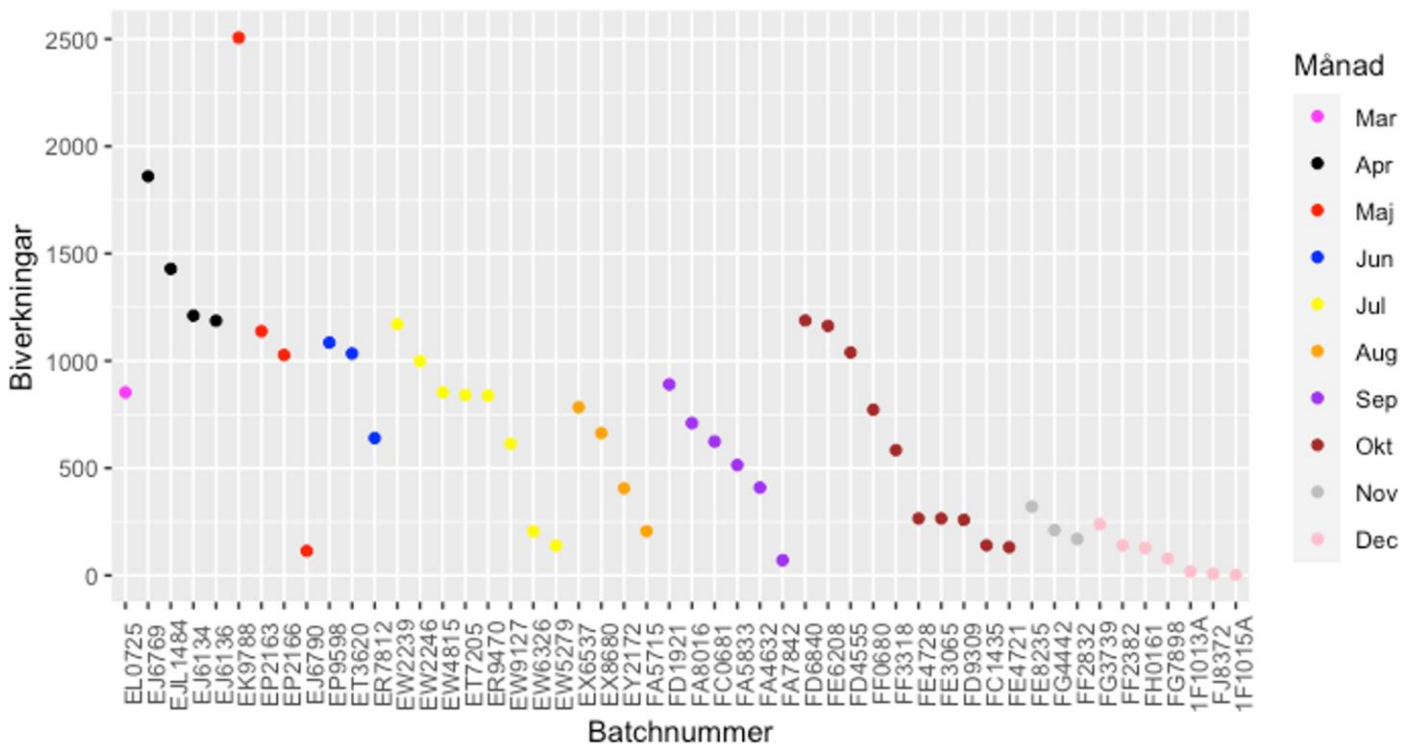


Pfizer Batch Pattern in Sweden



I downloaded a data package from "Folkhälsomyndigheten", equivalent to our CDC, and the data package contained every batch number Sweden has and will order with its expiration date. I made an excel file for Pfizer with all the batches with their corresponding ADVR from your data "Pfizer (outside USA)". I made a ggplot on RStudio with the batches on the X-axis and ADVR on the Y-axis, and I arranged the batches according to their expiration date (Every batch expires at the end of every month from March). I have given every batch that expires in the same month a specific color and as you can see, from the picture I have attached down below, the results are devastating.

Now, it is important to remember that this is data from all VAERS reports outside of the US but with the specific batch numbers shipped to Sweden. What I believe is that Pfizer has systematically shipped out specific batches which they themselves know the toxicity of and have received experimental results for every month, the batch number pattern is only one variable, I believe that the expiration date along with shipment is another one.

I will contact "Läkemedelsverket" (equivalent to our FDA) and ask for data of reported ADVR to the specific batches. I will follow up if they would send me it.

Best regards
Shandi Amin
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**TEMA**

Ligesom al anden medicin kan COVID-19-vacciner have bivirkninger. Det afgørende er, at de bivirkninger, vaccinerne kan give, ikke må være værre end de symptomer og den sygdom, som vaccinerne skal forebygge.

Oversigt over indberettede bivirkninger

- **Alle Covid-19 vacciner**
- **Pfizer/BioNTech (Comirnaty)**
- **Moderna (Spikevax)**
- **AstraZeneca (Vaxzevria)**
- **Covid-19 Vaccine Johnson & Johnson - Janssen Pharmaceutical**

Overvåger sikkerheden

Lægemiddelmyndighederne overvåger sikkerheden ved vaccinerne mod COVID-19. Det sker blandet andet ved hjælp af indberetninger om formodede bivirkninger fra borgere og sundhedspersoner. Lægemiddelmyndighederne overvåger og vurderer løbende, om der blandt de modtagne indberetninger om formodede bivirkninger kan være signaler om nye eller ændrede risici ved vaccinerne, som skal undersøges nærmere.

Her på siden opdateres oversigter og status ugentligt over antallet af vaccinerede borgere og indberetninger om formodede bivirkninger ved vaccinerne mod COVID-19.

Vurderer bivirkningsindberetninger løbende

De ugentlige oversigter indeholder en status om indberetninger, som er vurderet og behandlet.

Der vil altid være flere indberetninger, som er under behandling. Disse vil først komme med i en senere statusopdatering.

Bivirkningsindberetninger vurderes løbende. Indberetninger om formodede alvorlige bivirkninger prioriteres først. Derfor vil der være en større andel af formodede ikke-alvorlige bivirkninger, der ikke er færdigbehandlet endnu.

Når sundhedspersoner, borgere eller pårørende indberetter bivirkninger til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at de oplevede symptomer er bivirkninger til en bestemt medicin. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og de oplevede symptomer.

Indberetninger om formodede bivirkninger ved forskellige vacciner mod COVID-19 kan ikke sammenlignes direkte af flere grunde. Vaccinerne har forskellig sammensætning af indholdsstoffer, vaccinerne gives til et forskelligt antal af borgere samt til forskellige alders- og risikogrupper. Vaccinerne anvendes i øvrigt ikke i lige lang tid i vaccinationsprogrammet

Læs mere

- Lægemiddelmyndighedernes overvågning af sikkerheden ved vaccinerne
- Sådan skal du forholde sig som borger, hvis du mener, at du har fået bivirkninger af vaccinen
- Læs mere om Pfizer/BioNTechs COVID-19-vaccine
- Læs mere om Modernas COVID-19-vaccine
- Læs mere om AstraZenecas COVID-19-vaccine
- Læs mere om Johnson & Johnsons COVID-19-vaccine

Siden opdateres løbende

Alle Covid-19 vacciner

Oversigt over indberettede formodede bivirkninger ved COVID-19-vacciner

Status pr. 21. december 2021

Påbegyndt vaccination / antal personer

4.774.091^[1]

Heraf færdigvaccineret / antal personer

4.523.594^[1]^[1] Kilde: Statens Serum Institut (SSI)**Antal modtagne indberetninger om formodede bivirkninger****62.879*****Antal modtagne indberetninger om formodede bivirkninger
(Comirnaty)****30.933****Antal modtagne indberetninger om formodede bivirkninger
(Covid-19 Vaccine Moderna, Spikevax)****7.480****Antal modtagne indberetninger om formodede bivirkninger
(AstraZeneca COVID-19 Vaccine, Vaxzevria)****23.864****Antal modtagne indberetninger om formodede bivirkninger
(COVID-19 Vaccine Janssen, Johnson & Johnson)****492**

**Tallet indeholder alle modtagne indberetninger for Comirnaty (30.933), Spikevax (7.480), Vaxzevria (23.864), COVID-19 Vaccine Janssen, Johnson & Johnson (492) samt ubehandlede indberetninger (110), hvor indberetter mangler at angive navn på COVID-19-vaccine.*

Pfizer/BioNTech (Comirnaty)

Oversigt

Status pr. 21. december 2021

Påbegyndt vaccination / antal personer

3.999.328*

Heraf færdigvaccineret / antal personer

3.865.030*

* Kilde: Statens Serum Institut (SSI)

Antal modtagne indberetninger om formodede bivirkninger

30.933

Antal behandlede indberetninger om formodede bivirkninger

13.436

Status

Lægemiddelstyrelsen har frem til den 21. december 2021 modtaget 30.933 indberetninger om formodede bivirkninger ved Comirnaty, hvoraf 13.436 er behandlet. Indberetninger om formodede alvorlige bivirkninger behandles først.

- Langt de fleste indberettede formodede bivirkninger er milde og moderate. Det er hovedsageligt kendte og forbigående bivirkninger som f.eks. smerte ved indstiksstedet, træthed, hovedpine, utilpashed og feber.
- Når en vaccine aktiverer immunsystemet, vil mange opleve influenzalignende symptomer. Det er helt almindeligt og et tegn på, at kroppens immunsystem reagerer på vaccinen. Reaktionerne ses ved de fleste typer vacciner, og de plejer at være overstået inden for en dag eller to.
- Omvendt er mangel på symptomer fra immunsystemet ved vaccination ikke ensbetydende med manglende effekt af vaccinen. Det er bare forskelligt fra person til person, hvordan man reagerer på en vaccination.

- Som ved alle vaccinationer er der en lille risiko for sjældne, men kraftige allergiske reaktioner, herunder såkaldte anafylaktiske reaktioner, som kan være livstruende, hvis de ikke behandles omgående.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om kraftige allergiske reaktioner, herunder anafylaktiske reaktioner.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at kraftige allergiske reaktioner, herunder anafylaktiske reaktioner, som følge af vaccination med Comirnaty, forekommer hyppigere end forventet.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om kraftige allergiske reaktioner nøje.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om blodpropper efter vaccination.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at vaccinen kan give bivirkninger i form af blodpropper.
- Blodpropper kan have mange årsager og fx skyldes borgerens helbredsforhold, herunder anden sygdom, og ved vaccination kan stikket med nålen – også med korrekt teknik – i sjældne tilfælde give lokale blodpropper. Blodpropper kan blandt andet af ovenstående årsager tilfældigt forekomme kort efter vaccination, uden at der er en sammenhæng med vaccinen.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om blodpropper nøje.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om myokarditis (hjertermuskelbetændelse) og perikarditis (hjerterindebetændelse) efter vaccination.
- Lægemiddelstyrelsen har vurderet 64 indberetninger om myokarditis. I 11 tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I 43 tilfælde kan det ikke udelukkes, at vaccinen har været en medvirkende årsag. I 10 tilfælde er det ikke muligt at vurdere, om myokarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- Lægemiddelstyrelsen har vurderet 72 indberetninger om perikarditis. I 41 tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I 26 tilfælde kan det ikke udelukkes, at vaccinen har været en medvirkende årsag. I fem tilfælde er det ikke muligt at vurdere, om perikarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- Lægemiddelstyrelsen har herudover vurderet fem indberetninger om både myokarditis og perikarditis. I ét tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig, mens det i fire tilfælde ikke kan udelukkes, at vaccinen har været en medvirkende årsag.
- I juli 2021 blev myokarditis og perikarditis tilføjet som bivirkninger i produktinformationen for Comirnaty sammen med en advarsel til sundhedspersoner og vaccinerede om at holde øje med evt. symptomer. Symptomerne kan variere, men inkluderer ofte åndenød, hjertebanken, der kan være uregelmæssig, samt brystmerter.
- Den europæiske bivirkningskomité, PRAC, har nu foretaget en yderligere gennemgang af nye data herunder to store epidemiologiske undersøgelser baseret på henholdsvis nordiske registerdata og franske sundhedsdata. På grundlag af gennemgangen har PRAC den 3. december 2021 konkluderet, at myokarditis og perikarditis efter COVID-19-vaccination med mRNA-vaccinerne (Comirnaty og Spikevax), forekommer meget sjældent, og at risikoen for udvikling af myokarditis er størst hos drenge/ynge mænd.

[PRAC anbefaler, at produktinformationen opdateres med de nyeste konklusioner.](#)

- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om dødsfald efter vaccination.
- Lægemiddelstyrelsen har foreløbig modtaget og vurderet 119 indberetninger, der omhandler dødsfald i tiden efter vaccination. I alle 119 tilfælde er det Lægemiddelstyrelsens vurdering, at det er mindre sandsynligt, at der er sammenhæng med vaccinen, og at det er overvejende sandsynligt, at dødsfaldene skyldes andre forhold.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om dødsfald nøje.
- Lægemiddelstyrelsen har et særligt fokus på overvågning af grupperne 5-11-årige og 12-15-årige efter vaccination. Baseret på de foreliggende data er den generelle bivirkningsprofil i disse grupper sammenlignelig med det observerede i den øvrige del af befolkningen, som hovedsageligt omhandler kendte og forbigående bivirkninger.
- Lægemiddelstyrelsen har desuden et særligt fokus på overvågning af gravide og ammende efter vaccination. Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at bivirkningsprofilen i denne gruppe afviger fra bivirkningsprofilen i den øvrige del af befolkningen.
- Lægemiddelstyrelsen har behandlet en indberetning om en sjælden betændelsestilstand MIS-C (Multisystem Inflammatory Syndrom in Children) hos en 17-årig dreng. Den 17-årige er efter behandling rask igen. Lægemiddelstyrelsen har informeret EMA om den danske indberetning, og også i andre lande er der observeret enkelte tilfælde af MIS hos både børn og voksne efter vaccination med COVID-19-vacciner. På denne baggrund besluttede den europæiske bivirkningskomité PRAC at undersøge en mulig sammenhæng mellem MIS og de fire COVID-19-vacciner, læs mere i [Lægemiddelstyrelsens nyhed fra 3. september hér](#).
- PRAC har den 29. oktober 2021 meddelt, at der på nuværende tidspunkt ikke er tilstrækkelig dokumentation for at kunne etablere en sammenhæng mellem COVID-19-vaccinerne og MIS, læs mere i [Lægemiddelstyrelsens nyhed hér](#).
- Lægemiddelstyrelsen og EMA følger fortsat indberetninger om MIS efter vaccination mod COVID-19 nøje.

