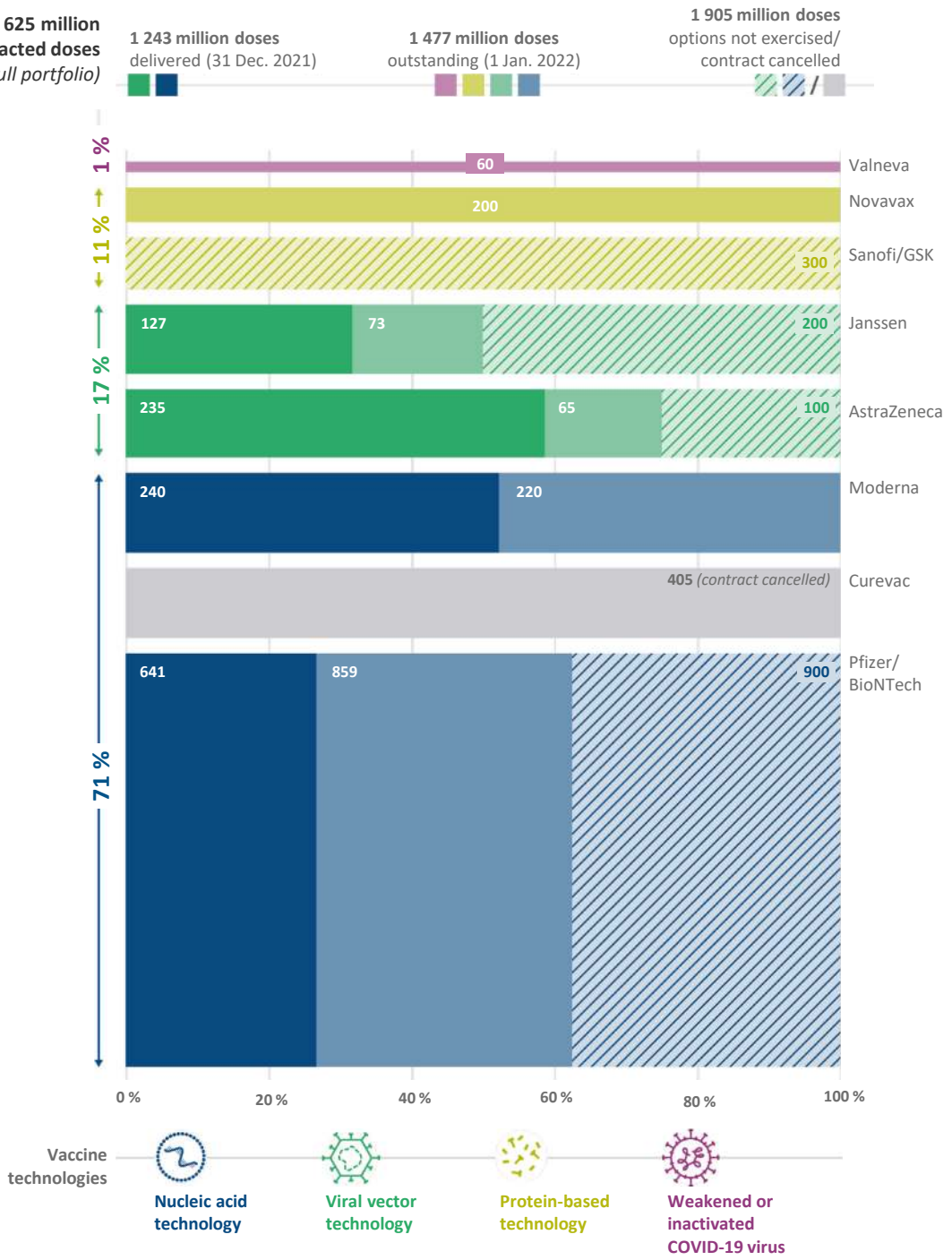
[40] European Ombudsman recommendation, case 1316/2021/MIG, 26.1.2022.

The Commission achieved a diversified vaccine portfolio, but the EU is mainly dependent on one supplier for 2022-2023

51 The steering board considered it important to have a diversified portfolio of vaccines based on different technologies. Vaccine development is a complex process and most vaccines in early development fail. Investing in a wide range of vaccine technologies is a means of spreading risk. The UK and the US have followed a similar approach. The EU included eight vaccine candidates in its portfolio, covering four different vaccine technologies (see ***Annex***).

52 By 31 December 2021, five vaccines had been authorised for use in the EU, and four manufacturers covering two of the main vaccine technologies had delivered a total of 952 million doses (***Figure 8***). The majority of vaccine doses delivered use mRNA technology. The share of mRNA doses administered is still higher as many of the doses donated to third countries up to January 2022 are from AstraZeneca and Janssen, both viral vector technology.

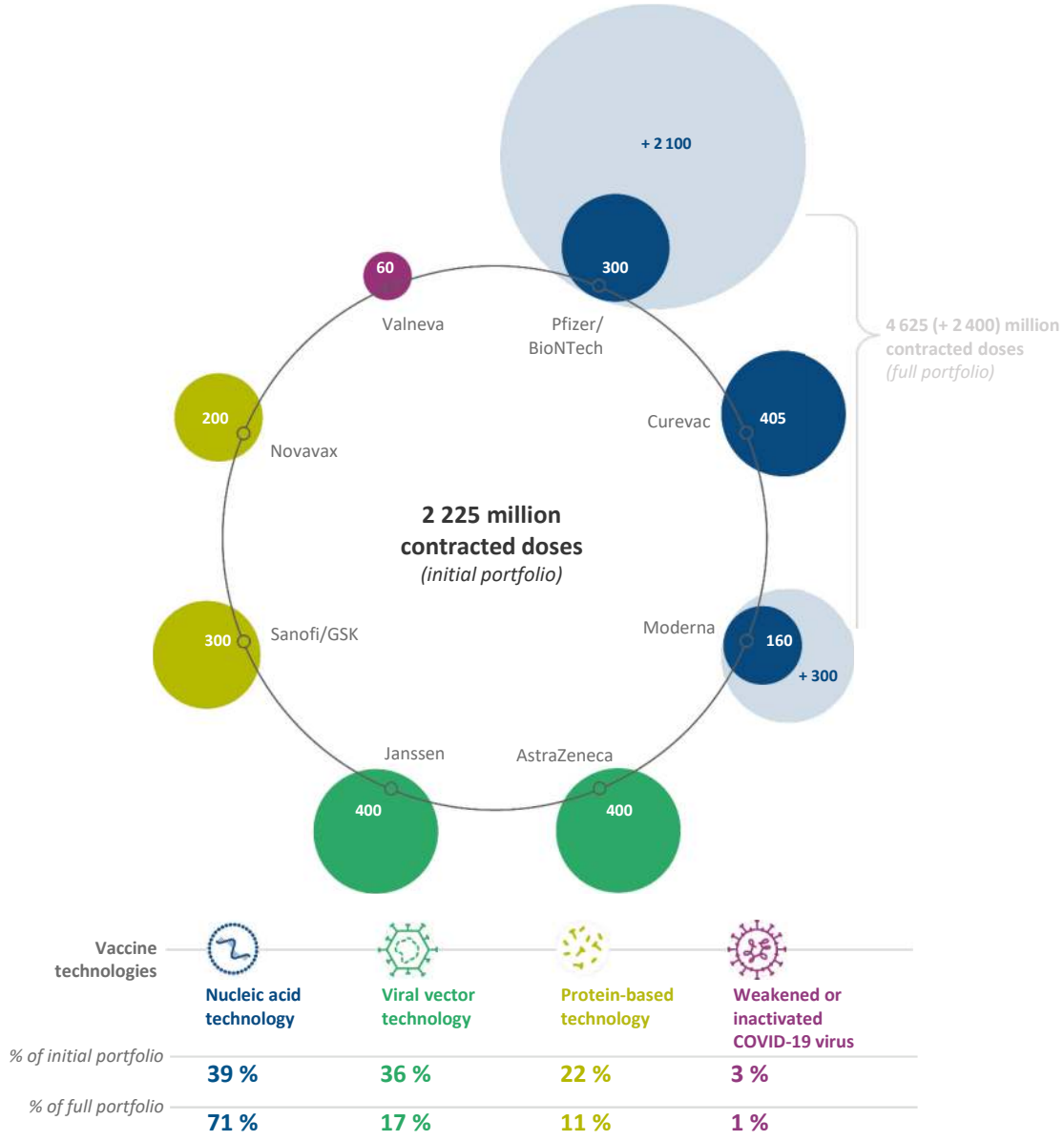
Figure 8 – Proportion of contracted doses versus doses delivered by company, and outstanding quantities to be delivered



Source: ECA based on contracts and ECDC data.