Nedenstående tabel viser aldersfordelingen i forhold til de indberettede formodede bivirkninger, som Lægemiddelstyrelsen har modtaget og behandlet, vedrørende Comirnaty.

Indberettede formodede bivirkninger fordelt på aldersgrupper									
<5	5-11	12-15	16-39	40-59	60-69	70-79	80-89	90+	Ukendt alder
0,1%	0,2%	2,0 %	35,1 %	42,0 %	8,9 %	5,1 %	3,9 %	1,6 %	1,1 %

Læs mere om status på behandlede indberetninger om formodede bivirkninger:

- **22.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 51**

- **16.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 50**
- **09.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 49**
- **02.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 48**
- **25.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 47**
- **18.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 46**
- **11.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 45**
- **04.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 44**
- **28.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 43**
- **14.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 41**
- **07.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 40**
- **30.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 39**
- **23.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 38**
- **16.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 37**
- **09.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 36**
- **02.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 35**
- **26.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 34**
- **19.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 33**
- **12.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 32**
- **05.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 31**
- **29.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 30**
- **22.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 29**
- **15.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 28**
- **08.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 27**
- **01.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 26**
- **24.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved**

- Comirnaty (Pfizer/BioNTech), uge 25**
- **17.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 24**
 - **10.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 23**
 - **03.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 22**
 - **27.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 21**
 - **20.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 20**
 - **12.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 19**
 - **06.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 18**
 - **29.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech), uge 17**
 - **22.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech)**
 - **16.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech)**
 - **09.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 550.000 danskere**
 - **31.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 500.000 danskere**
 - **25.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 450.000 danskere**
 - **18.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 410.000 danskere**
 - **11.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 391.802 danskere**
 - **04.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 340.000 danskere**
 - **25.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (Pfizer/BioNTech) efter vaccination af mere end 277.900 danskere**
 - **18.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (BioNTech/Pfizer) efter vaccination af mere end 219.000 danskere**
 - **11.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (BioNTech/Pfizer) efter vaccination af mere end 194.000 danskere**
 - **04.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved Comirnaty (BioNTech/Pfizer) efter vaccination af mere end 186.000 danskere**
 - **18.01.2021: Status på overvågning af Pfizer/BioNTech vaccinen**
 - **06.01.2021: Status på overvågning af BioNTech/Pfizer-vaccinen efter vaccination med de første to leverancer**
 - **30.12.2020: Status på overvågning af Pfizer/BioNTech vaccinen, efter vaccination med første sending**

Moderna (Spikevax)

Oversigt

Status pr. 21. december 2021

Påbegyndt vaccination / antal personer

571.876*

Heraf færdigvaccineret / antal personer

609.602*

* Kilde: Statens Serum Institut (SSI)

Antal modtagne indberetninger om formodede bivirkninger

7.480

Antal behandlede indberetninger om formodede bivirkninger

6.470

Status

Lægemiddelstyrelsen har frem til den 21. december 2021 modtaget 7.480 indberetninger om formodede bivirkninger ved Spikevax, hvoraf 6.470 indberetninger er behandlet. Indberetninger om formodede alvorlige bivirkninger behandles først.

- Langt de fleste indberettede formodede bivirkninger er milde og moderate. De handler hovedsageligt om kendte og forbigående bivirkninger som f.eks. træthed, hovedpine, feber og lokale reaktioner ved indstiksstedet såsom smerter og kløe.
- Når en vaccine aktiverer immunsystemet, vil mange opleve influenzalignende symptomer. Det er helt almindeligt og et tegn på, at kroppens immunsystem reagerer på vaccinen. Reaktionerne ses ved de fleste typer vacciner, og de plejer at være overstået inden for en dag eller to.
- Omvendt er mangel på symptomer fra immunsystemet ved vaccination ikke ensbetydende med manglende effekt af vaccinen. Det er bare forskelligt fra person til person, hvordan man reagerer på en vaccination.

- Som ved alle vaccinationer er der en lille risiko for sjældne, men kraftige allergiske reaktioner, herunder såkaldte anafylaktiske reaktioner, som kan være livstruende, hvis de ikke behandles omgående.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om kraftige allergiske reaktioner, herunder anafylaktiske reaktioner.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at kraftige allergiske reaktioner, herunder anafylaktiske reaktioner, som følge af vaccination med Spikevax, forekommer hyppigere end forventet.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om kraftige allergiske reaktioner nøje.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om blodpropper efter vaccination.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at vaccinen kan give bivirkninger i form af blodpropper.
- Blodpropper kan have mange årsager og fx skyldes borgerens helbredsforhold, herunder anden sygdom, og ved vaccination kan stikket med nålen – også med korrekt teknik – i sjældne tilfælde give lokale blodpropper. Blodpropper kan blandt andet af ovenstående årsager tilfældigt forekomme kort efter vaccination uden at der er en sammenhæng med vaccinen.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om blodpropper nøje.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om myokarditis (hjertermuskelbetændelse) og perikarditis (hjerterindebetændelse) efter vaccination.
- Lægemiddelstyrelsen har vurderet 30 indberetninger om myokarditis. I tre tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I 26 tilfælde kan det ikke udelukkes, at vaccinen har været en medvirkende årsag. I ét tilfælde er det ikke muligt at vurdere, om myokarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- Lægemiddelstyrelsen har vurderet 23 indberetninger om perikarditis. I seks tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I 15 tilfælde kan det ikke udelukkes, at vaccinen har været en medvirkende årsag. I to tilfælde er det ikke muligt at vurdere, om perikarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- I juli 2021 blev myokarditis og perikarditis tilføjet som bivirkninger i produktinformationen for Spikevax sammen med en advarsel til sundhedspersoner og vaccinerede om at holde øje med evt. symptomer. Symptomerne kan variere, men inkluderer ofte åndenød, hjertebanken, der kan være uregelmæssig, samt brystmerter.
- Den europæiske bivirkningskomité, PRAC, har nu foretaget en yderligere gennemgang af nye data herunder to store epidemiologiske undersøgelser baseret på henholdsvis nordiske registerdata og franske sundhedsdata. På grundlag af gennemgangen har PRAC den 3. december 2021 konkluderet, at myokarditis og perikarditis efter COVID-19-vaccination med mRNA-vaccinerne (Comirnaty og Spikevax), forekommer meget sjældent, og at risikoen for udvikling af myokarditis er størst hos drenge/ynge mænd. [PRAC anbefaler at produktinformationen opdateres med de nyeste konklusioner.](#)
- Lægemiddelstyrelsen har modtaget og vurderet 16 indberetninger, der handler om dødsfald i tiden efter vaccination med Spikevax. I 15 tilfælde er det Lægemiddelstyrelsens vurdering, at det er mindre sandsynligt, at der er sammenhæng

med vaccinen, og at det er overvejende sandsynligt, at dødsfaldene skyldes andre forhold. I ét tilfælde er det ikke muligt at vurdere, om dødsfaldet er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.

- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om dødsfald nøje.
- Lægemiddelstyrelsen har et særligt fokus på overvågning af gruppen 12-15-årige efter vaccination. Baseret på de foreliggende data er den generelle bivirkningsprofil i denne gruppe sammenlignelig med det observerede i den øvrige del af befolkningen, som hovedsageligt omhandler kendte og forbigående bivirkninger.
- Lægemiddelstyrelsen har desuden et særligt fokus på overvågning af gravide og ammende efter vaccination. Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at bivirkningsprofilen i denne gruppe afviger fra bivirkningsprofilen i den øvrige del af befolkningen.

Nedenstående tabel viser aldersfordelingen i forhold til de indberettede formodede bivirkninger, som Lægemiddelstyrelsen har modtaget og behandlet, vedrørende Spikevax.

Indberettede formodede bivirkninger fordelt på aldersgrupper								
<12	12-15	16-39	40-59	60-69	70-79	80-89	90+	Ukendt alder
0,2%	0,1%	48,8 %	25,3 %	11,9 %	6,8 %	4,8 %	1,5 %	0,6 %

Læs mere om status på behandlede indberetninger om formodede bivirkninger:

- **22.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 51**
- **16.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 50**
- **09.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 49**
- **02.12.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 48**
- **25.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 47**
- **18.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 46**
- **11.11.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 45**
- **04.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 44**
- **28.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 43**
- **14.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 41**
- **07.10.2021: Status på behandlede indberetninger om formodede bivirkninger ved**

- Spikevax (Moderna), uge 40**
- **30.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 39**
 - **23.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 38**
 - **16.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 37**
 - **09.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 36**
 - **02.09.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 35**
 - **26.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 34**
 - **19.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 33**
 - **12.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 32**
 - **03.08.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 31**
 - **29.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 30**
 - **22.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 29**
 - **15.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 28**
 - **08.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Spikevax (Moderna), uge 27**
 - **01.07.2021: Status på behandlede indberetninger om formodede bivirkninger ved Spikevax (Moderna), uge 26**
 - **24.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna (Spikevax), uge 25**
 - **17.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 24**
 - **10.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 23**
 - **03.06.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 22**
 - **27.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 21**
 - **20.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 20**
 - **12.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 19**
 - **06.05.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 18**
 - **29.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna, uge 17**
 - **22.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna**

- **16.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Moderna**
- **09.04.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 60.000 danskere**
- **31.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 48.000 danskere**
- **23.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 37.000 danskere**
- **18.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 25.000 danskere**
- **11.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 21.170 danskere**
- **04.03.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 14.000 danskere**
- **25.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 12.500 danskere**
- **18.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 12.000 danskere**
- **11.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 7800 danskere**
- **04.02.2021: Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 vaccine Moderna efter vaccination af mere end 2600 danskere**

Covid-19 Vaccine AstraZeneca (Vaxzevria)

AstraZeneca-vaccinen Vaxzevria taget ud af vaccinationsprogrammet mod COVID-19 i Danmark

Link:

[Danmark fortsætter vaccineudrulning uden AstraZeneca-vaccinen](#)

Link:

[Lægemiddelmyndigheder undersøger indberetninger om blodpropper efter AstraZeneca-vaccinationer.](#)

Oversigt

Status pr. 21. december 2021

bilag 2

Påbegyndt vaccination / antal personer**152.106*****Heraf færdigvaccineret / antal personer****2.172***

** Opgørelsen omfatter også administrerede vacciner Vaxzevria (AstraZenecas COVID-19-vaccine) fra andre lande end Danmark, hvis de er registreret i Det Danske Vaccinationsregister (DDV). Det fremgår af DDV, at 199 personer har modtaget første vaccination via tilvalgsordningen hos Practio ApS, og at 371 personer er færdigvaccineret via tilvalgsordningen.*

Antal modtagne indberetninger om formodede bivirkninger**23.864****Antal behandlede indberetninger om formodede bivirkninger****5.129**

Status

Lægemiddelstyrelsen har frem til den 21. december 2021 modtaget 23.864 indberetninger om formodede bivirkninger ved vaccinen, hvoraf 5.129 er behandlet. Indberetninger om formodede alvorlige bivirkninger behandles først.

- Langt de fleste indberettede formodede bivirkninger er milde og moderate. Det handler hovedsageligt om kendte og forbigående bivirkninger som f.eks. feber, hovedpine, kulderystelser og muskel- og ledsmerter.
- Når en vaccine aktiverer immunsystemet, vil mange opleve influenzalignende symptomer. Det er helt almindeligt og et tegn på, at kroppens immunsystem reagerer på vaccinen. Reaktionen ses ved de fleste typer vacciner, og de plejer at være overstået inden for en dag eller to.
- Omvendt er mangel på symptomer fra immunsystemet ved vaccination ikke ensbetydende med manglende effekt af vaccinen. Det er bare forskelligt fra person til person, hvordan man reagerer på en vaccination.
- Som ved alle vaccinationer er der en lille risiko for sjældne, men kraftige allergiske reaktioner, herunder såkaldte anafylaktiske reaktioner, som kan være livstruende, hvis de ikke behandles omgående.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget

- indberetninger om kraftige allergiske reaktioner, herunder anafylaktiske reaktioner.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at kraftige allergiske reaktioner – herunder anafylaktiske reaktioner – som følge af vaccination med Vaxzevria forekommer hyppigere end forventet.
 - Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om kraftige allergiske reaktioner nøje.
 - Der er både i Danmark og udlandet set meget sjældne, men alvorlige tilfælde af en kombination af blodpropper og et lavt antal blodplader, kaldet *trombose med trombocytopeni-syndrom* (TTS), i nogle tilfælde ledsaget af blødning. Blodpropperne er i disse tilfælde set på forskellige eller usædvanlige steder og med overdreven blodstørkning (koagulation) eller blødning i hele kroppen. De fleste af disse tilfælde er opstået inden for de første tre uger efter vaccinationen. Nogle tilfælde har haft dødeligt udfald.
 - Lægemiddelstyrelsen har behandlet i alt tre indberetninger, hvor det vurderes, at der er tale om TTS. To af de tre sager omhandler dødsfald. Lægemiddelstyrelsen har i alle tre tilfælde vurderet, at en sammenhæng med vaccinen er sandsynlig. TTS er beskrevet i produktinformationen som en meget sjælden bivirkning til denne vaccine.
 - Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – også modtaget indberetninger om blodpropper efter vaccination, hvor der ikke er en kombination med et lavt antal blodplader (og dermed ikke TTS).
 - Blodpropper kan have mange årsager. De kan fx skyldes borgerens helbredsforhold, herunder anden sygdom, og ved vaccination kan stikket med nålen – også med korrekt teknik – i sjældne tilfælde give lokale blodpropper. Blodpropper kan blandt andet af ovenstående årsager tilfældigt forekomme kort efter vaccination, uden at der er en sammenhæng med vaccinen.
 - På baggrund af de seneste sikkerhedsdata er produktinformationen for Vaxzevria blevet opdateret den 24. november 2021 med tilføjelse af bivirkningen Cerebral venøs sinustrombose (CVST, blodpropper i hjernen) uden trombocytopeni (lavt antal blodplader).
 - Lægemiddelstyrelsen har modtaget og behandlet få indberetninger om CVST efter vaccination med Vaxzevria.
 - Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om blodpropper nøje.
 - Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om myokarditis (hjertermuskelbetændelse) og perikarditis (hjerterindebetændelse) efter vaccination.
 - Lægemiddelstyrelsen har behandlet tre indberetninger om myokarditis. I ét tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I to tilfælde kan det ikke udelukkes, at vaccinen har været en medvirkende årsag.
 - Lægemiddelstyrelsen har behandlet tre indberetninger om perikarditis. I to tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I ét tilfælde kan det ikke udelukkes, at vaccinen har været medvirkende årsag.
 - Lægemiddelstyrelsen følger nøje indberetninger om myokarditis og perikarditis i samarbejde med EMA og andre lægemiddelmyndigheder i EU og globalt. Der er ikke påvist en årsagssammenhæng mellem vaccinen og myokarditis eller perikarditis, og EMA er ved at undersøge, om der kan være en sådan årsagssammenhæng.
 - Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om dødsfald efter vaccination.
 - Der er som beskrevet ovenfor to dødsfald, der er relateret til det usædvanlige

sygdomsbillede med blodpropper i kombination med et lavt antal blodplader og blødninger. Lægemiddelstyrelsen har derudover modtaget og vurderet to indberetninger, der omhandler dødsfald i tiden efter vaccination. I begge tilfælde er det Lægemiddelstyrelsens vurdering, at det er mindre sandsynligt, at der er sammenhæng med vaccinen, og at det er overvejende sandsynligt, at dødsfaldene skyldes andre forhold.

- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om dødsfald nøje.
- I Danmark har Vaxzevria ikke været anvendt i det generelle vaccinationsprogram siden den 11. marts 2021, hvor Sundhedsstyrelsen satte brugen af Vaxzevria på pause ([læs nyheden på SST.dk](#)). Sundhedsstyrelsen besluttede den 14. april 2021 at fortsætte COVID-19 vaccinationsprogrammet uden Vaxzevria ([læs nyheden på SST.dk](#)). Fra den 20. maj 2021 til og med den 31. august 2021 kunne borgere blive vaccineret med Vaxzevria som en del af tilvalgsordningen. Lægemiddelstyrelsen overvåger vaccinen på samme måde som de vacciner, der indgår i det generelle vaccinationsprogram. Alle COVID-19-vacciner overvåges desuden af lægemiddelmyndigheder over hele verden.

Nedenstående tabel viser aldersfordelingen i forhold til de indberettede formodede bivirkninger, som Lægemiddelstyrelsen har modtaget og behandlet, vedrørende COVID-19 Vaccine AstraZeneca.

Indberettede formodede bivirkninger fordelt på aldergrupper*				
16-39	40-59	60-69	70-79	Ukendt alder
42,6 %	48,5 %	8,1 %	0,1 %	0,7 %

Læs mere om status på behandlede indberetninger om formodede bivirkninger

- **22.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 51
- **16.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 50
- **09.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 49
- **02.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 48
- **25.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 47
- **18.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 46
- **11.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 45
- **04.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 44
- **28.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 43

- **14.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 41
- **07.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 40
- **30.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 39
- **23.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 38
- **16.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 37
- **09.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 36
- **02.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 35
- **26.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 34
- **19.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 33
- **12.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 32
- **05.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 31
- **29.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 30
- **22.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 29
- **15.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 28
- **08.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 27
- **01.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 26
- **24.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 25
- **17.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 24
- **10.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 23
- **03.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 22
- **27.05.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 21
- **20.05.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 20
- **12.05.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 19
- **06.05.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria, uge 18
- **29.04.2021:** Status på behandlede indberetninger om formodede bivirkninger ved

Vaxzevria, uge 17

- **22.04.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria
- **16.04.2021:** Status på behandlede indberetninger om formodede bivirkninger ved Vaxzevria 16 april
- **09.04.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 150.000 danskere
- **31.03.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca (Vaxzevria) efter vaccination af mere end 150.000 danskere
- **25.03.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 140.000 danskere
- **18.03.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 140.000 danskere
- **11.03.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 136.090 danskere
- **04.03.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 87.000 danskere
- **18.02.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine AstraZeneca efter vaccination af mere end 18.000 danskere

Covid-19 Vaccine Johnson & Johnson

Oversigt

Status pr. 21. december 2021

Heraf færdigvaccineret / antal personer

46.760*

**Opgørelsen viser alle, der har fået registreret en Covid-19 Vaccine Janssen i Det Danske Vaccinationsregister (DDV). Opgørelsen omfatter også administrerede vacciner fra andre lande end Danmark, hvis de er registreret i DDV. Det fremgår af DDV, at 47.555 personer har fået vaccinen via tilvalgsordningen hos Practio ApS.*

Antal modtagne indberetninger om formodede bivirkninger**492****Antal behandlede indberetninger om formodede bivirkninger****434****Status**

Lægemiddelstyrelsen har frem til den 21. december 2021 modtaget 492 indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson). Heraf er 434 indberetninger behandlet. De omhandler hovedsageligt kendte og forbigående bivirkninger som f.eks. smerte ved indstiksstedet, træthed, hovedpine, utilpashed og feber.

- I Danmark anvendes COVID-19 Vaccine Janssen (Johnson & Johnson) p.t. ikke i det generelle vaccinationsprogram.
- I perioden fra den 20. maj 2021 til og med den 31. august 2021 kunne borgere vælge at blive vaccineret med COVID-19 Vaccine Janssen (Johnson & Johnson) som en del af tilvalgsordningen. Fra den 14. september 2021 har borgere kunnet vælge – mod betaling – at blive vaccineret med denne vaccine. Lægemiddelstyrelsen overvåger vaccinen på samme måde som de vacciner, der indgår i det generelle vaccinationsprogram. Alle COVID-19-vacciner overvåges desuden af lægemiddelmyndigheder over hele verden.
- Som ved alle vaccinationer er der en lille risiko for sjældne, men kraftige allergiske reaktioner, herunder såkaldte anafylaktiske reaktioner, som kan være livstruende, hvis de ikke behandles omgående.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om kraftige allergiske reaktioner, herunder anafylaktiske reaktioner.
- Lægemiddelstyrelsens datagrundlag giver ikke anledning til mistanke om, at kraftige allergiske reaktioner, herunder anafylaktiske reaktioner, som følge af vaccination med COVID-19 Vaccine Janssen, forekommer hyppigere end forventet.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemiddelmyndigheder i EU, indberetninger om kraftige allergiske reaktioner nøje.
- Lægemiddelstyrelsen har behandlet én indberetning, hvor det vurderes, at der er tale om det usædvanlige sygdomsbillede med blodpropper og lavt antal blodplader kaldet *trombose med trombocytopeni-syndrom* (TTS). Lægemiddelstyrelsen har vurderet, at en sammenhæng med vaccinen er sandsynlig.
- Der er også indberettet tilfælde af samme sygdomsbillede efter vaccination med COVID-19 Vaccine Janssen (Johnson & Johnson) i andre lande, og tilstanden er

beskrevet i produktinformationen som en meget sjælden bivirkning til denne vaccine.

- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – også modtaget indberetninger om blodpropper efter vaccination, hvor der ikke er en kombination med et lavt antal blodplader (og dermed ikke TTS).
- Blodpropper kan have mange årsager. De kan fx skyldes borgerens helbredsforhold, herunder anden sygdom, og ved vaccination kan stikket med nålen – også med korrekt teknik – i sjældne tilfælde give lokale blodpropper. Blodpropper kan blandt andet af ovenstående årsager tilfældigt forekomme kort efter vaccination, uden at der er en sammenhæng med vaccinen. *Venøs tromboemboli*, en særlig type af blodpropper, er en kendt, sjælden bivirkning ved COVID-19 Vaccine Janssen.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om blodpropper nøje.
- Lægemiddelstyrelsen har – ligesom myndigheder i andre lande – modtaget indberetninger om myokarditis (hjertemuskelbetændelse) og perikarditis (hjerterindebetændelse) efter vaccination.
- Lægemiddelstyrelsen har vurderet tre indberetninger om myokarditis. I to tilfælde kan det ikke udelukkes, at vaccinen har været medvirkende årsag. I ét tilfælde er det ikke muligt at vurdere, om myokarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- Lægemiddelstyrelsen har vurderet fem indberetninger om perikarditis. I to tilfælde vurderes en sammenhæng med vaccinen mindre sandsynlig. I to tilfælde kan det ikke udelukkes, at vaccinen har været medvirkende årsag. I ét tilfælde er det ikke muligt at vurdere, om perikarditis er forårsaget af vaccinen eller af sygdomsforhold hos borgeren.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemiddelmyndigheder i EU, indberetninger om perikarditis og myokarditis nøje. Der er ikke påvist en årsagssammenhæng mellem vaccinen og perikarditis eller myokarditis, og EMA er ved at undersøge, om der kan være en sådan årsagssammenhæng.
- Lægemiddelstyrelsen har modtaget og vurderet én indberetning, der handler om dødsfald i tiden efter vaccination med COVID-19 Vaccine Janssen. Det er Lægemiddelstyrelsens vurdering, at det er mindre sandsynligt, at der er sammenhæng med vaccinen, og at det er overvejende sandsynligt, at dødsfaldet skyldes andre forhold.
- Lægemiddelstyrelsen følger, i samarbejde med EMA og de andre nationale lægemyndigheder i EU, indberetninger om dødsfald nøje.

Nedenstående tabel viser aldersfordelingen i forhold til de indberettede formodede bivirkninger, som Lægemiddelstyrelsen har modtaget og behandlet, vedrørende COVID-19 Vaccine Janssen.

Indberettede formodede bivirkninger fordelt på aldersgrupper*						
16-39	40-59	60-69	70-79	80-89	90+	Ukendt alder
89,7 %	8,9 %	0 %	0,5 %	0 %	0 %	0,9 %

Læs mere om status på behandlede indberetninger om formodede

bivirkninger:

- **21.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 51
- **16.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 50
- **09.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 49
- **02.12.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 48
- **25.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 47
- **18.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 46
- **11.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 45
- **04.11.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 44
- **28.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 43
- **14.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 41
- **07.10.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 40
- **30.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 39
- **23.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 38
- **16.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 37
- **09.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 36
- **02.09.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 35
- **26.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 34
- **19.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 33
- **12.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 32
- **05.08.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 31
- **29.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 30
- **22.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 29
- **15.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 28
- **08.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved

- COVID-19 Vaccine Janssen (Johnson & Johnson), uge 27
- **01.07.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 26
 - **24.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 25
 - **17.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 24
 - **10.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 23
 - **03.06.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 22
 - **27.05.2021:** Status på behandlede indberetninger om formodede bivirkninger ved COVID-19 Vaccine Janssen (Johnson & Johnson), uge 21
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LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Lægemiddelstyrelsen

Axel Heides Gade 1

2300 København S

Email: dkma@dkma.dk

Kontakt Lægemiddelstyrelsen

44 88 95 95 (kl. 9 - 15)

Kontakt DKMAnet - Medicinpriser

44 88 96 94 (kl. 9 - 15)

Følg os



CVR-nr. 37 05 24 85

EAN 5798 000 36 33 66

[Cookie politik](#)

[Tilgængelighedserklæring](#)

Interaktive bivirkningsoversigter

Resumé

Interaktive bivirkningsoversigter viser oplysninger om danske bivirkningsindberetninger. Bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne. Læs også om brugen af interaktive bivirkningsoversigter nederst på siden.

TOZINAMERAN

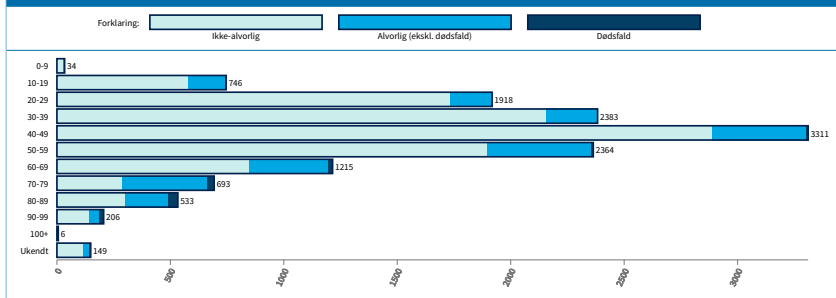
- Handelsnavne med ét enkelt indholdsstof: COMIRNATV, TOZINAMERAN [not otherwise coded]

- Antal indberetninger: 13558 - Antal bivirkninger: 40121
- Antal alvorlige indberetninger (ekskl. dødsfald): 2447 - Antal indberetninger om dødsfald: 124
- Oversigterne viser oplysninger om alle 13558 indberetninger om TOZINAMERAN i Danmark.
- Indberetningsdata opdateret: 31-Dec-2021

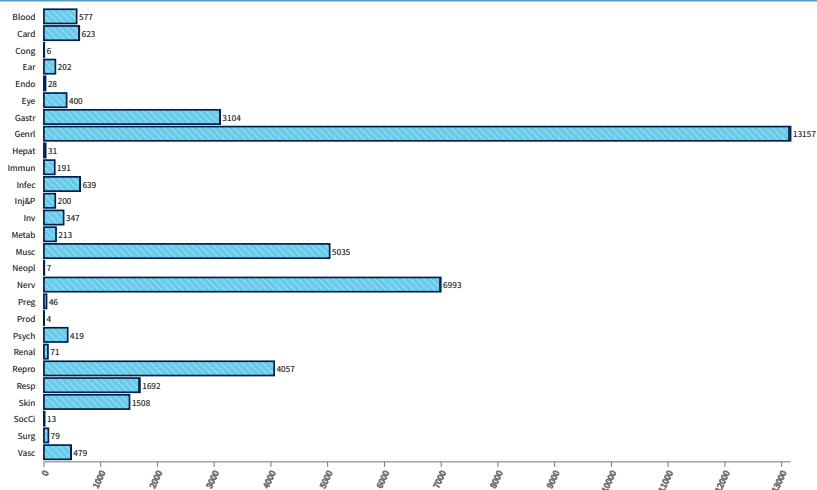
Indberetninger fordelt på køn

Køn	Ikke-alvorlig	Alvorlig (ekskl. dødsfald)	Dødsfald	Total
Mand	1330	891	61	2282
Kvinde	9634	1551	59	11244
Ukendt	23	5	4	32
Total	10987	2447	124	13558