53 The vaccine portfolio has evolved and relies heavily on mRNA technology-based vaccines up to the end of 2023 (see ***Figure 9***), due mainly to the contract of 900 million doses (with an optional additional 900 million doses) with Pfizer/BioNTech. The Commission informed us that the decision to rely on this company was motivated by its ability to reliably supply the EU.

Figure 9 – Initial and full EU vaccine portfolio



Source: Advance Purchase Agreements.

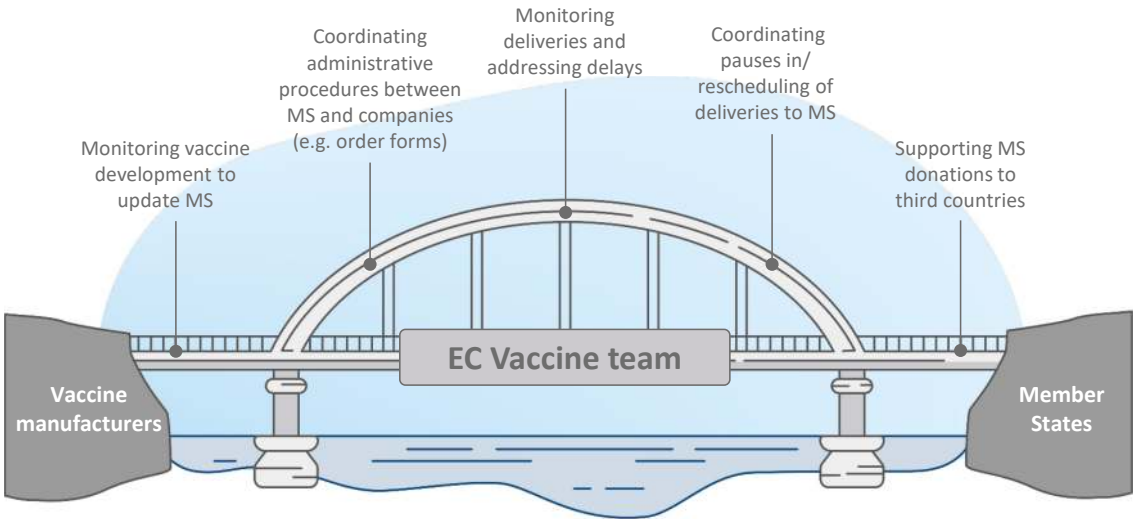
The Commission supported contract implementation but had limited leverage to overcome supply challenges

54 Once the contracts were concluded, the Commission followed up their implementation. We assessed whether the Commission ensured the timely implementation of the contracts and addressed any issues impacting the supply of vaccines.

The Commission acted as a bridge between companies and Member States for contract implementation

55 The Commission bought doses on behalf of the Member States through the contracts. The Member States are therefore the manufacturers' counterparties as regards payment, order forms, receipt of doses, etc. Nevertheless, the Commission took some actions to support the implementation of the contracts (see ***Figure 10***).

Figure 10 – Contract implementation: the Commission's main activities



Source: ECA.

56 As the volume of doses delivered to Member States has increased, the Commission has coordinated vaccine donations aiming to fulfil the EU's pledge to donate 500 million doses to third countries. It has also coordinated the postponement or acceleration of deliveries to some Member States to avoid oversupply or shortages. These activities, while not all formally part of the agreement between the Commission and Member States, supported the execution of the contracts and delivery of doses.

The EU faced vaccine delivery problems in the first half of 2021

57 The supply shortfalls from AstraZeneca and Janssen in 2021 highlight the challenges the EU faced addressing production and supply disruptions. AstraZeneca and Janssen each delivered a third of contractually agreed volumes by the end of June 2021[41]. Pfizer/BioNTech and Moderna also experienced disruptions to their supply to the EU that were either temporary (Pfizer/BioNTech) or in the second half of 2021 and therefore had less impact on overall supply (Moderna).

58 Most of the contracts did not include specific provisions to prioritise deliveries to the Member States. This left the Commission with few options other than taking manufacturers to court for failing to make "best reasonable efforts" to deliver vaccines, or for breaching the warranty on the absence of conflicting contracts. The Commission did take AstraZeneca to court (see ***Box 4***) but not Janssen, which communicated to the Commission the challenges it faced and efforts it made trying to ramp-up production once its vaccine received market approval in March 2021[42]. Deliveries from both companies remained well below expected volumes in 2021 despite Commission actions to support or enforce delivery timetables.

[41] ECDC vaccine tracker.

[42] Johnson & Johnson statement, 31.3.2021.

Box 4

The Commission took AstraZeneca to court for breach of contract

On 4 December 2020, AstraZeneca informed the Commission that it would not be able to deliver the number of doses agreed in the contract in the first quarter of 2021.

In the first quarter of 2021, deliveries were significantly lower than agreed (30 million doses instead of 120 million foreseen in the contract), with AstraZeneca submitting explanations the Commission considered incomplete and invalid. The contract with AstraZeneca did not explicitly provide remedies for such a situation. In March 2021, the Commission therefore launched a legal case against AstraZeneca under Belgian law for late delivery, and another in April seeking faster delivery and financial compensation.

In June 2021, the Brussels Court of First Instance ruled that AstraZeneca was in intentional breach of the contract in that it had chosen not to use its Halix (NL) and Oxford (UK) manufacturing sites to supply the EU, thereby giving priority to supplying the UK. The Court ordered AstraZeneca to deliver 50 million doses of vaccine by 27 September 2021, in accordance with a binding schedule, and set a penalty of €10 per dose not delivered by that date.

On 3 September 2021, the EU and AstraZeneca agreed a new delivery schedule for the period up to March 2022 for the outstanding doses, with more binding delivery obligations on AstraZeneca. This agreement also led the Commission to withdraw all requests for compensation.

59 While supplementary Pfizer/BioNTech deliveries enabled the EU to overcome the shortfall in deliveries from AstraZeneca and Janssen, these delays were a factor impacting the scale and speed of vaccinations in the first half of 2021, when the EU was slower to vaccinate its population than the UK and the US (see ***Figure 4***). The US in particular had legal recourse to support security of supply (see ***Box 3***).

60 The EU put in place an export authorisation scheme for COVID-19 vaccines on 30 January 2021[43], which ran until the end of December 2021[44]. This scheme allowed the Commission and Member States to track vaccine exports and block them if for example a vaccine manufacturer did not respect its delivery obligations. One shipment

[43] Commission Implementing Regulation 2021/111.

[44] Commission Implementing Regulation 2021/1728.

was blocked using this scheme[45]. Blocking vaccine exports is an instrument of last resort for the Commission, which has stressed its commitment to exporting vaccines to help fight the pandemic[46].