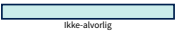
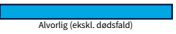
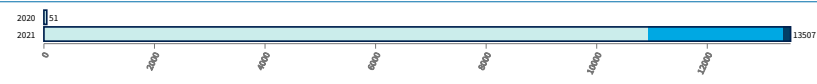
Indberetninger fordelt på aldersgruppe



Bivirkninger fordelt på MedDRA organklasser

Forklaring:  

Indberetninger fordelt på år

Forklaring:   

Bivirkninger fordelt på MedDRA organklasser		
Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Blod og lymfesystem (Blood)	577	2
 Hjerte (Card)	623	17
 Medfødte, familiære og genetiske sygdomme (Cong)	6	3
 Øre og labyrint (Ear)	202	0
 Det endokrine system (Endo)	28	0
 Øjne (Eye)	400	0
 Mave-tarm-kanalen (Gastr)	3104	2
 Almene symptomer og reaktioner på administrationsstedet (Genrl)	13157	39
 Lever og galdeveje (Hepat)	31	2
 Immunsystemet (Immun)	191	0
 Infektioner og parasitære sygdomme (Infec)	639	12
 Traumer, forgiftninger og behandlingskomplikationer (Inj&P)	200	1
 Undersøgelser (Inv)	347	0
 Metabolisme og ernæring (Metab)	213	0
 Knogler, led, muskler og bindevæv (Musc)	5035	0
 Benigne, maligne og uspecifiserede tumorer, inkl.cyster og polypper (Neopl)	7	0
 Nervesystemet (Nerv)	6993	14
 Graviditet, puerperium og den perinatale periode (Preg)	46	1
 Produktfejl (Prod)	4	0
 Psykiske forstyrrelser (Psych)	419	0
 Nyrer og urinveje (Renal)	71	1
 Det reproduktive system og mammae (Repro)	4057	0
 Luftveje, thorax og mediastinum (Resp)	1692	26
 Hud og subkutane væv (Skin)	1508	0
 Sociale forhold (SocCi)	13	0
 Kirurgiske og medicinske procedurer (Surg)	79	0
 Vaskulære sygdomme (Vasc)	479	4
Bivirkninger i alt	40121	124

Vigtig information om Interaktive bivirkningsoversigter

Interaktive bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne.

For mere information om sikkerheden ved en bestemt medicin, kan du læse medicinens indlægsseddel eller produktresumé.

Brug af oplysninger fra interaktive bivirkningsoversigter:

- Interaktive bivirkningsoversigter kan ikke bruges til at beregne sandsynligheden for at opleve bivirkninger ved en bestemt type medicin.
- Når læger, patienter eller pårørende melder bivirkninger til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at symptomerne er bivirkninger til medicinen. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og den oplevede bivirkning.
- Der er mange forhold, der skal tages i betragtning, når man skal vurdere, om en bestemt medicin har forårsaget en bivirkning. Når Lægemiddelstyrelsen overvåger sikkerheden ved medicin, bliver alle forhold grundigt analyseret.
- Man kan ikke sammenligne sikkerheden ved forskellig medicin ved at sammenligne tallene i de interaktive bivirkningsoversigter.

Hvis du er bekymret over den medicin, du tager, skal du kontakte den læge, som har ordineret medicinen, eller spørge på apoteket. Det er vigtigt, at du ikke stopper med at tage ordineret medicin uden først at have talt med en læge.

Få mere information om interaktive bivirkningsoversigter her [Interaktive bivirkningsoversigter \(http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger\)](http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger).

DAP version: 1.0.0
MedSRA version: 24.1
Indberetningsniveau: Substance

bilag 3a Pfizer

Interaktive bivirkningsoversigter

Resumé

Interaktive bivirkningsoversigter viser oplysninger om danske bivirkningsindberetninger. Bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne. Læs også om brugen af interaktive bivirkningsoversigter nederst på siden.

MRNA-1273

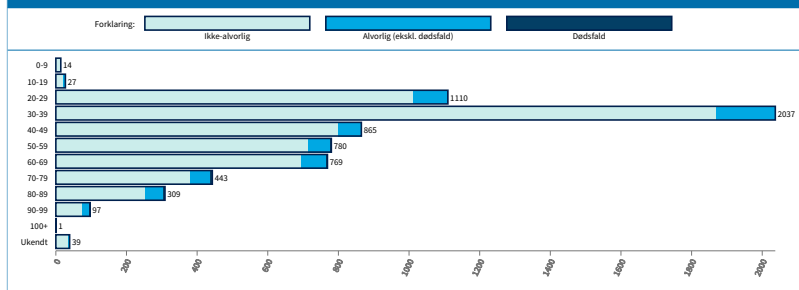
▪ Handelsnavne med ét enkelt indholdsstof: SPIKEVAX

- Antal indberetninger: 6491 - Antal bivirkninger: 16894
- Antal alvorlige indberetninger (ekskl. dødsfald): 596 - Antal indberetninger om dødsfald: 17
- Oversigterne viser oplysninger om alle 6491 indberetninger om MRNA-1273 i Danmark.
- Indberetningsdata opdateret: 31-Dec-2021

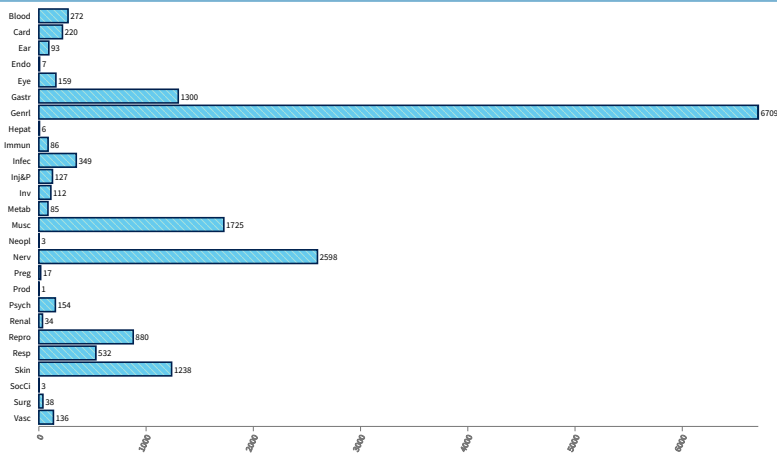
Indberetninger fordelt på køn

Køn	Ikke-alvorlig	Alvorlig (ekskl. dødsfald)	Dødsfald	Total
Mand	1084	211	10	1305
Kvinde	4773	384	7	5164
Ukendt	21	1	0	22
Total	5878	596	17	6491

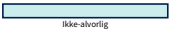
Indberetninger fordelt på aldersgruppe



Bivirkninger fordelt på MedDRA organklasser

Forklaring:  Alle bivirkninger (ekskl. dødsfald)  Dødsfald

Indberetninger fordelt på år

Forklaring:  Ikke-alvorlig  Alvorlig (ekskl. dødsfald)  Dødsfald

Bivirkninger fordelt på MedDRA organklasser

Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Blod og lymfesystem (Blood)	272	0
 Hjerte (Card)	220	3
 Øre og labyrint (Ear)	93	0
 Det endokrine system (Endo)	7	0
 Øjne (Eye)	159	0

Bivirkninger fordelt på MedDRA organklasser		
Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Mave-tarm-kanalen (Gastr)	1300	1
 Almene symptomer og reaktioner på administrationsstedet (Genrl)	6709	5
 Lever og galdeveje (Hepat)	6	0
 Immunsystemet (Immun)	86	0
 Infektioner og parasitære sygdomme (Infec)	349	1
 Traumer, forgiftninger og behandlingskomplikationer (Inj&P)	127	0
 Undersøgelser (Inv)	112	0
 Metabolisme og ernæring (Metab)	85	0
 Knogler, led, muskler og bindevæv (Musc)	1725	0
 Benigne, maligne og uspecificerede tumorer, inkl.cyster og polypyper (Neopl)	3	0
 Nervesystemet (Nerv)	2598	2
 Graviditet, puerperium og den perinatale periode (Preg)	17	0
 Produktfejl (Prod)	1	0
 Psykiske forstyrrelser (Psych)	154	0
 Nyrer og urinveje (Renal)	34	0
 Det reproduktive system og mammae (Repro)	880	0
 Luftveje, thorax og mediastinum (Resp)	532	3
 Hud og subkutane væv (Skin)	1238	0
 Sociale forhold (SocCi)	3	0
 Kirurgiske og medicinske procedurer (Surg)	38	0
 Vaskulære sygdomme (Vasc)	136	2
Bivirkninger i alt	16884	17

Vigtig information om Interaktive bivirkningsoversigter

Interaktive bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne.

For mere information om sikkerheden ved en bestemt medicin, kan du læse medicinens indlægsseddel eller produktresumé.

Brug af oplysninger fra interaktive bivirkningsoversigter:

- Interaktive bivirkningsoversigter kan ikke bruges til at beregne sandsynligheden for at opleve bivirkninger ved en bestemt type medicin.
- Når læger, patienter eller pårørende melder bivirkning til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at symptomerne er bivirkninger til medicinen. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og den oplevede bivirkning.
- Der er mange forhold, der skal tages i betragtning, når man skal vurdere, om en bestemt medicin har forårsaget en bivirkning. Når Lægemiddelstyrelsen overvåger sikkerheden ved medicin, bliver alle forhold grundigt analyseret.
- Man kan ikke sammenligne sikkerheden ved forskellig medicin ved at sammenligne tallene i de interaktive bivirkningsoversigter.

Hvis du er bekymret over den medicin, du tager, skal du kontakte den læge, som har ordineret medicinen, eller spørge på apoteket. Det er vigtigt, at du ikke stopper med at tage ordineret medicin uden først at have talt med en læge.

Få mere information om interaktive bivirkningsoversigter her [Interaktive bivirkningsoversigter \(http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger\)](http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger).

DAP version: 1.0.0
MedDRA version: 24.1
Indberetningsniveau: Substance

bilag 3b Moderna

Interaktive bivirkningsoversigter

Resumé

Interaktive bivirkningsoversigter viser oplysninger om danske bivirkningsindberetninger. Bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne. Læs også om brugen af interaktive bivirkningsoversigter nederst på siden.

CHADOX1 NCOV-19

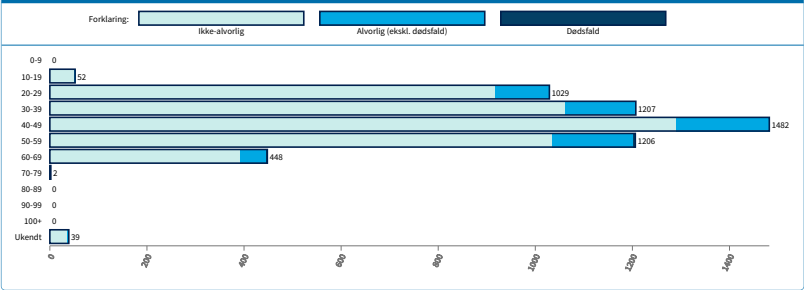
▪ Handelsnavne med ét enkelt indholdsstof: COVID-19 VACCINE ASTRAZENECA

- Antal indberetninger: 5465 - Antal bivirkninger: 25749
- Antal alvorlige indberetninger (ekskl. dødsfald): 676 - Antal indberetninger om dødsfald: 4
- Oversigterne viser oplysninger om alle 5465 indberetninger om CHADOX1 NCOV-19 i Danmark.
- Indberetningsdata opdateret: 31-Dec-2021

Indberetninger fordelt på køn

Køn	Ikke-alvorlig	Alvorlig (ekskl. dødsfald)	Dødsfald	Total
Mand	476	84	1	561
Kvinde	4300	592	3	4895
Ukendt	9	0	0	9
Total	4785	676	4	5465

Indberetninger fordelt på aldersgruppe

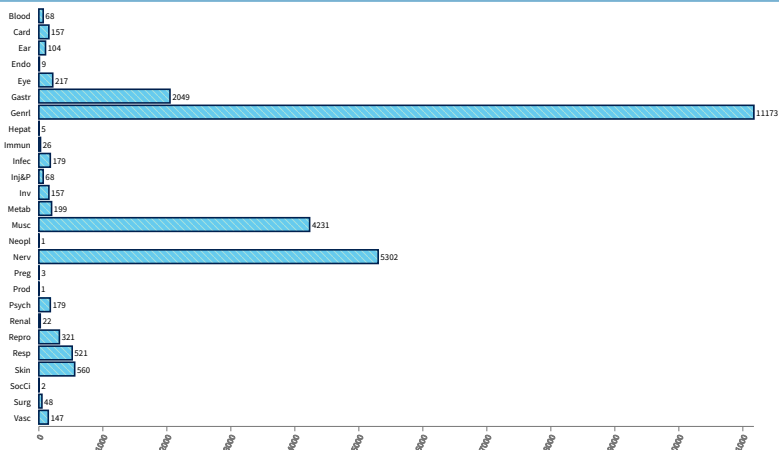


Bivirkninger fordelt på MedDRA organklasser

Forklaring:

Alle bivirkninger (ekskl. dødsfald)

Dødsfald



Indberetninger fordelt på år

Forklaring:

Ikke- alvorlig

Alvorlig (ekskl. dødsfald)

Dødsfald



Bivirkninger fordelt på MedDRA organklasser

Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Blod og lymfesystem (Blood)	68	2
 Hjerte (Card)	157	1
 Øre og labyrint (Ear)	104	0
 Det endokrine system (Endo)	9	0
 Øjne (Eye)	217	0

Bivirkninger fordelt på MedDRA organklasser		
Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Mave-tarm-kanalen (Gastr)	2049	0
 Almene symptomer og reaktioner på administrationsstedet (Genrl)	11173	1
 Lever og galdeveje (Hepat)	5	0
 Immunsystemet (Immun)	26	0
 Infektioner og parasitære sygdomme (Infec)	179	0
 Traumer, forgiftninger og behandlingskomplikationer (Inj&P)	68	0
 Undersøgelser (Inv)	157	0
 Metabolisme og ernæring (Metab)	199	0
 Knogler, led, muskler og bindevæv (Musc)	4231	0
 Benigne, maligne og uspecificerede tumorer, inkl.cyster og polypyper (Neopl)	1	0
 Nervesystemet (Nerv)	5302	0
 Graviditet, puerperium og den perinatale periode (Preg)	3	0
 Produktfejl (Prod)	1	0
 Psykiske forstyrrelser (Psych)	179	0
 Nyrer og urinveje (Renal)	22	0
 Det reproduktive system og mammae (Repro)	321	0
 Luftveje, thorax og mediastinum (Resp)	521	0
 Hud og subkutane væv (Skin)	560	0
 Sociale forhold (SocCi)	2	0
 Kirurgiske og medicinske procedurer (Surg)	48	0
 Vaskulære sygdomme (Vasc)	147	0
Bivirkninger i alt	25749	4

Vigtig information om Interaktive bivirkningsoversigter

Interaktive bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne.