The Commission only created a task force to support manufacturing and supply chains in February 2021

61 In February 2021, the OECD cautioned that there is "a high degree of trade interdependence in the goods needed to produce, distribute and administer vaccines", and "existing evidence on production capacity is scarce"[47]. The President of the Commission acknowledged that producing a new vaccine is a complex process and admitted that "overall we have underestimated the difficulties inherent in mass production"[48].

62 The Commission's Task Force for Industrial Scale-up of COVID-19 vaccines (TFIS) was set up in February 2021, eight months after the steering board for vaccine procurement and JNT had started work. It was also nine months after the Commission had committed to exploring supporting the scaling up of vaccine production[49] and eight months after the Commission had assessed the likelihood of other economies imposing export restrictions on vaccines. The TFIS was not specifically created to support ongoing negotiations but rather as part of the preparations for the launch of Health Emergency Preparedness and Response Authority (HERA)[50], to help respond to production issues blocking the scaleup of COVID-19 vaccine production. The TFIS's main activities include:

- identifying and removing vaccine production bottlenecks in the EU;

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[45] Statement by President von der Leyen at the joint press conference with President Michel, 25.3.2021.

[46] Speech by President von der Leyen at the launch of the Belgian Biopharma Platform, 26.10.2021.

[47] OECD, "Using trade to fight COVID-19: Manufacturing and distributing vaccines", 10.2.2021.

[48] Speech by President von der Leyen at the European Parliament Plenary on the state of play of the EU's COVID-19 Vaccination Strategy, 10.2.2021.

[49] Joint European Roadmap towards lifting COVID-19 containment measures, 17.4.2020.

[50] Commission Communication on the HERA Incubator, COM(2021) 78.

- mapping EU vaccine production capacities throughout the supply chain;
- facilitating partnerships through matchmaking events for vaccine and therapeutics production;
- ensuring sufficient long-term manufacturing capacity in Europe;
- supporting global vaccine access and vaccine sharing efforts[51].

63 The TFIS mapped and monitored COVID-19 vaccine production in the EU. It did this mainly through meetings with the contract signatories, suppliers to these vaccine manufacturers and Member State authorities. The TFIS carried out more detailed research, including site visits, on four vaccine manufacturers and their subcontractors to ascertain their production capacities and supply networks and assess potential risks to their capacity to deliver. In all but one case, these assessments were completed just days before the contracts were signed, and thus too late to influence contract negotiations.

64 By comparison, both the UK and the US anticipated manufacturing and supply problems earlier in the process, either by funding the development of industrial capacity or by having officials actively monitoring and supporting companies production efforts (see ***Box 2*** and ***Box 3***).

65 The proposed Council Regulation on an emergency framework for medical countermeasures[52] provides for the Commission to create inventories of relevant production facilities (including their supply chains) when the relevant measure the emergency framework is activated. HERA will prepare for the eventual activation of this provision through continuous monitoring and mapping of relevant supply chains and production capacities[53].

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[51] European Commission website: "Task Force for Industrial Scale-up of COVID-19 vaccines", accessed 1.4.2022.

[52] Proposal for a Council regulation on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level, COM/2021/577 final.

[53] Commission Communication, "Introducing HERA", COM(2021) 576.

The Commission helped resolve bottlenecks although the size of its impact on the ramp up of production is unclear

66 The Commission monitored and mapped EU-based vaccine production to identify where the vaccine production and supply chain was experiencing shortages or bottlenecks, or risked doing so. It did this in order to help address such problems and ramp up production. According to the Commission, the most critical shortages facing vaccine manufacturers in the EU in the first half of 2021 were of bioreactor bags, filters and tubes.

67 The TFIS supported vaccine manufacturers facing such shortages, as well as those looking for spare production or fill and finish capacity, by acting as a facilitator, establishing contacts between different companies and between companies and the relevant Member State authorities. It also held regular meetings with its US counterpart to help mitigate shortages in the EU linked to US government "priority orders" of vaccine-related inputs (see ***Box 3***). These contacts were formalised in September 2021 through the creation of the EU-US joint COVID-19 Manufacturing and Supply Chain Taskforce[54].

68 The TFIS was able to play a facilitating and supporting role in this area but the size of the impact on its stated aim to "ramp-up production capacity for vaccines in the EU"[55] is unclear. Increases in production capacity resulted to a significant extent from commercial decisions taken by manufacturers in response to contracts signed with the Commission and other customers, often before the TFIS had been set up.

The Commission has not evaluated or benchmarked its procurement of COVID-19 vaccines

69 The EU's COVID-19 vaccine procurement efforts secured, from different manufacturers, sufficient doses both to vaccinate all EU adult citizens and to make donations to third countries by the end of 2021. The proposed Council Regulation on

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[54] US-Commission joint statement: Launch of the joint COVID-19 Manufacturing and Supply Chain Taskforce, 22.9.2021.

[55] European Commission website: "EU vaccine strategy", accessed 4.1.2022.

an emergency framework for medical countermeasures[56] provides for the possibility to activate a similar procurement structure to that used in response to COVID-19 in case of future health emergencies.

70 The Council[57] and Commission[58] have each published a "lessons learned" document on COVID-19 and public health. Neither examined the performance of the vaccine procurement process, beyond its overall outcome, in order to identify areas for improvement. This is despite the Council inviting the Commission to evaluate and report on, within the first half of 2021, "the procurement of medical countermeasures and the Emergency Support Instrument with respect to, *inter alia*, governance structure, transparency and information exchange between the Commission and the Member States"[59]. The Commission's proposal for the Council Regulation on an emergency framework for medical countermeasures was not supported by a dedicated impact assessments or public consultation. The proposed regulation on an emergency framework for medical countermeasures mandates a review of its provisions by 2024.

71 The Commission did not consider in detail the operation and structure of EU vaccine procurement to understand what enabled it to secure sufficient doses and what were the risks to that outcome. It has also not benchmarked this process against other vaccine procurement systems to identify best practices. The Commission told us that it has not analysed the publicly available information on the vaccine manufacturers' contractual clauses obtained by third countries to identify examples of what the EU could aim for in future negotiations to improve the security of vaccines supply.

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[56] Proposal for a Council regulation on a framework of measures for ensuring the supply of crisis-relevant medical countermeasures in the event of a public health emergency at Union level, COM/2021/577 final.

[57] Council conclusions on COVID-19 lessons learnt in health, 18.12.2020.

[58] Commission Communication, "Drawing the early lessons from the COVID-19 pandemic", COM/2021/380.

Conclusions and recommendations

72 We examined the Commission's preparations for the procurement of COVID-19 vaccines as well as the conduct of the negotiations and the extent to which the EU's negotiators were able to secure the EU's procurement objectives in the contracts it signed with vaccine manufacturers. We also examined what remedies the EU could use when faced with supply disruptions and how the Commission helped support the production of vaccines for the EU.

73 We conclude that by signing contracts with a number of different manufacturers covering different technologies in order to spread and reduce the risk of failed vaccine development, the EU managed to procure COVID-19 vaccines it needed.

74 We found that the EU's preparations for the procurement of COVID 19 vaccines were mostly effective. The EU identified vaccines as a key element in the fight against COVID-19 early on in the pandemic (see paragraph ***18***) and took steps to create an ad hoc and tailor-made procurement system to secure vaccines for EU citizens. However, the EU started this procurement process later than the UK and the US (see ***Figure 4***).

75 The EU had to act ahead of clear scientific data on vaccine candidates' safety and efficacy (see paragraph ***30***), and therefore chose to back a range of candidates in its initial portfolio. The initially diversified portfolio of vaccines is dominated by the Pfizer/BioNTech vaccine for 2022-2023 (see ***Figure 8***), which the Commission states is necessary for reasons of security of supply. The Commission produced its vaccine strategy in the early stages of the pandemic, at a time when there were no COVID-19 vaccines on the market (see paragraph ***24***).

76 The EU's negotiators were better able to secure the EU's procurement objectives in the later contracts it signed with vaccine manufacturers. The terms of the contracts evolved over time and those signed in 2021 have stronger provisions on key issues such as delivery schedules and production location than those signed in 2020. EU negotiators took a flexible approach to negotiations with vaccine manufacturers, imposing only one negotiating red line: adherence to the Product Liability Directive (see paragraph ***46***). The liability and indemnification clauses have remained the same: Member States have taken over some of the financial risk (i.e. compensation payments and legal costs) linked to vaccine administration from the manufacturers. This reflects the unique circumstances at the time these clauses were agreed. The Commission and

ten of the 14 Member States that responded to our survey wish to see a more standard liability regime when the standard marketing authorisation has been granted.

77 We found that the Commission had limited leverage to overcome supply challenges. The Commission acted as a bridge between companies and Member States for contract implementation (see paragraph ***56***) but it did not fully analyse the production and supply chain challenges of vaccine production until after signing most of the contracts (see paragraph ***63***) and most contracts did not include specific provisions to address supply disruptions (see paragraph ***58***). The Commission could, and in one case did, take manufacturers to court (see ***Box 4***). The Commission only set up a task force to support manufacturing and supply chains in February 2021 (see paragraph ***62***) and while it did help resolve bottlenecks, its impact on the ramp-up of vaccine production was unclear(see paragraph ***67***).

78 A new procurement system was rapidly set up and delivered a diversified portfolio of vaccine candidates for the EU. The Commission proposed to continue the procurement approach set up for COVID-19 for future health crises, but neither the Commission's nor the Council's "lessons learned" reports on the COVID-19 pandemic examined the performance of the vaccine procurement process, beyond its overall outcome. The Commission has not studied third country procurement systems to identify good practices (see paragraph ***71***).

Recommendation 1 – Create pandemic procurement guidelines on the basis of lessons learnt

Once the Emergency Framework Regulation and the revised Financial Regulation have been adopted, after consulting Member State authorities and relevant stakeholders, and benchmarking with other procurement systems to identify good practices, the Commission should produce pandemic procurement guidelines and/or lessons learnt for future negotiating teams.

Target implementation date: one year from the adoption of the two legal bases

79 The EU is putting in place a range of new pandemic preparedness and response measures following the outbreak of the COVID-19 pandemic. It is as a result taking on a greater role in preparing for and responding to pandemics, notably in the field of procurement (see paragraph ***69***). The Commission did not evaluate and report on the procurement of medical countermeasures and the use of the Emergency Support Instrument, despite having been invited by the Council to do so (see paragraph ***71***).

80 The EU's new competences and activities were not determined on the basis of an ex-ante impact assessment (see paragraph ***70***). Issues in the EU's procurement process such as identifying which skills are needed in the EU's negotiating team (see paragraph ***26***) or how the EU can best contribute to solving supply chain and production issues remain to be addressed (see paragraph ***68***).

81 Despite the WHO considering pandemic planning exercises to be an integral part of preparedness and despite the Commission supporting preparedness and response projects at EU and Member State level since 2003 (see paragraph ***22***), the Commission is not currently planning to test its new competences for procurement of medical countermeasures through exercises and simulations to identify and address areas for improvement.

Recommendation 2 – Stress-test the EU's medical countermeasures procurement approach

The Commission should, in order to be in line with best practices and contribute to the review of the Council Regulation on an emergency framework for medical countermeasures:

(a) carry out a risk assessment of the EU's procurement approach and propose appropriate measures;

(b) run exercises to test all parts of its updated pandemic procurement framework, including information and intelligence gathering, to identify any weaknesses and areas for improvement and publish the results.

Target implementation date: Q2 2024

This report was adopted by Chamber I, headed by Ms Joëlle Elvinger, Member of the Court of Auditors, in Luxembourg at its meeting of 6 July 2022.

For the Court of Auditors

Klaus-Heiner Lehne
President

Annex

Vaccine technologies in the EU COVID-19 vaccine portfolio

Vaccine technologies in EU portfolio	**Nucleic acid** *(mRNA)*	**Viral vector** *(replicating or non-replicating)*	**Protein-based**	**Virus** *(weakened or inactivated)*
Description	The vaccine contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2, the virus that causes COVID-19.	The vaccine is made up of another virus (e.g. of the adenovirus family) that has been modified to contain the gene for making a protein from SARS-[redacted]	The vaccine contains a version of a protein found on the surface of SARS-CoV-2 (the spike protein), which has been produced in the laboratory.	The vaccine contains the COVID-19 virus itself, in a weakened or inactivated form.
Existing vaccines using this technology	-	Recent vaccine against ebola	Vaccines against seasonal influenza, human papillomavirus (HPV) and hepatitis B (HBV)	Vaccines against measles, mumps, rubella and polio
Vaccine candidates in EU portfolio	Moderna Pfizer/BioNTech Curevac	Janssen AstraZeneca	Novavax Sanofi Pasteur	Valneva
Authorised for use in the EU?	**Yes:** Spikevax (Moderna) Comirnaty (Pfizer/BioNTech) **No:** Curevac withdrew its vaccine CVnCoV from the autorisation process in October 2021.	**Yes:** COVID-19 Vaccine Janssen (Janssen) Vaxzevria (AstraZeneca)	**Yes:** Nuvaxovid (Novavax) **No:** Vidprevtyn (Sanofi Pasteur) under rolling review	**No:** VLA2001 (Valneva) under rolling review

Source: ECA based on GAO and EMA data.

Acronyms and abbreviations

APA: Advance purchase agreement

EEA: European Economic Area

ECDC: European Centre for Disease Prevention and Control

ESI: Emergency Support Instrument

EMA: European Medicines Agency

HERA: European Health Emergency Preparedness and Response Authority

IFPMA: International Federation of Pharmaceutical Manufacturers & Associations

IVA: Inclusive Vaccine Alliance

JNT: joint negotiation team

mRNA: Messenger RNA

OECD: Organisation for Economic Co-operation and Development

PA: Purchase agreement

TFIS: Task Force for Industrial Scale-up of COVID-19 vaccines

WHO: World Health Organisation

Glossary

Advance Purchase Agreements: Agreement concluded with a supplier to purchase a specified quantity of a product in the future.

Bioreactor bags: A single-use bioreactor is a plastic bag made of a multilayered polymer film.

Conditional marketing authorisation: Emergency authorisation to make a medicine available even though the requirement for comprehensive clinical data has not yet been met.

Containment measure: Action or policy to contain the spread or transmission of the SARS-CoV-2 virus in areas or communities where it has already taken hold. These measures include lockdowns, quarantine, isolation, and cordon sanitaire.

Emergency Support Instrument: Financial instrument directly managed by the Commission that allows it to provide support within the EU in case of disasters.

European Medicines Agency: EU agency that provides independent recommendations on medicines for human and veterinary use, based on a comprehensive scientific evaluation of data. The Agency's evaluations of marketing-authorisation applications provide the basis for the authorisation of medicines in Europe.

European Health Emergency Preparedness and Response Authority: A Commission service that has been set up to improve preparedness and response to serious cross-border threats in the area of medical countermeasures.

Financial Regulation: The rules governing how the EU budget is set and used, and the associated processes such as internal control, reporting, audit and discharge.

Operation Warp Speed: U.S. initiative to develop and deliver 300 million doses of a COVID-19 vaccine by January 2021.