For mere information om sikkerheden ved en bestemt medicin, kan du læse medicinens indlægsseddel eller produktresumé.



Brug af oplysninger fra interaktive bivirkningsoversigter:

- Interaktive bivirkningsoversigter kan ikke bruges til at beregne sandsynligheden for at opleve bivirkninger ved en bestemt type medicin.
- Når læger, patienter eller pårørende melder bivirkninger til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at symptomerne er bivirkninger til medicinen. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og den oplevede bivirkning.
- Der er mange forhold, der skal tages i betragtning, når man skal vurdere, om en bestemt medicin har forårsaget en bivirkning. Når Lægemiddelstyrelsen overvåger sikkerheden ved medicin, bliver alle forhold grundigt analyseret.
- Man kan ikke sammenligne sikkerheden ved forskellig medicin ved at sammenligne tallene i de interaktive bivirkningsoversigter.

Hvis du er bekymret over den medicin, du tager, skal du kontakte den læge, som har ordineret medicinen, eller spørge på apoteket. Det er vigtigt, at du ikke stopper med at tage ordineret medicin uden først at have talt med en læge.

Få mere information om interaktive bivirkningsoversigter her [Interaktive bivirkningsoversigter \(http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger\)](http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger).

DAP version: 1.0.0
MedDRA version: 24.1
Indberetningsniveau: Substance

bilag 3c Astrazeneca

Interaktive bivirkningsoversigter

Resumé

Interaktive bivirkningsoversigter viser oplysninger om danske bivirkningsindberetninger. Bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne. Læs også om brugen af interaktive bivirkningsoversigter nederst på siden.

AD26.COVID.S

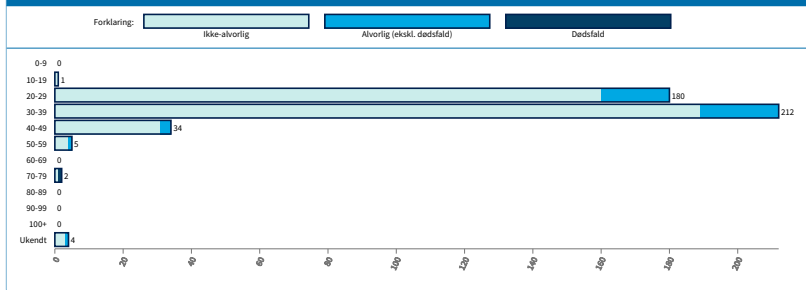
- Handelsnavne med ét enkelt indholdsstof: COVID-19 VACCINE JANSEN

- Antal indberetninger: 438 - Antal bivirkninger: 1388
- Antal alvorlige indberetninger (ekskl. dødsfald): 48 - Antal indberetninger om dødsfald: 1
- Oversigterne viser oplysninger om alle 438 indberetninger om AD26.COVID.S i Danmark.
- Indberetningsdata opdateret: 31-Dec-2021

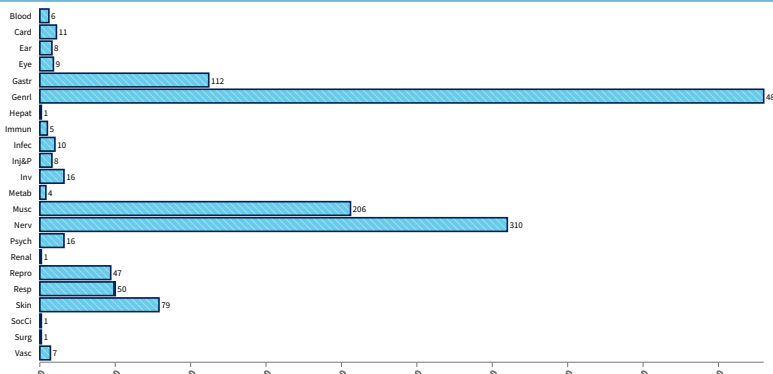
Indberetninger fordelt på køn

Køn	Ikke-alvorlig	Alvorlig (ekskl. dødsfald)	Dødsfald	Total
Mand	248	30	1	279
Kvinde	141	18	0	159
Ukendt	0	0	0	0
Total	389	48	1	438

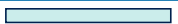
Indberetninger fordelt på aldersgruppe



Bivirkninger fordelt på MedDRA organklasser

Forklaring:  Alle bivirkninger (ekskl. dødsfald)  Dødsfald

Indberetninger fordelt på år

Forklaring:  Ikke- alvorlig  Alvorlig (ekskl. dødsfald)  Dødsfald

Bivirkninger fordelt på MedDRA organklasser

Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Blod og lymfesystem (Blood)	6	0
 Hjerte (Card)	11	0
 Øre og labyrint (Ear)	8	0
 Øjne (Eye)	9	0
 Mave-tarm-kanalen (Gastr)	112	0
 Almene symptomer og reaktioner på administrationsstedet (Genrl)	480	0
 Lever og galdeveje (Hepat)	1	0

Bivirkninger fordelt på MedDRA organklasser		
Bivirkninger i MedDRA	Bivirkninger i alt	
	Alle	Dødsfald
 Immunsystemet (Immun)	5	0
 Infektioner og parasitære sygdomme (Infec)	10	0
 Traumer, forgiftninger og behandlingskomplikationer (Inj&P)	8	0
 Undersøgelser (Inv)	16	0
 Metabolisme og ernæring (Metab)	4	0
 Knogler, led, muskler og bindevæv (Musc)	206	0
 Nervesystemet (Nerv)	310	0
 Psykiske forstyrrelser (Psych)	16	0
 Nyrer og urinveje (Renal)	1	0
 Det reproduktive system og mammae (Repro)	47	0
 Luftveje, thorax og mediastinum (Resp)	50	1
 Hud og subkutane væv (Skin)	79	0
 Sociale forhold (SocCi)	1	0
 Kirurgiske og medicinske procedurer (Surg)	1	0
 Vaskulære sygdomme (Vasc)	7	0
Bivirkninger i alt	1388	1

Vigtig information om Interaktive bivirkningsoversigter

Interaktive bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne.

For mere information om sikkerheden ved en bestemt medicin, kan du læse medicinens indlægsseddel eller produktresumé.

Brug af oplysninger fra interaktive bivirkningsoversigter:

- Interaktive bivirkningsoversigter kan ikke bruges til at beregne sandsynligheden for at opleve bivirkninger ved en bestemt type medicin.
- Når læger, patienter eller pårørende melder bivirkning til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at symptomerne er bivirkninger til medicinen. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og den oplevede bivirkning.
- Der er mange forhold, der skal tages i betragtning, når man skal vurdere, om en bestemt medicin har forårsaget en bivirkning. Når Lægemiddelstyrelsen overvåger sikkerheden ved medicin, bliver alle forhold grundigt analyseret.
- Man kan ikke sammenligne sikkerheden ved forskellig medicin ved at sammenligne tallene i de interaktive bivirkningsoversigter.

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Få mere information om interaktive bivirkningsoversigter her [Interaktive bivirkningsoversigter \(http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger\)](http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger).

DAP version: 1.0.0
MedDRA version: 24.1
Indberetningsniveau: Substance

bilag 3d Jansen

Coronavirus - Anslået antal bivirkninger

status pr. 21/12/2021

Vaccinationer - Covid-19Kilde: <https://laegemiddelstyrelsen.dk/da/nyheder/temaer/indberettede-bivirkninger-ved-covid-19-vacciner>

	Påbegyndt v	Modtagne	% indberet	Behandlede	Andel behandlede
Pfizer	3999328	30933	0,77%	13436	43,4%
Moderna	571876	7480	1,31%	6470	86,5%
AstraZeneca	152106	23864	15,69%	5129	21,5%
Johnson & J	46760	492	1,05%	434	88,2%
I alt	4774091	62879	1,32%	25469	40,5%

Vaccinationer - InfluenzaKilde: <https://www.ssi.dk/aktuelt/nyheder/2019/flere-end-nogensinde-for-blev-vaccineret-mod-influenza>

Påbegyndt v	846000
-------------	--------

Influenza 2018-2019<https://laegemiddelstyrelsen.dk/bivirkninger/bivirkninger-ved-medicin/interaktive-bivirkningsoversigter/.aspx?letter=A>

Behandlede bivirkninger

Ikke alvorlig	96
Alvorlig	28
Dødsfald	3
I alt	127

Anslåede antal totale bivirkninger Covid-19 vaccination

	Behandlede indberetninger				Anslået antal totale indberetninger				
Bivirkning	Pfizer	Moderna	AstraZene	Johnson &	Pfizer	Moderna	AstraZene	Johnson &	Anslået antal totale bivirkninger
Ikke alvorlig	10987	5878	4785	389	25295	6796	22263	441	54795
Alvorlig	2447	596	676	48	5634	689	3145	54	9522
Dødsfald	124	17	4	1	285	20	19	1	325
I alt	13558	6491	5465	438	31214	7504	25427	497	64642

Anslået antal bivirkninger for Influenza vaccine pr år. ved vaccination af 4774091 personer

Bivirkning	Behandlet	Faktor	Anslåede antal totale bivirkninger
Ikke alvorlig	96	2,821567	271
Alvorlig	28	2,821567	79
Dødsfald	3	2,821567	8
I alt	127	2,821567	358

Anslået forhold mellem bivirkninger for influenzavaccine og coronavaccine

Ikke alvorlig	202
Alvorlig	121
Dødsfald	38
I alt	180

Interaktive bivirkningsoversigter

Resumé

Interaktive bivirkningsoversigter viser oplysninger om danske bivirkningsindberetninger. Bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne. Læs også om brugen af interaktive bivirkningsoversigter nederst på siden.

INFLUENZA VIRUS

- Handelsnavne med ét enkelt indholdsstof: INFLUENZA VIRUS [not otherwise coded], INFLUENZA VACCINE, PANDEMRIX, TRIVALENT INFLUENZA VACCINE HIGH DOSE
- Handelsnavne med flere indholdsstoffer: AGRIPPAL, ALORBAT, FLUARIX, FLUENZ TETRA, FLUVIRIN, FLUZONE, FLUZONE HIGH DOSE QUADRIVALENT, INFLEXAL V, INFLUENZA VACCINE "DUPHAR", INFLUVAC, INFLUVACTETRA, VAXIGRIP, VAXIGRIPTETRA

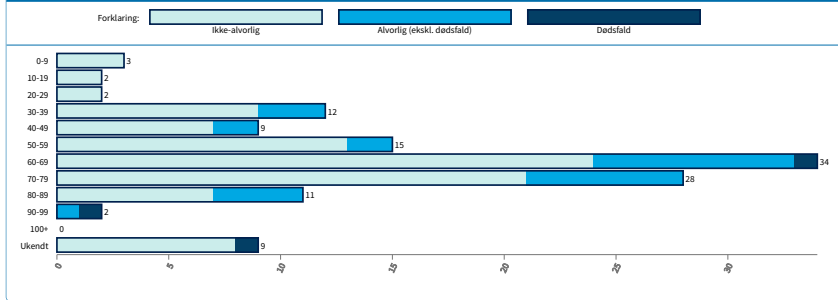
- Antal indberetninger: 1833 - Antal bivirkninger: 5588
- Antal alvorlige indberetninger (ekskl. dødsfald): 448 - Antal indberetninger om dødsfald: 40
- Oversigterne viser oplysninger om 127 ud af 1833 indberetninger om INFLUENZA VIRUS i Danmark.
- Indberetningsdata opdateret: 31-Dec-2021

Grafer og tabeller filtreres, så de kun viser indberetninger, som opfylder alle følgende kriterier:
Indberetningsår: mellem 2018 og 2019

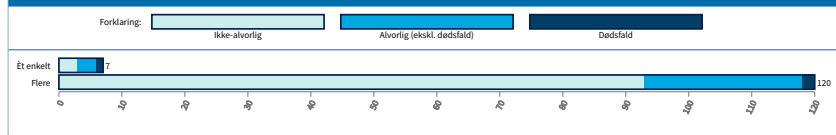
Valgte indberetninger fordelt på køn

Køn	Ikke-alvorlig	Alvorlig (ekskl. dødsfald)	Dødsfald	Total
Mand	35	13	2	50
Kvinde	60	15	1	76
Ukendt	1	0	0	1
Total	96	28	3	127

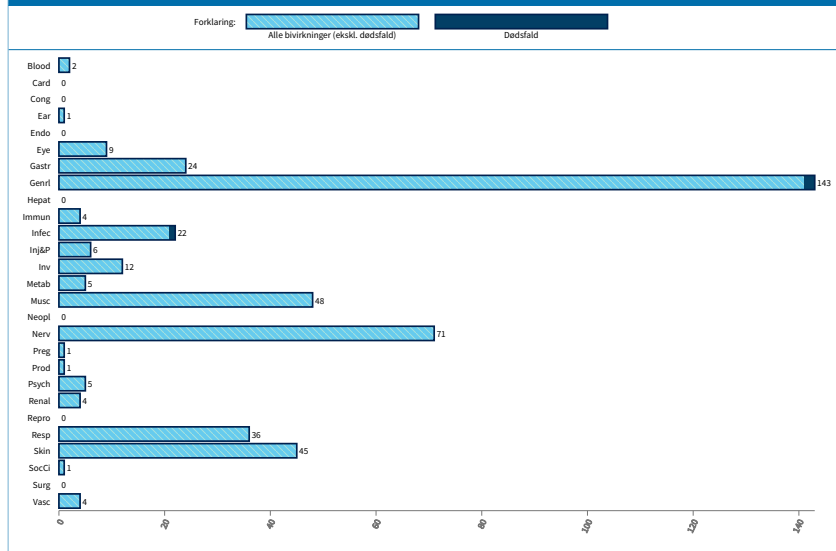
Valgte indberetninger fordelt på aldersgruppe