Standard Marketing authorisation: Marketing authorisation granted by the European Commission after evaluation by the EMA of complete data confirming that the medicine's benefits continue to outweigh its risks. Initially valid for five years, it can then be renewed indefinitely.

Task Force for Industrial Scale-up of COVID-19 Vaccines: Team set up within DG GROW with the involvement of several Commission services to support the increase in COVID-19 vaccine production capacity.

Vaccine candidate: Potential vaccine under development at the time of negotiations between the EU and vaccine manufacturer.

Replies of the Commission

https://www.eca.europa.eu/en/Pages/DocItem.aspx?did=61899

Timeline

https://www.eca.europa.eu/en/Pages/DocItem.aspx?did=61899

Audit team

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This performance audit was carried out by Audit Chamber I Sustainable use of natural resources, headed by ECA Member Joëlle Elvinger. The audit was led by ECA Member Joëlle Elvinger, supported by Ildikó Preiss, Head of Private Office and Paolo Pesce, Private Office Attaché; Nicholas Edwards, Head of Task; Paul Stafford, Principal Manager; Els Brems, Auditor; Aleksandra Melesko, Legal Support and Marika Meisenzahl, Auditor and graphic design. Judita Frangež provided secretarial support.

From left to right: Aleksandra Melesko, Paul Stafford, Joëlle Elvinger, Nicholas Edwards, Ildikó Preiss, Marika Meisenzahl and Paolo Pesce.

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The EU launched its vaccine procurement strategy in June 2020. By the end of 2021, it had signed €71 billion worth of contracts securing up to 4.6 billion doses. We conclude that the EU secured a diversified vaccine portfolio for Member States, though it started procurement later than the UK and the US. The contracts signed in 2021 have stronger provisions on key issues than those signed in 2020. We found that the Commission had limited leverage to overcome supply challenges and the size of its impact on the ramp-up of vaccine production was unclear. Our recommendations focus on the need to draw lessons learnt and run exercises to test the EU's updated pandemic preparedness framework.

ECA special report pursuant to Article 287(4), second subparagraph, TFEU.

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Productie 54

mRNA vaccines are distinct from gene therapy, which alters recipient's genes

By Reuters Fact Check
August 10, 20213:58 PM GMT+2Updated 3 years ago

Vaccines that use mRNA technology are not gene therapy because they do not alter your genes, experts have told Reuters after contrary claims were posted online.

Thousands of social media users have shared such posts since the rollout of COVID-19 vaccines began (here) – and have continued to do so through August.

"It's not a vaccine. It's gene therapy!" wrote one Facebook user on Aug. 9, noting that gene therapy "manipulates genetic code" (here and here).

Pfizer/BioNTech and Moderna have both developed shots that use a piece of genetic code from SARS-CoV-2, the coronavirus that causes COVID-19, to prompt an immune response in recipients (here). However, experts told Reuters that this is not the same as gene therapy.

“As mRNA is genetic material, mRNA vaccines can be looked at as a genetic-based therapy, but they are classified as vaccines and are not designed to alter your genes,” said Dr Adam Taylor, a virologist and research fellow at the Menzies Health Institute, Queensland, Griffith University.

“Gene therapy, in the classical sense, involves making deliberate changes to a patient’s DNA in order to treat or cure them. mRNA vaccines will not enter a cell's nucleus that houses your DNA genome. There is zero risk of these vaccines integrating into our own genome or altering our genetic makeup.”

Taylor explained that mRNA enters cells shortly after vaccination and instructs them to create a SARS-CoV-2 spike protein, prompting the immune response.

He added that unlike gene therapy, mRNA vaccines are then “rapidly degraded” by the body.

“In fact, because mRNA is degraded so quickly chemical modifications can be made to mRNA vaccines to make them a little more stable than regular mRNA.”

Gene therapy, on the other hand, involves a process whereby an individual’s genetic makeup is deliberately modified to cure or treat a specific genetic condition (here).

It can be done in several ways, such as replacing a disease-causing gene with a healthy alternative, disabling a disease-causing gene or introducing a new gene to help treat a disease, according to the U.S. Food and Drug Administration (FDA) (here).

“If we suffer from an inherited blood disease then the defect in our genes can be corrected in blood cells and then we can be cured,” said David Schaffer, professor of Chemical and Biomolecular Engineering and Director of the Berkeley Stem Cell Center at the University of California, Berkeley, in an email to Reuters.

“In most cases, the DNA is therapeutic because it encodes a mRNA, which encodes a protein that has a beneficial effect on a patient. So, if someone has a disease where the gene encoding an important protein is mutated - such as hemophilia, cystic fibrosis, retinitis pigments - then it can be possible to deliver the DNA encoding the correct copy of that protein in order to treat the disease.”

He added: “Because DNA has the potential to persist in the cells of a patient for years, this raises the possibility of a single gene therapy treatment resulting in years of therapeutic benefit.”

Moderna, which has developed one of the mRNA COVID-19 vaccines used across the world, explained in a fact sheet that mRNA and gene therapy take “fundamentally different” approaches.

“Gene therapy and gene editing alter the original genetic information each cell carries,” the company writes. “The goal is to produce a permanent fix to the underlying genetic problem by changing the defective gene. Moderna is taking a different approach to address the underlying cause of MMA and other diseases. mRNA transfers the instructions stored in DNA to make the proteins required in every living cell. Our approach aims to help the body make its own missing or defective protein” (www.modernatx.com/about-mrna).

Reuters has in the past debunked claims that COVID-19 vaccines can genetically modify humans here and here .

VERDICT

Missing context. Scientists told Reuters that while mRNA vaccines can be considered “genetic-based therapy” because they use genetic code from COVID-19, they are not technically gene therapy. This is because the mRNA does not change the body’s genetic makeup.

This article was produced by the Reuters Fact Check team. Read more about our work to fact-check social media posts here .

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Productie 55

COLLEGE TER
BEOORDELING VAN
GENEESMIDDELEN

Column 'Over medicijnen': Coronavaccins experimenteel?

Nieuwsbericht | 02-06-2021 | 11:00

Medio mei had ik een interview met Frank Leeman van het BNR-radioprogramma Factgurus. Aanleiding was een al wat oudere, ingezonden brief in Trouw. De briefschrijfster, een hoogleraar, beweerde dat de coronavaccins nog experimenteel zouden zijn. De vaccins zouden alleen voorlopig zijn goedgekeurd, tot 2023. Liet je je nu vaccineren, dan was je dus eigenlijk een soort proefkonijn. Of dat klopte, wilde Frank graag weten.

Nee, dat klopt niet. Daar kon ik gelukkig kort over zijn. De coronavaccins zijn niet experimenteel. De coronavaccins zijn wel ‘voorwaardelijk’ goedgekeurd. En daar zit vaak het misverstand. Voorwaardelijk klinkt als ‘voorlopig’, alsof het vaccin eigenlijk nog niet aan alle eisen voldoet. Alsof er nog gegevens missen. Alsof de eerste proeven nog lopen. Maar dat beeld klopt niet.

Een voorwaardelijk goedgekeurd vaccin voldoet aan de eisen wat betreft werkzaamheid, veiligheid en kwaliteit. De fabrikant moet alleen nog voldoen aan voorwaarden. Zo moet zij nog het eindrapport van de studies en de lange termijn gegevens aanleveren. Bijvoorbeeld of het vaccin ook werkt bij kinderen. Of bij zwangere vrouwen. Ook moet de fabrikant op gezette tijden gegevens aanleveren, bijvoorbeeld over bijwerkingen. Dat helpt ons om zeldzame bijwerkingen snel in beeld te krijgen. Zulke extra checks komen vaker voor bij nieuwe vaccins en medicijnen.

Dankzij de vergunning met extra voorwaarden konden we al in december 2020 starten met prikken tegen het coronavirus. Verder wisten we na een paar weken dat sommige vaccins heel soms kunnen leiden tot ernstige bijwerkingen. Daardoor konden we snel ingrijpen. De fabrikanten van Pfizer en Moderna hebben inmiddels hun kinderstudies afgerond en ingeleverd. Vorige week leverde dit de eerste goedkeuring op voor gebruik bij kinderen van 12 jaar en ouder. Het gaat dus hard.

En als de vaccins straks aan alle voorwaarden voldoen? Krijgen ze dan alsnog een volledige goedkeuring? Jazeker. Maar ook dan verliezen we ze niet uit het oog. Ook dan moeten fabrikanten op gezette tijden gegevens blijven aanleveren.

Onderzoek naar vaccins is ingewikkelde materie. De regels voor goedkeuring zijn dat ook. Een misverstand is zo geboren. En het is een hele klus dat de wereld weer uit te krijgen. Geloof niet alles wat u hoort. Kijk bij twijfel eens op de websites van de overheid, zoals het RIVM, de Rijksoverheid, of van het CBG. Of van media die zich baseren op betrouwbare bronnen. Ik was in ieder geval blij dit op BNR te mogen vertellen.

Over de column

Voorzitter prof. dr. Ton de Boer schrijft elke maand een column ‘Over medicijnen’, over gezondheid en welzijn. De column verschijnt in de Fit-bijlage van de Holland Media Combinatie (Noordhollands Dagblad, Haarlems Dagblad, Leidsch Dagblad, Gooi- en Eemlander en IJmuider Courant). De column verschijnt ook op Gezondheid&Co, het gezondheidsplatform voor Noord-Nederland, van de Noordelijke Dagblad Combinatie (de NDC Mediagroep). De columns staan in het teken van de actualiteit en onze rol en ons werk als Nederlandse medicijnautoriteit.

Zie ook

Hoort bij

Productie 56

Bijwerkingen coronavaccins

Voor bescherming tegen het coronavirus kun je een coronavaccin nemen. De coronavaccinatie kan bijwerkingen geven. Op deze pagina staat meer informatie over de aard en de duur van bijwerkingen van coronavaccins. Kijk voor meer informatie over de bijwerkingen per vaccinmerk in de vaccinkennisbank.

Bijwerkingen van coronavaccinaties in het kort:

- Veelvoorkomende bijwerkingen van de coronavaccinatie zijn onder andere: hoofdpijn, je niet lekker voelen, vermoeidheid, reacties op de prikplek, spierpijn en pijn in de gewrichten. Deze bijwerkingen kan je bij iedere vaccinatie weer verwachten.
- Bijwerkingen ontstaan meestal binnen een paar dagen na vaccinatie en gaan meestal vanzelf over.
- Pfizer en Moderna hebben hun coronavaccins aangepast zodat ze naast de originele stam ook de heersende omikronvariant bevatten. De bijwerkingen van de aangepaste coronavaccins zijn vergelijkbaar met de bijwerkingen na een prik met de eerdere coronavaccins.
- Heb je een allergische reactie na de een coronavaccinatie gehad? Overleg dan altijd met een behandelend arts/allergoloog of je alsnog de volgende coronavaccinatie (ongeacht merk) mag krijgen.
- Maak je je zorgen of twijfel je over jouw klachten, neem dan contact op met jouw huisarts. Ook bij vragen over behandeling van de bijwerking of over de (vervolg)vaccinatie.
- Bekijk hier de meldingen die wij hebben ontvangen op de coronavaccins. Wil je zelf een bijwerking melden? Dat kan via ons meldformulier.

Wie ervaart bijwerkingen na coronavaccinatie?

Iedereen kan bijwerkingen ervaren na vaccinatie. Als je eerder bijwerkingen hebt ervaren, hoeft dit niet te betekenen dat je dezelfde klachten weer zult krijgen bij een nieuwe vaccinatie. En andersom geldt dit ook. Als je eerder geen bijwerkingen hebt ervaren, kan het zijn dat je deze nu wel ervaart.

Jongere mensen ervaren over het algemeen vaker bijwerkingen dan ouderen. De meeste bijwerkingen na coronavaccinatie bij kinderen zijn hetzelfde als de bijwerkingen bij (jong)volwassenen.

Uit onderzoek blijkt dat mensen die eerder COVID-19 hebben gehad vaker en hevigere bijwerkingen van een coronavaccinatie kunnen ervaren. Dit is ook gezien in ons vragenlijstonderzoek.

Het combineren van twee of meer coronavaccins kan soms een iets hogere kans op kortdurende, wat heftiger bijwerkingen geven. Dit is met name onderzocht voor bekende bijwerkingen zoals pijn op de prikplek, koorts, spierpijn en misselijkheid.

Wanneer treden bijwerkingen na coronavaccinatie op en hoelang duren ze?

Bijwerkingen ontstaat meestal binnen 48 uur na de vaccinatie. Soms kunnen bijwerkingen ook later ontstaan. De kans op bijwerkingen die pas later optreden, is over het algemeen erg klein. Bijwerkingen gaan meestal vanzelf over binnen enkele dagen. Soms kunnen klachten na coronavaccinatie langer aanhouden. Hier wordt meer onderzoek naar gedaan.

Voor de mRNA coronavaccinaties (Pfizer/BioNTech en Moderna) komen de bekende bijwerkingen vaker voor na je 2e vaccinatie. Voor Moderna werd dit ook gezien in het vragenlijstonderzoek van Lareb.

Houden klachten langer dan twee weken aan en/of maak je je zorgen over klachten? Neem dan altijd contact op met je huisarts.

Welke bijwerkingen treden op na coronavaccinatie?

De meest voorkomende bijwerkingen na de coronavaccinaties zijn:

- Reacties op de plek van de prik (pijn, roodheid)

- Vermoeidheid
- Hoofdpijn
- Niet lekker voelen
- Koorts
- Spierpijn
- Pijn in de gewrichten
- Maag-/darmklachten (zoals misselijkheid, braken en diarree)
- Koude rillingen

Er kunnen ook specifieke bijwerkingen optreden na coronavaccinatie. Enkele hiervan worden hieronder toegelicht. Neem contact op met je huisarts als je vermoedt een van deze bijwerkingen te hebben.

Aangezichtsverlamming van Bell

Aangezichtsverlamming van Bell is een zeldzame bijwerking van de coronavaccins van Pfizer/BioNTech, Moderna en AstraZeneca. Bij de aangezichtsverlamming van Bell is er sprake van een plotselinge spierverlamming in één helft van het gezicht Het risico op de aangezichtsverlamming van Bell na vaccinatie is kleiner dan het risico op de aandoening na het doormaken van een corona-infectie.
Lees hier meer over aangezichtsverlamming van Bell

Allergische reacties

Heftige allergische reacties na een coronavaccinatie zijn zeldzaam. Een heftige allergische reactie treedt meestal op binnen 15 tot 30 minuten na je prik. Er kan dan sprake zijn van: zwellingen rond de ogen, van de lippen, tong of keel, acute benauwdheid, huiduitslag of jeuk over je hele lichaam en een lage bloeddruk met een snelle hartslag. Soms ontstaan vergelijkbare klachten zonder aantoonbare allergische reactie. Of een vervolgvaccinatie mogelijk is na mogelijke allergische klachten, kun je bespreken met uw (huis)arts.
Lees hier meer over allergische reacties na vaccinatie.