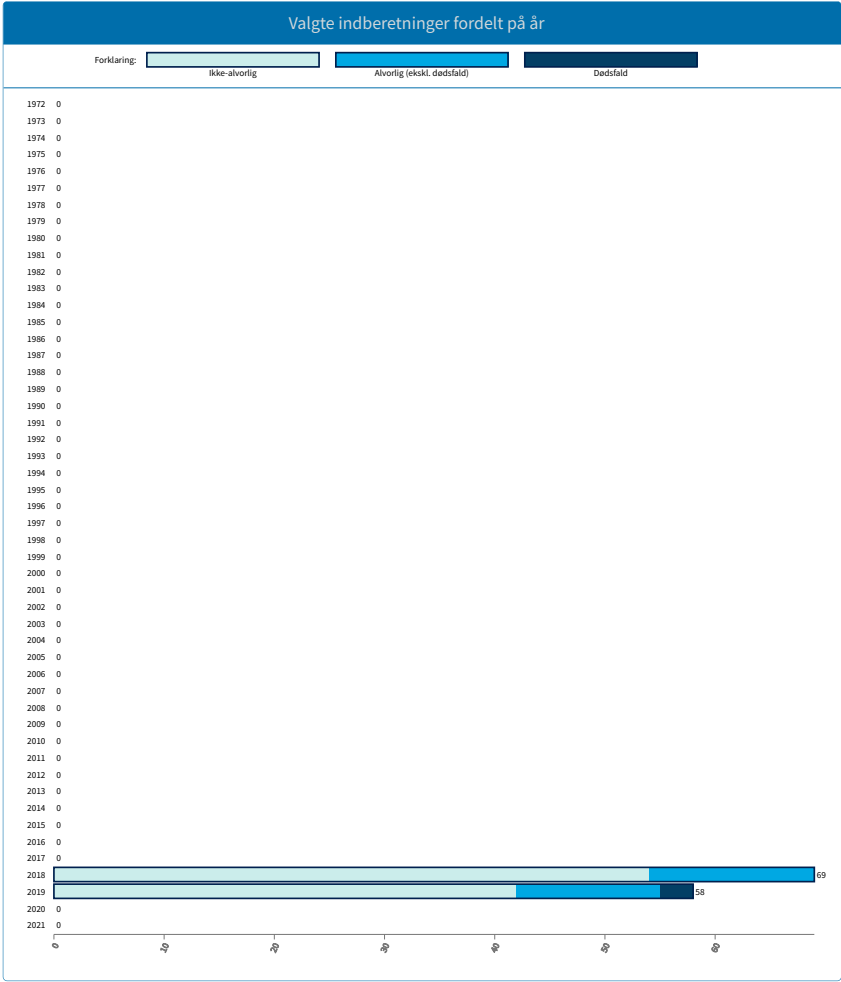


Valgte indberetninger fordelt på medicin med hhv. ét enkelt indholdsstof eller flere indholdsstoffer



Valgte bivirkninger fordelt på MedDRA organklasser





Valgte bivirkninger fordelt på MedDRA organklasser						
Bivirkninger i MedDRA	Ét aktivt indholdsstof		Flere aktive indholdsstoffer		Bivirkninger i alt	
	Alle	Dødsfald	Alle	Dødsfald	Alle	Dødsfald
☒ Blod og lymfesystem (Blood)	0	0	2	0	2	0
☒ Hjerte (Card)	0	0	0	0	0	0
☒ Medfødte, familiære og genetiske sygdomme (Cong)	0	0	0	0	0	0
☒ Øre og labyrint (Ear)	0	0	1	0	1	0
☒ Det endokrine system (Endo)	0	0	0	0	0	0
☒ Øjne (Eye)	0	0	9	0	9	0
☒ Mave-tarm-kanalen (Gastr)	1	0	23	0	24	0
☒ Almene symptomer og reaktioner på administrationsstedet (Genrl)	5	0	138	2	143	2
☒ Lever og galdeveje (Hepat)	0	0	0	0	0	0
☒ Immunsystemet (Immun)	0	0	4	0	4	0
☒ Infektioner og parasitære sygdomme (Infec)	2	1	20	0	22	1
☒ Traumer, forgiftninger og behandlingskomplikationer (Inj&P)	0	0	6	0	6	0
☒ Undersøgelser (Inv)	0	0	12	0	12	0
☒ Metabolisme og ernæring (Metab)	0	0	5	0	5	0
☒ Knogler, led, muskler og bindevæv (Musc)	6	0	42	0	48	0
☒ Benigne, maligne og uspecifiserede tumorer, inkl.cyster og polypper (Neopl)	0	0	0	0	0	0
☒ Nervesystemet (Nerv)	9	0	62	0	71	0
☒ Graviditet, puerperium og den perinatale periode (Preg)	0	0	1	0	1	0
☒ Produktfejl (Prod)	0	0	1	0	1	0
☒ Psykiske forstyrrelser (Psych)	1	0	4	0	5	0
☒ Nyrer og urinveje (Renal)	2	0	2	0	4	0
☒ Det reproduktive system og mammae (Repro)	0	0	0	0	0	0
☒ Luftveje, thorax og mediastinum (Resp)	2	0	34	0	36	0
☒ Hud og subkutane væv (Skin)	0	0	45	0	45	0
☒ Sociale forhold (SocCi)	1	0	0	0	1	0
☒ Kirurgiske og medicinske procedurer (Surg)	0	0	0	0	0	0
☒ Vaskulære sygdomme (Vasc)	0	0	4	0	4	0
Bivirkninger i alt	29	1	415	2	444	3

Vigtig information om Interaktive bivirkningsoversigter

Interaktive bivirkningsoversigter kan være et nyttigt værktøj til at identificere mulige sikkerhedsmæssige problemer ved medicin. Dog kan bivirkningsoversigterne ikke give et fuldstændigt overblik over risici, der kan være forbundet med brug af medicin. Der kan derfor ikke drages konklusioner om sikkerhed og risici ved medicin udelukkende fra oplysningerne i bivirkningsoversigterne.

For mere information om sikkerheden ved en bestemt medicin, kan du læse medicinens indlægsseddel eller produktresumé.

Brug af oplysninger fra interaktive bivirkningsoversigter:

- Interaktive bivirkningsoversigter kan ikke bruges til at beregne sandsynligheden for at opleve bivirkninger ved en bestemt type medicin.
- Når læger, patienter eller pårørende melder bivirkninger til Lægemiddelstyrelsen, behøver de blot at have en formodning om, at symptomerne er bivirkninger til medicinen. En indberetning om en formodet bivirkning er derfor ikke det samme som en faktisk sammenhæng mellem medicinen og den oplevede bivirkning.
- Der er mange forhold, der skal tages i betragtning, når man skal vurdere, om en bestemt medicin har forårsaget en bivirkning. Når Lægemiddelstyrelsen overvåger sikkerheden ved medicin, bliver alle forhold grundigt analyseret.
- Man kan ikke sammenligne sikkerheden ved forskellig medicin ved at sammenligne tallene i de interaktive bivirkningsoversigter.

Hvis du er bekymret over den medicin, du tager, skal du kontakte den læge, som har ordineret medicinen, eller spørge på apoteket. Det er vigtigt, at du ikke stopper med at tage ordineret medicin uden først at have talt med en læge.

Få mere information om interaktive bivirkningsoversigter her [Interaktive bivirkningsoversigter \(http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger\)](http://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/drug-analysis-prints-indberettede-bivirkninger).

DAP version: 1.0.0
MedSRA version: 24.1
Indberetningsniveau: Substance

[Forside](#) / [Aktuelt og presse](#) / [Nyheder](#) / [2019](#) / **Flere end nogensinde før blev vaccineret mod influenza**

Flere end nogensinde før blev vaccineret mod influenza

Tal fra Det Danske Vaccinationsregister viser, at 762.500 borgere i risikogrupperne blev vaccineret i den just overståede influenzasæson.

Senest redigeret den 3. juni 2019



Influenzasæsonen 2018/2019 var officielt forbi for nogle uge siden. Og aldrig er så mange blevet vaccineret mod influenza som i denne sæson.

Nye tal fra Det Danske Vaccinationsregister (DDV) viser, at i alt 846.000 borgere blev vaccineret. Det svarer til 15% af befolkningen og er det højeste antal vaccinationer, der er givet nogensinde.

Flere vaccineret i risikogrupperne

Tallene fra DDV viser også, at over 90% af vaccinationerne – i alt 762.500 – blev givet til borgere i risikogrupperne.

Det drejer sig blandt andet om 588.100 borgere på 65 år og derover, 131.400 kronisk syge, 22.100 førtidspensionister, 16.900 gravide og 4.000 husstandskontakter til personer med immundefekt.

”Der blev simpelthen givet flere vaccinationer til alle risikogrupper i 2018/2019-sæsonen i forhold til året før. Blandt andet steg vaccinationsdækningen blandt ældre på 65 og derover fra 50% til 52%, hvilket jo er glædeligt”, siger afdelingschef Tyra Grove Krause fra SSI og tilføjer:

”Der er stadig ret store geografiske forskelle på tilslutningen. Hørsholm kommune slår rekord med en tilslutning på 62% blandt de ældre, men der er stadig kommuner med tilslutninger, der kun sniger sig op over de 40%.”

Der blev også registeret næsten 83.400 vaccinationer til personer under 65 år, der ikke tilhører en af de officielle risikogrupper. Også dette tal er lidt højere end sidste sæson.

[Find flere oplysninger om vaccinationstilslutningen til blandt andet risikogrupper fordelt på aldersgrupper, landsdel og kommuner her.](#)



Kontakt

Tyra Grove Krause, Faglig direktør, Infektionsberedskab - Ledelse og stab / Epidemiologisk Infektionsberedskab
T. [32688613](tel:32688613) @. tgy@ssi.dk [Se profil](#)

Statens Serum Institut Artillerivej 5, 2300 Kbh S. T. [3268 3268](tel:32683268) @. serum@ssi.dk F. [3268 3868](tel:32683868) EAN 5798000362192

[Webtilgængelighedserklæring](#) [Cookies](#) [Persondatapolitik](#) [Kontakt](#) [Følg os](#)

Crosstabs

Notes

Output Created		14-JAN-2022 16:00:55
Comments		
Input	Data	C: \\Users\\Max\\Documents\\Projekter\\Co rona\\2022 01 06 Åbent brev til folketinget 2\\Chi2 test.sav
	Active Dataset	DataSet1
	Filter	<none>
	Weight	Count
	Split File	<none>
	N of Rows in Working Data File	4
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics for each table are based on all the cases with valid data in the specified range(s) for all variables in each table.
Syntax		CROSSTABS /TABLES=DB BY Group /FORMAT=AVALUE TABLES /STATISTICS=CHISQ /CELLS=COUNT EXPECTED SRESID /COUNT ROUND CELL.
Resources	Processor Time	00:00:00,00
	Elapsed Time	00:00:00,01
	Dimensions Requested	2
	Cells Available	524629

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
DB * Group	2875	100,0%	0	0,0%	2875	100,0%

DB * Group Crosstabulation

			Group		Total
			High	Low	
DB	DK	Count	16	1	17
		Expected Count	1,7	15,3	17,0
		Standardized Residual	11,1	-3,7	
	VAERS	Count	265	2593	2858
		Expected Count	279,3	2578,7	2858,0
		Standardized Residual	-,9	,3	
	Total	Count	281	2594	2875
		Expected Count	281,0	2594,0	2875,0

Chi-Square Tests

	Value	df	Asymptotic Significance (2- sided)	Exact Sig. (2- sided)	Exact Sig. (1- sided)
Pearson Chi-Square	137,953 ^a	1	,000	,000	,000
Continuity Correction ^b	128,499	1	,000		
Likelihood Ratio	67,842	1	,000		
Fisher's Exact Test					
N of Valid Cases	2875				

a. 1 cells (25,0%) have expected count less than 5. The minimum expected count is 1,66.

b. Computed only for a 2x2 table



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Amsterdam, 30 November 2020

EMA/CHMP/641856/2020

Committee for Medicinal Products for Human Use (CHMP)

Quality rolling review CHMP overview and list of questions

COVID-19 mRNA Vaccine BioNTech

BNT162b2, 5'capped mRNA encoding full length SARS-CoV-2 Spike protein

Procedure No. EMEA/H/C/005735/RR/02

Applicant: BioNTech Manufacturing GmbH

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Administrative information

Invented name of the medicinal product:	COVID-19 mRNA Vaccine BioNTech
INN (or common name) of the active substance(s):	BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein
Applicant:	BioNTech Manufacturing GmbH
Applied Indication(s):	TBD
Pharmaco-therapeutic group (ATC Code):	J07BX
Pharmaceutical form(s) and strength(s):	Concentrate for suspension for injection 0,225 mg
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In accordance with Article 6(3) of Regulation (RC) No 726/2004, I the Rapporteur hereby declare that I have completed my assessment report in less than 80 days.	Date 2020-11-19 Signature Filip Josephson

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Declarations

This application includes an Active Substance Master File (ASMF):

☐ Yes

☒ No

☒ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, including the Product Information, unless there are previous contracts and/or agreements with the third party(ies).