Capillairleksyndroom

Ook het capillairleksyndroom is als ernstige zeldzame bijwerking in de bijsluiter opgenomen AstraZeneca en Janssen coronavaccin. Het capillairleksyndroom komt zeer zelden voor. Bij deze ernstige ziekte lekt vloeistof weg uit de haarvaten. Dat zorgt voor een lage bloeddruk, zwelling van vooral de armen en benen, verdikking van het bloed en te weinig albumine in het bloed.

Klachten die hierbij passen zijn:

- Een snelle zwelling van de armen en benen
- Plotselinge gewichtstoename
- Vaak in combinatie met een duizelig gevoel (door lage bloeddruk)

Mensen die eerder systemisch capillairleksyndroom hebben gehad, mogen geen AstraZeneca vaccin of Janssen vaccin krijgen. Dit is namelijk als contra-indicatie en als bijwerking toegevoegd aan de bijsluiter van deze vaccins. Bij het Moderna vacccin is bekend dat mensen met een voorgeschiedenis van deze ziekte een opvlamming kunnen krijgen.

Cerebrale veneuze sinustrombose (CVST)

Ook cerebrale veneuze sinustrombose is opgenomen als zeldzame bijwerking in de bijsluiter van het AstraZeneca vaccin. CVST is een zeldzame vorm van beroerte. Hierbij raken één of meerdere grote aders (sinussen) in de hersenen verstopt door een bloedstolsel. Deze bijwerking trad in de meeste gevallen binnen 4 weken na vaccinatie op. Symptomen zijn onder andere:

- Hoofdpijn
- Uitvalsverschijnselen
- Mogelijk epileptische aanvallen

Als er naast CVST ook een tekort aantal bloedplaatjes is, kan het gaan om de zeldzame bijwerking trombose met een tekort aan bloedplaatjes (TTS). Maar CVST kan ook optreden zonder een tekort aan bloedplaatjes.

Cutane vasculitis

Ontsteking van de kleine bloedvaten in de huid (cutane vasculitis) is als bijwerking toegevoegd aan de bijsluiter van het Janssen vaccin. Bij cutane vasculitis blijft de bloedvatontsteking beperkt tot de huid. Dit kan zich uiten in huiduitslag of bloeduitstortingen.

Guillain-Barré syndroom

De zeldzame aandoening Guillain-Barré is toegevoegd in de bijsluiter van het AstraZeneca en Janssen coronavaccin. Bij Guillain-Barré syndroom valt het immuunsysteem zenuwen buiten het centraal zenuwstelsel aan en beschadigt deze. De aangedane zenuwen zijn vooral gevoelszenuwen en zenuwen die spieren aansturen. De klachten die optreden zijn daarom meestal spierzwakte en gevoelsstoornissen zoals tintelingen in de benen en armen.
Lees hier meer over Guillain-Barré na vaccinatie.

Hevige bloedingen tijdens de menstruatie

Hevige bloedingen tijdens de menstruatie is opgenomen in de bijsluiters van de coronavaccins van Pfizer/BioNTech en Moderna. De meeste gevallen blijken niet ernstig en tijdelijk van aard te zijn.
Lees hier meer over menstruatiestoornissen na vaccinatie.

Laag aantal bloedplaatjes

Immuun trombocytopenie is toegevoegd als bijwerking aan de bijsluiter van het AstraZeneca en Janssen vaccin. Hierbij is er sprake van een laag aantal bloedplaatjes. Klachten die kunnen ontstaan bij ITP zijn: spontane bloedingen, blauwe plekken en/of rood, paarse puntvormige bloedinkjes op de huid buiten de prikplek.

Ontsteking van de hartspier of het hartzakje

Ontsteking van de hartspier (myocarditis) en hartzakje (pericarditis) is opgenomen als bijwerking in de bijsluiter van het Pfizer/BioNTech, Moderna en Novavax coronavaccin. Het gaat om zeldzame bijwerkingen, die meestal binnen 1 tot 5 dagen na de vaccinatie ontstaan. Klachten zijn onder andere:

- Kortademigheid
- Pijn op de borst

- Hartkloppingen die soms onregelmatig zijn

De klachten gaan meestal vanzelf over of zijn met medicijnen goed te behandelen.

Ontsteking van het ruggenmerg

Ontsteking van het ruggenmerg (myelitis transversa) is een zeldzame bijwerking van het AstraZeneca en Janssen coronavaccin. Door een ontsteking van het ruggenmerg ontstaan klachten die passen bij een dwarslaesie. Klachten kunnen zijn:

- Acute zwakte in de benen
- Gevoelsstoornissen
- Verstoring van de blaas of de darmen

Het ontstaat door een auto-immuunreactie. Dit kan veroorzaakt worden door onder andere ziektes en infecties, ook een COVID-19 infectie.

Oorsuizen

Oorsuizen (tinnitus) is in de bijsluiter van het Janssen vaccin opgenomen als bijwerking.

Bij oorsuizen hoort iemand een piep, sis of bromgeluid zonder dat dat geluid er werkelijk is. Het kan gevolg zijn van langdurige blootstelling aan lawaai, maar ook van afwijkingen aan het gehoororgaan, de hersenen of het kaakgewricht. Daarnaast komt het voor als bijverschijnsel van andere aandoeningen of ontstaat het als bijwerking van bepaalde medicijnen.

Stolsel in de aderen

Veneuze trombose (stolsel in aderen) is opgenomen als bijwerking in de bijsluiter van het Janssen vaccin. Bij mensen die eerder een veneuze trombose hebben gehad, moet vóór vaccinatie een afweging worden gemaakt van de risico's. Klachten die passen bij veneuze trombose zijn: kortademigheid, pijn op de borst, zwelling van de benen en/of pijn in de benen en/of aanhoudende buikpijn.

Trombose met een laag aantal bloedplaatjes (TTS)

Een combinatie van uitgebreide trombose en een laag aantal bloedplaatjes is beschreven als zeldzame ernstige bijwerking in de bijsluiter van het AstraZeneca en Janssen vaccin. Het wordt 'trombose met trombocytopenie syndroom' (TTS) genoemd. Klachten die passen bij dit zeldzame beeld zijn: kortademigheid, pijn op de borst, zwelling van de benen en/of pijn in de benen, aanhoudende buikpijn, ernstige of aanhoudende hoofdpijn, wazig zien of na een paar dagen blauwe plekken of rode/paarse puntvormige bloedingen op de huid buiten de prikplek.

Vergrote lymfeklieren

Vergrote lymfeklieren is een bekende bijwerking van de coronavaccins. Dit wordt ook wel lymfadenopathie genoemd. Deze bijwerking wordt relatief vaker gemeld na de boosterprik dan na de eerste of tweede coronavaccinatie. Melders hebben er gemiddeld ook meer last van na de boosterprik. Lymfeklieren, meestal in de oksel van de gevaccineerde arm, kunnen opzwellen bij een ontsteking, een infectie, auto-immuunziekte of na vaccinatie. Dit komt doordat de immuun cellen in de lymfeklieren actief worden. De zwelling kan soms zo groot worden als een golf- of tennisbal. Meestal ontstaan vergrote lymfeklieren 2 tot 3 dagen na vaccinatie. Na de boostervaccinatie kan het ook al eerder ontstaan, gemiddeld 1 dag na vaccinatie. Vergrote lymfeklieren verdwijnen meestal vanzelf na een week.

Vragenlijstonderzoek bijwerkingen coronavaccins

Wij hebben ook een vragenlijstonderzoek gedaan waarbij we de ervaringen met de verschillende soorten coronavaccins in kaart wilden brengen. We hebben hier onder andere gekeken naar welke bijwerkingen optreden, hoelang ze duren en wie bijwerkingen ervaart. Dit onderzoek is inmiddels afgerond.
Lees hier meer over dit onderzoek en de resultaten.