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located (including the Product Information document) here:

List of abbreviations

5' cap	5' capping structure, (m27,3'-OGppp(m12'-O)ApG)
AF4-MALS-QELS	Asymmetric Flow Field-Flow Fractionation (AF4) Multi-Angle Static and Quasi-Elastic Light Scattering
ALC-0159	PEG-lipid, 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
ALC-0315	Cationic lipid, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
AQL	Acceptance Quality Limit
ATP	adenosine triphosphate
AUC	Area under the curve
BNT162b2	Vaccine candidate encoding the SARS-CoV-2 full-length spike protein, modified by 2 proline mutations (P2 S)
BSE	bovine spongiform encephalopathies
C&E	Cause and Effect Matrices
C&E	Cause and Effects
CAD	Charged Aerosol Detection
CCI	Container Closure Integrity
CDI	N,N-carbonyldiimidazole
CGE	Capillary Gel Electrophoresis
CMA	Conditional marketing authorisation
CoA	Certificate of Analysis
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRM	Clinical Reference Material
CTM	Clinical Trial Material
ddPCR	Droplet digital PCR
DL	Detection Limit
DLS	Dynamic Light Scattering
DOE	Design of experiments
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry

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DSPC	Phospholipid, (1,2-distearoyl-sn-glycero-3-phosphocholine)
DVS	Dynamic Vapor sorption
EDTA	Ethylenediaminetetraacetic acid
ELSD	Evaporative Light Scattering Detection
EVA	Ethylene Vinyl Acetate
EVA	Ethylene vinyl acetate
FID	Flame Ionization Detector
FMEA	Failure Modes and Effects Analysis
FTIR	Fourier-Transform Infrared
GC	Gas Chromatography
GMP	Good Manufacturing Practice
GTP	Guanidine triphosphate
HEPA filter	High Efficiency Particulate Arresting filter
HEPES	N-(2-hydroxyethyl)-piperazine-N-(2-ethanesulfonic acid)
HPLC	High Performance Liquid Chromatography
HTF	Heat Transfer Fluid
ICH	International Council for Harmonisation
ICP	Inductively Coupled Plasma
IP-RP-HPLC	ion-paired reversed-phase high performance liquid chromatography
IPT-C	In-Process Tests for Control
IPT-M	In-Process Tests for Monitoring
IR	Infrared spectroscopy
IVE	In-Vitro Expression
IVT	In vitro transcription
JP	Japanese Pharmacopeia
LC	Liquid Chromatography
LNP	Lipid nanoparticle
MAA	Marketing authorization application
MFAT	Multi-factor-at-a-time
MBC	Master cell bank
mRNA	Messenger RNA
MS	Mass Spectroscopy

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N/P	Molar ratio of the amine in the cationic lipid (N) to the phosphate in anionic phosphodiester backbone of RNA (P)
NGS	Next Generation Sequencing
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
NTP	Nucleotide triphosphate
OFAT	One-factor-at-a-time
OQ	Operational Qualification
PAR	Proven acceptable ranges
PBS	Phosphate-Buffered Saline
PCR	Polymerase Chain Reaction
PEG	Polyethylene glycol
PES filter	Polyethersulfone filter
Ph. Eur.	European Pharmacopeia
poly(A)	polyadenosine
PPQ	Process Performance Qualification
PQ	Performance Qualification
PRM	Primary Reference Materials
PTFE	Polytetrafluoroethylene
PV	Process Validation
QA	Quality Attributes
QC	Quality Control
QL	Quantitation Limit
QTPP	Quality Target Product Profile
RPN	Risk Priority Number
RP-HPLC/UV-ESI MS	ion-pair reversed-phase high performance liquid chromatography- ultraviolet light detection at 260 nm and online electrospray ionization mass spectrometry
RR	Rolling review
RSF	Residual Seal Force
RT-PCR	Reverse Transcription Polymerase Chain Reaction
Rz/Rh	Overall ratio between root mean square radius (Rz) and hydrodynamic radius

	(Rh)
S	Spike glycoprotein
SARS	Severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
TFF	Tangential Flow Filtration
TLC	Thin Layer Chromatography
TOC	Total Organic Carbon
TSE	transmitting transmissible spongiform encephalopathies
UFDF	ultrafiltration/diafiltration
USP	United States Pharmacopeia
UTP	uridine triphosphate
UTR	Untranslated region
UV	Ultraviolet
WCB	Working cell bank
WRM	Working Reference Materials
XRD	X-Ray Diffraction

1. Executive summary

Rolling Review is an *ad hoc* procedure used in an emergency context. Rolling Review procedures allow the CHMP to review quality, non-clinical and clinical data as they become available, before a formal regulatory application is submitted to the Agency. The main objective of the rolling review is to expedite the future assessment of the scientific data once submitted in the context of a formal regulatory application. As such, the scientific standards and regulatory principles applied in rolling reviews are the same as those applicable to formal regulatory procedures. Consequently, concepts such as “Major Objections” or “Other Concerns” are used in this Rolling Review report to categorise, in the same manner as in a formal regulatory application, the deficiencies identified by the CHMP on the preliminary data submitted.

The assessment performed for Rolling Review procedures is without prejudice to additional considerations that may be held during the subsequent assessment of the formal regulatory application. Only the scientific opinion adopted on the formal regulatory application constitutes the final view of the CHMP on whether the medicinal product satisfies the criteria for marketing authorisation.

1.1. Scope of the rolling review submission

RR1 – concluded on 06.11.2020

Non-clinical dossier has been submitted for the first rolling review cycle 1 (RR1).

RR2 – subject of this assessment

For this second rolling review cycle (RR2) quality data has been submitted. This second rolling review cycle is the first rolling review that contains quality documentation, RR2 (CMC1).

The applicant plans to update several sections in the Quality part of dossier as part of upcoming submission for quality data package and states the following:

“Data for this section is pending and will be updated once the data has been generated, analyzed, and verified”.

Only partial information on the quality and non-clinical data has been submitted. Other modules of the dossier (e.g. clinical) have not been submitted.

Only the opinion adopted by the CHMP in the context of the application for marketing authorisation constitutes the final position of the committee on the quality, safety and efficacy of the medicinal product.

New active substance status

Based on the review of the data the active substance BNT162b2, 5’capped mRNA encoding full length SRAS-CoV-2 Spike protein contained in the medicinal product COVID-19 mRNA Vaccine BioNTech is considered to be qualified as a new active substance in itself.

1.2. The development programme/compliance with CHMP guidance/scientific advice

N/A

1.3. General comments on compliance with GMP, GLP, GCP

Regarding the non-clinical dossier, the pivotal toxicological studies are stated to be GLP compliant. There are some issues with repeat-dose toxicity study #38166 regarding the documentation which led to a request for an GLP inspection of the laboratory site (as adopted by the CHMP).

The EMA Compliance and Inspection Service has reviewed the manufacturer information contained in the application form and available certificates from the EEA National Competent Authorities. EMA confirms that a GMP Distant Assessment (DA) of the US Andover and Chesterfield sites are on-going.

1.4. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application will be provided as part of the marketing authorisation application submission refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

New active substance status

The applicant requested the active substance BNT162b2, 5'capped mRNA encoding full length SRAS-CoV-2 Spike protein 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.

1.5. Steps taken for the rolling review of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Co-Rapporteur: Jean Michel RACE

CHMP Peer reviewer: Ingrid Wang

Submission of the first package (NC) via eCTD	06 November 2020
Validation and start of 1st RR round	07 November 2020
Rapporteurs' CHMP ARs and draft overviews to peer reviewer, ETF, CHMP and EMA for 48 h consultation and comments	19 November 2020
Deadline for comments	23 November 2020
BWP extraordinary advice: agreement on BWP report and draft LoQ & proposals for SOBs/RECs	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	25 November 2020
ETF discussions on the consolidated List of Questions	26 November 2020
CHMP written procedure	27 November 2020
Adoption of the 2nd interim opinion for this rolling review of COVID-19 mRNA Vaccine BioNTech on	30 November 2020

2. Scientific overview and discussion on new data

2.1. Quality aspects

2.1.1. Introduction

The vaccine is based on the SARS CoV-2 spike glycoprotein (S) encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BNT162b2).

The finished product is presented as 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 containing 30 µg/dose of the active substance BNT162b2, 5'capped mRNA encoding full length SARS-CoV-2 Spike protein as active substance.

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), DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), cholesterol, sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water.

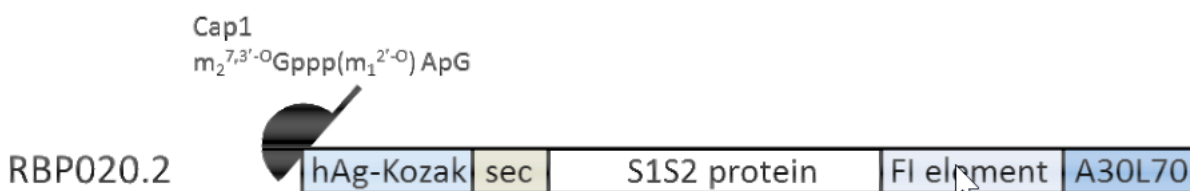
The product is available in glass vial sealed with a bromobutyl rubber stopper and an aluminium seal with flip-off plastic cap.

2.1.2. Active Substance

General Information

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. Figure 1 illustrates the general structure of the antigen-encoding RNA: In addition to the codon-optimized sequence encoding the antigen, the RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (5'-cap, 5'-UTR, 3'-UTR, poly(A)-tail; see below). Furthermore, an intrinsic signal peptide (sec) is part of the open reading frame and is translated as an N-terminal peptide. The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis.

Figure 1. General structure of the RNA



Schematic illustration of the general structure of the BNT162b2 drug substance with 5'-cap, 5'- and 3'-untranslated regions (hAg-Kozak and FI element, respectively), coding sequence with mutations and intrinsic signal peptide (sec) as well as poly(A)-tail (A30L70). Individual elements are not drawn to scale compared to their respective sequence lengths.

Manufacture, process controls and characterisation

Manufacturers

The Drug Substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, (steps 1-3) and Rentschler Biopharma SE, Laupheim, Germany (steps 4 and 5). Of note, the manufacturing process at the European sites is not yet included in the application.

Release and stability testing sites are listed. As Mutual Recognition Agreement is not in force for human vaccines, the provided documentation for manufacturing and testing sites located in the USA is not considered sufficient **(MO)**.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for the manufacturing site BNT Mainz & Rentschler is not yet provided. Therefore, the comments below are related only to the Andover site. It is expected that no significant differences between the two processes are envisaged. However, minor process adaption could be accepted provided that they will be appropriately validated.

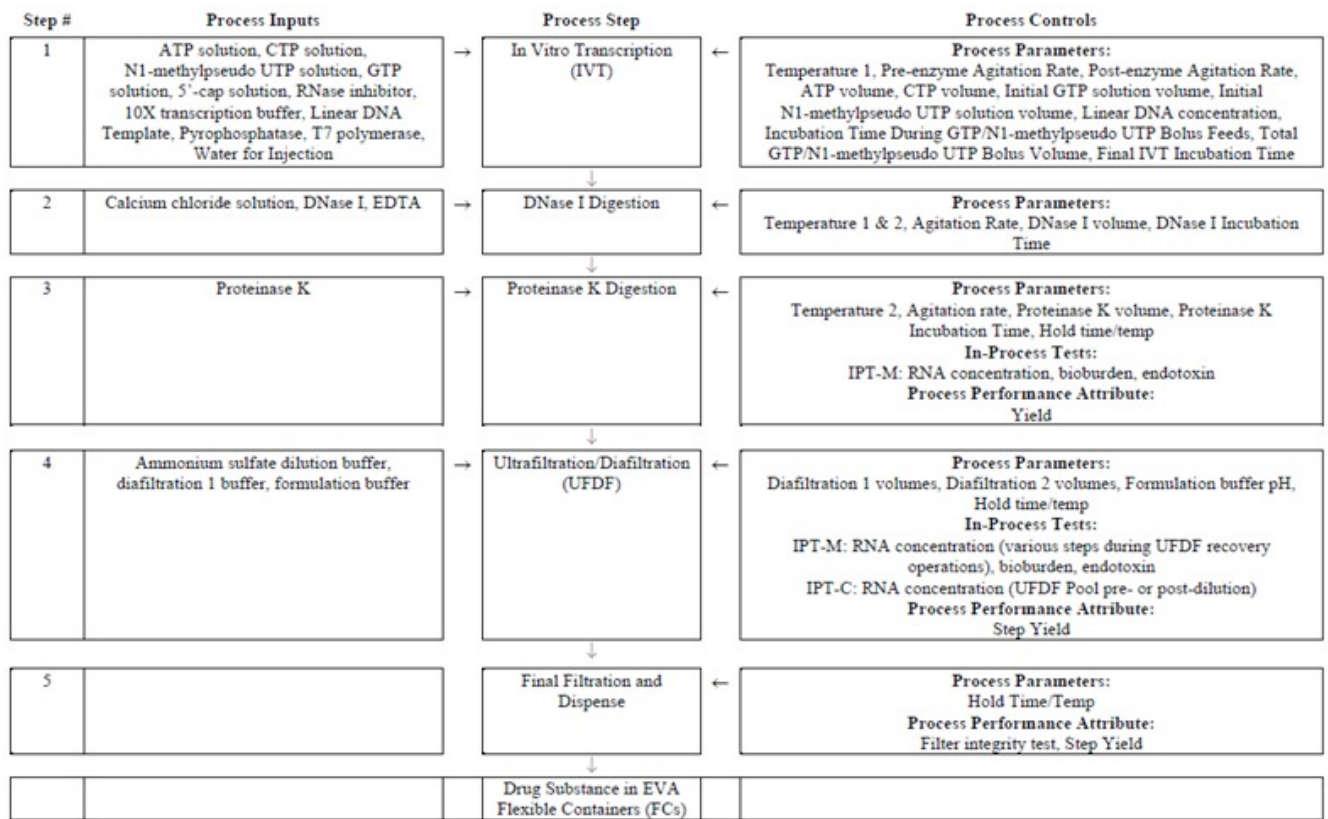
Overall description of the manufacturing process steps

The manufacturing process of BNT162b2 drug substance (DS) involves five major steps. The DS is produced at a scale of 37.6 L. The RNA is first synthesized from linear DNA via an in vitro transcription (IVT) step. It should be observed that the linear DNA template is defined as a starting material, and therefore manufacturing of the template via plasmid DNA is not included in the process. The IVT step is followed by two enzymatic steps, i.e. the DNase I (this reaction is stopped with EDTA addition) and proteinase K digestion steps, which aid in purification. The crude RNA is then purified through a two-stage ultrafiltration/diafiltration (UFDF) step. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen in EVA flexible containers.