Andere relevante informatie

Coronavaccinaties bij kinderwens of zwangerschap
Coronavaccins bij het geven van borstvoeding
Meldingen na coronavaccinatie
Informatie over overlijdens na vaccinatie
Algemene informatie bijwerkingen van vaccins

Coronanieuws van Het Instituut Verantwoord Medicijngebruik (IVM)

Heb je een vraag over de coronavaccins die niet over bijwerkingen gaat? Bijvoorbeeld over de werking of effectiviteit van de vaccins? Kijk dan op de website van de Rijksoverheid.

Productie 57

Voortdurende coronacrisis leidt tot toename psychische klachten en behoefte aan perspectief

25 februari 2021

Het coronavirus is helaas nog niet onder controle. Het opkomen van de Britse coronavariant zorgde voor een verdere verzwaring van de maatregelen op woensdag 20 januari. Wat betekent dit voor de mentale gezondheid van de bevolking? Het Trimbos-instituut deed eind januari 2021 voor de derde keer onderzoek naar de impact van de coronacrisis op de psychische gezondheid van volwassenen.

Toename psychische klachten

We zien een toename van psychische klachten, zoals gevoelens van depressie en angst en problemen met slapen. Deelnemers tussen de 20 en 35 jaar hebben de meeste klachten. Perspectief en het krijgen van meer mogelijkheden tot sociaal contact waren voor deelnemers belangrijk om deze voortdurende crisis goed door te komen.

Van 25 januari tot 2 februari 2021 werd een online meting uitgezet via een representatief volwassenen panel van I&O Research. Net als in juni en oktober 2020 werd aan panelleden vragen gesteld over verandering van mentaal welbevinden tijdens corona en welk cijfer ze hun leven nu geven. Verder vroegen we naar ervaren psychische klachten zoals depressie en angst. Ook wilden we

weten of mensen iets positiefs konden benoemen aan de crisis, en wat ze nodig zouden hebben om deze voortdurende crisis goed door te komen. 1297 mensen hebben de vragenlijst ingevuld. 632 (49%) daarvan was man. De gemiddelde leeftijd was 48 jaar. We vergeleken de antwoorden van deze nieuwe meting met de meting van oktober. In de analyses hielden we rekening met de samenstelling van de twee steekproeven.

Meer slaapproblemen en emotionele eenzaamheid

Wanneer gevraagd wordt naar de psychische gezondheid voor en na het begin van de coronacrisis gaf bijna 1 op de 4 (23.5%) deelnemers aan dat deze achteruit was gegaan. In oktober 2020 was dit nog 1 op de 6. Vergeleken met de meting in oktober was ook het aantal mensen dat aangaf depressie- of angstklachten te hebben in de laatste meting toegenomen. Meer mensen gaven aan slaapproblemen te hebben en ervaarden vaker gevoelens van emotionele eenzaamheid. De jongste groep respondenten, tussen de 20 en 35, scoorden slechter dan de andere respondenten. Net zoals in andere studies zien we dat respondenten hun leven in het begin van 2021 een lager rapportcijfer gaven (6.6) dan in de maanden daarvoor (7.0).

De angst voor het virus zelf was niet veranderd, maar mensen rapporteerden wel vaker stress door corona en de maatregelen vergeleken met oktober. Meer mensen hadden ook een heftige gebeurtenis zoals ontslag of overlijden van een dierbare meegemaakt tijdens de corona periode.

Wel gaf het merendeel van de respondenten (60%) nog steeds aan dat ze ook positieve dingen konden noemen van de crisis, zoals meer rust en meer samenhorigheid.

Behoefte aan perspectief

In deze meting hebben we voor het eerst gevraagd wat mensen nodig hebben om door deze periode heen te komen. Perspectief en de mogelijkheid tot meer sociale contacten werden het vaakst genoemd.

Nu de crisis nog voortduurt is het van belang om extra aandacht te hebben voor de psychische gezondheid. Op mentaalvitaal.nl staan 10 tips die kunnen helpen om deze periode zo goed mogelijk door te komen. Ook biedt de site tips rondom slaap en piekeren die gezien de resultaten van dit onderzoek nuttig zouden kunnen zijn. Wanneer deze tips niet voldoende helpen om bijvoorbeeld beter te slapen of minder te piekeren adviseren wij om contact te zoeken met uw huisarts. De huisarts biedt laagdrempelige zorg voor psychische problemen, en kan met u meedenken om mentaal vitaal te blijven. Daarnaast formuleerde Trimbos 7 adviezen voor beleidsmakers, bestuurders en andere professionals.

Productie 58

Nederlands Jeugdinstituut

Onderwerp

Coronavirus

Onderzoek naar corona en mentaal welbevinden

Laatste actualisatie: 4 augustus 2023

Professionals | Lees voor

Het mentaal welbevinden van jongeren lijkt negatief beïnvloed door de coronapandemie. Vooral wanneer kinderen en jongeren weinig contact konden hebben met leeftijdsgenoten had dit negatieve gevolgen voor het mentaal welbevinden.

Resultaten samengevat

Mentale klachten verergerd

Mentale klachten leken in coronatijd vooral te zijn verergerd bij kinderen en jongeren met al bestaande mentale problemen. Mentale klachten zijn voornamelijk angst, depressieve gevoelens, eenzaamheid, stress en slaapproblemen.

Deze negatieve ontwikkeling leek tijdens de tweede lockdown sterker dan tijdens de eerste lockdown. Onderzoek suggereert ook dat hoe langer de pandemie duurde, hoe negatiever de gevolgen waren voor het mentaal welbevinden van alle kinderen en jongeren.

Tegelijkertijd voelde een groot deel van de jongeren van middelbare schoolleeftijd zich goed en is het onderzoek niet altijd even eenduidig. Zo rapporteren sommige onderzoeken tijdens de tweede lockdown meer mentale klachten, terwijl andere onderzoeken geen stijging laten zien. Er zijn helaas weinig studies gedaan naar kinderen tot 12 jaar. Daarnaast is er nog weinig bekend over de impact van de laatste lockdown (november 2021 tot en met januari 2022) en de versoepelingen. Wel zijn er signalen dat jongeren moeten wennen aan de (sociale) drukte na de coronacrisis en onzeker zijn over de achterstanden die ze hebben opgelopen.

Verbondenheid met leeftijdsgenoten als beschermende factor

Gedurende de hele pandemie leek de mate van verbondenheid met vrienden en leeftijdgenoten een belangrijke factor te zijn voor het mentaal welbevinden. Zo hadden adolescenten die tijdens de eerste lockdown meer verbondenheid hadden met hun vrienden minder last van internaliserende problemen dan leeftijdsgenoten die dat niet hadden.

Bovendien lijkt in de eerste fase van de pandemie de sluiting van de scholen een belangrijke factor te zijn geweest die van invloed was op het mentaal welbevinden van leerlingen in het primair, voortgezet, praktijk- en hoger onderwijs. Maar ook de avondklok heeft invloed gehad. Voornamelijk in de leeftijdsgroep 16 tot 22 jaar is een deel van de jongeren zich slechter gaan voelen.

De resultaten van veel studies, peilingen, enquêtes en analyses uit de periode maart 2020 - april 2022 heeft het NJi gebundeld in de overzichtsstudie Mentaal welbevinden van de jeugd: lessen uit de coronacrisis.

Overzicht onderzoeken

Gepubliceerd wetenschappelijk artikel of preprint

20 april 2023 –Maastricht Universiteit en Hogeschool Rotterdam
Impact of the Covid-19 pandemic on students with relatives with addiction problems: A longitudinal qualitative study