A flow diagram is provided (Figure 3.2.S.2.2-1), presenting the process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The hold times, process parameters and corresponding acceptance criteria are listed 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. In general, it is agreed that the key process parameters are described in section 3.2.S.2.2. However, for the IVT step, the added volumes of the enzymes T7 polymerase and pyrophosphatase should be regarded as critical, unless justified. It should also be noted that future changes to any of the process parameters listed in S.2.2, regardless of the classification as CPP or non-CPP, should be applied for as variation applications. A few concerns are raised regarding the incubation time during GTP/N1-methylpseudo UTP bolus feeds, the transfers of the UFDF pool into a single PE flexible container and DS filling volume range.

The Applicant explains that the UFDF membrane lifetime remain to be established and the concurrent validation plan is found adequately described in the dossier. The strategy could be found acceptable, provided that the Applicant will update the manufacturing process description with control of feed flow rates, transmembrane pressure and membrane surface area.

Figure 3.2.S.2.2-1. RNA Manufacturing Process



Drug substance transportation

The drug substance is stored between -15 °C and -25 °. Transportation using an insulated shipper is qualified for a shipping time up to 106 hours at ≤-15 °C.

Reprocessing

It is stated that if the post-use integrity test on the final 0.45/0.2 µm filter fails, refiltration is allowed. It is clearly defined that reprocessing at the final filtration step is only allowed once. This is found acceptable.

Batch scale and definition

It is explained that commercial scale drug substance batches are executed at a scale of 37.6 L starting volume for in vitro transcription (IVT). All material produced is purified by a single, two-stage ultrafiltration/diafiltration (UFDF) to produce drug substance. The batch numbering system is sufficiently described. Each batch is assigned one batch number for the entire process. This is found acceptable. However, in addition, information on the final DS volume should be provided.

Control of materials

An adequate overview of the raw materials and solutions used in the Drug Substance manufacturing process is provided. Limited acceptance criteria are included in a tabular format for all raw materials but representative CoAs should also be provided for the non-compendial materials. In general, the

submitted information seem to support an appropriate quality of raw materials, however, several concerns are raised at this point.

Starting materials:

The listed starting materials include ATP solution, CTP solution, GTP solution, N1-methylpseudo UTP solution and 5'-cap solution and the linear DNA template. The approach is acceptable. As the 5'-cap structure is complex, additional information on its synthesis and discussion on its impurities are requested. Clarifications are also requested on materials testing.

Linear DNA template

BNT162b2 drug substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA (pST4-1525) from transformed DH10B 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 its adequate control. 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. Therefore, the level of details included in the dossier with respect to the manufacturing process and the control strategy for this starting material, although shortly described, is not yet considered adequate to allow for a proper assessment.

The functional elements of the pST4-1525 are sufficiently described in graphic and tabular formats and the sequence is included. However, details regarding the bacterial strain and the source and generation of the pST4-1525 plasmid used remain to be documented.

The cell banks involved in the plasmid manufacturing process are described. MCB and WCB qualification tests are listed and include morphologic and genotypic identity, restriction map analysis and DNA sequencing, absence of contaminating bacteriophages, viability, plasmid retention and plasmid copy number. 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 consisting of viability and plasmid retention assays conducted at all stability time points. The strategy is, in general, considered adequate, although some details are requested.

pST4-1525 is manufactured by a fed-batch fermentation process initiated from the bacterial working cell bank (WCB). Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified by ultrafiltration/diafiltration and anion exchange chromatography. The circular plasmid DNA is filtered via 0.2 µm filtration and stored frozen at -60 to -90 °C; the hold time for this intermediate is not defined. The filtrate is sampled for the circular plasmid DNA specifications. After thawing, the plasmid is linearized, concentrated, filtered and stored frozen at -15 to -25 °C. No additional information nor data are provided to support stability. The filtrate is sampled for the linear DNA template specification. A list of the raw materials as well as the chromatography resins and filters 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 quantified routinely. The reference material for plasmid identity testing is not described. Results from three different batches are provided for the circular and linearized plasmid and the proposed specification limits seem to be justified by the yet limited available data. No descriptions of the analytical methods used for the control of the linear DNA template nor evidence regarding their qualification/validation have been yet provided. This information

is, however, considered critical for quality of the final product. The Applicant is reminded that implementation of 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 drug substance quality are provided. The Applicant claims that due to rapid development of additional process knowledge, process parameters and ranges are expected to be updated in a subsequent submission to the MAA prior to its approval. This is found acceptable, but the Applicant is reminded that all process parameters and ranges should be sufficiently validated. All changes in future submissions prior to MAA or CMA approval should be clearly stated. Some clarifications about the list of critical process parameters (CPPs), in-process tests for control (IPT-C), and hold times are already requested.

The in-process test methods are defined either as in-process testing for control (IPT-C) or in-process testing for monitoring (IPT-M). The sole IPT-C is determination of RNA concentration in the ultrafiltration/diafiltration (UFDF) pool (pre- or post-dilution) by UV spectroscopy. This method is performed as described for the corresponding DS specification test. Three IPT-Ms are listed; determination of RNA concentration in the proteinase K pool by UV Spectroscopy (same as above), bioburden and bacterial endotoxin testing. All three methods are applied to test the proteinase K pool (post-hold), the UFDF pool (post-hold), and the UFDF end of diafiltration 2 retentate (pre-recovery) samples. Bioburden and bacterial endotoxin testing are compendial methods.

Process validation

The process validation is ongoing at Wyeth BioPharma, Andover. For the process validation studies a total of five validation batches will be included, all these batches have been manufactured representing the commercial batch size of 37.6 L. Results are available for three out of the five consecutive batches. The results from batches PPQ4 and PPQ5 are still pending.

No validation data are available to confirm consistent removal of impurities, which is not acceptable. In addition, residual DNA template is present at higher level in PPQ3 batch (211 ng DNA / mg RNA) than in PPQ1 and PPQ2 batches (10 and 23 ng/mg) which does not confirm the robustness of DNase I digestion.

The final filtration refiltration was validated at lab scale using a commercial scale filtration pool and will be confirmed at commercial scale. This is acceptable.

Several validation studies are still pending and will be updated once the data has been generated. ATP and CTP volumes added at the beginning of IVT were increased from the third PPQ batch and onwards. The results for PPQ4 and PPQ5 batches are therefore necessary to confirm the consistency of the process after this change. Therefore, a time-plan for the submission of these additional process validation data should be provided before marketing authorisation approval.

Hold times

It is stated that in-process pool hold times are not required for routine processing, but strategic holds in the process ≥ 24 hours to aid in manufacturing scheduling were validated. The small scale in-process hold studies are intended to support biochemical stability at commercial scale. The hold times for the Proteinase K pool, UFDF pool and DS before freezing as listed in S.2.2 are all acceptably validated for hold times ≤ 72 hours.

Filter Qualification and Validation

The final filtration/refiltration was validated at lab scale using a commercial scale filtration pool, and will be confirmed at commercial scale, which is pending. This is acceptable.

Shipping Performance Qualification

The shipping qualification strategy are described in detail and considered both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen DS to the DP manufacturing sites were validated to maintain product temperature in the acceptable range for durations up to 106 hours.

UFDF membrane lifetime

The strategy for UFDF membrane lifetime validation is to perform concurrent validation of the membranes at commercial scale. Parameters related to performance and cleaning of membranes will be evaluated as listed in Table S.2.5-9. This strategy is found appropriate since control of process parameters and IPC-tests are in place for every batch.

Manufacturing process development

Data for this section is pending.

Development history and Comparability

Process development changes were adequately summarised. Two DS processes have been used during the development history; Process 1 and 2. Details about process differences, justifications for making changes, and results from a comparability study is provided. The major changes between DS Process 1 and 2 are; increased process scale, DNA template changed from a PCR template to linearized plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UFDF steps.

No comparability study was provided for non-clinical versus clinical batches, but the batch analysis results are provided.

The comparability study was performed between process 1 GMP batches and process 2 batches manufactured at Andover and will be completed when all PPQ data will be available.

In the comparability study a decrease in RNA integrity was observed for the Process 2 batches compared to Process 1 batches (78.1-82.8% compared to 59.7%). After adjustment of process parameters for CTP and ATP volumes batch 20Y513C501 (PPQ3) was manufactured with RNA integrity level of 75%, more consistent with the Process 1 batches. No analysis of the capillary electropherogram was provided. It is therefore not possible to conclude if the differences in RNA integrity are quantitative or qualitative. Additional batch data are needed to confirm that the optimized Process 2 allows to reach RNA integrity levels consistent with the Process 1 batches. **(Part of MO).**

Regarding the 5' cap end of the DS, LC-UV/MS characterisation confirmed that the 5'-capped and uncapped structures are the same in Process 1 and 2, but that there is a slight shift towards higher 5'-capping levels in Process 2. It is noted that the capped-intact RNA was not measured, but only deducted from the results of 5'-cap and RNA integrity. Therefore, this argument cannot be used to fully confirm the comparability of Process 2 versus Process 1.

Furthermore, the poly(A) tail of the 3' end was characterised by LC-UV/MS. The expected short (A30) and long (L70) segments of the poly(A) tail were observed after RNase T1 cleavage. While the results for the A30 segment were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified for the L70 segment. As expected, poly(A) tail heterogeneity was

observed both for Process 1 and Process 2 batches, due to transcriptional slippage. Longer poly(A) tails were observed for the Process 2 batch, while the most abundant L70 segments of the Process 1 batch were demonstrated to contain an additional cytidine residue. Differences in the poly(A) tail pattern were observed when comparing the Process 1 and Process 2 DS batches. The differences in the extent of cytidine monophosphate incorporation and transcriptional slippage needs to be further investigated and the possible impact on efficacy and safety should be discussed. The only Process 2 DS included in the comparison was manufactured prior to the adjustment of CTP and ATP volumes. Results obtained on the PPQ batches manufactured after adjustment (PPQ 3, 4 and 5) also needs to be presented.

The overall primary sequence of BNT162b2 drug 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 DS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 drug substance was determined using Western blot. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, the method is only briefly described, and the relevance of the results is therefore difficult to assess.

Critical Quality Attributes (CQAs)

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 identified CQAs are; RNA integrity, 5'-cap, Poly(A) tail, residual DNA template and double stranded RNA (dsRNA). To be noted, for poly(A) tails, both percentage of Poly(A) positive mRNA molecules as well as the length of the Poly(A) tails are considered CQAs. A related concern is raised in S.4.

Process Development and Characterization

Data for this section is pending.

Process characterisation studies based on Cause and Effect Matrices (C&E) assessment, Failure Modes and Effects Analysis (FMEA), design of experiments (DOE), using scale-down models of individual unit operations, were/will be performed. To be noted, the overall control strategy including the approaches taken to identify critical process parameters (CPPs) are presented but some parameter and ranges may be updated after PPQ and additional characterization studies are completed. As for assessment of overall control strategy, a complete set of data and information is needed and therefore the final evaluation of the control strategy cannot be made at this point.

It should also be noted that future changes to any of the process parameters listed in S.2.2, regardless of the classification of CPP or non-CPP, should be applied for as variation applications.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following the Pfizer GMP campaigns and additional smalls scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. The approach to only change the higher end of the ranges need to be further justified and clarified. It is noted that after the adjustment of these volumes the percentage of RNA integrity was increased to levels more consistent with the Process 1 batches.

In the In vitro transcription (IVT) step T7 RNA polymerase and pyrophosphatase are added to start the reaction. The ribonucleotide building blocks are assembled by the T7 polymerase. T7 polymerase is magnesium dependent, but the magnesium can be chelated by pyrophosphate released by the addition of each ribonucleotide to the growing chain. Pyrophosphatase is used to maintain sufficient levels of free magnesium by breaking down the pyrophosphate. It is claimed that the added volumes of these

two enzymes have been identified as non-CPPs as they are most likely to impact yield only. This conclusion is not agreed upon, the added volumes of the enzymes should be classified as CPPs.

Risk Assessment of Process Related Impurities

Data for this section is pending.

A safety risk assessment for potential process-related impurities included in the drug substance process relative to patient safety is provided in this section. The potential impurities include small molecules, enzymes and the NTP/Capping Structure. 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. If the worst-case level of an impurity exceeds the pre-determined safety limits, any available commercial scale data for the specific impurity will be provided in the relevant section and at a minimum will be monitored as part of process validation to demonstrate consistent removal to acceptable levels.

The worst-case levels of NTPs, 5' cap, small molecule process related impurities, RNase inhibitor, DNase I and pyrophosphatase from the BNT162b2 drug substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable. The T7 RNA polymerase and proteinase K levels were further investigated and it was demonstrated that the detected concentrations in the clinical, initial emergency supply and PPQ BNT162b2 DS batches were well below the safety concern threshold. The Applicant states that data will be provided for additional batches once testing is complete. This is found acceptable. However, the Applicant should provide data on the T7 RNA polymerase and proteinase K levels in additional commercial scale DS batches, once testing is complete. In addition, the Applicant should briefly describe the methods applied to determine the concentrations of these two enzymes in the BNT162b2 DS samples.

Characterisation

Elucidation of structure and other characteristics

Analytical characterisation was performed on BNT162b2 drug substance batch 20Y513C101, which was manufactured by DS Process 2 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 the Illumina MiSeq 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, but that there are also other minor species including phosphorylated, truncated and extended species. Analysis of the 3' poly A-tail demonstrated that BNT162b2 DS contains the expected tail, but that there is some heterogeneity due to transcriptional slippage. Un-capped RNA and/or truncated/extended forms are possible at minor to trace levels but a precise quantification of each uncapped or incompletely capped specie was not provided. It is also not specified if and how these species contribute to the potency of the BNT162b2 DS. The higher order structure of BNT162b2 mRNA DS was characterized in solution using circular dichroism (CD) spectroscopy. Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes.

A severe deficiency of the characterisation section is that no biological characterisation is presented and that the mode of action is not described. This is not found acceptable and the dossier should be

updated with relevant information. Even though full biological characterisation is not possible to perform on DS, the strategy to determine potency and relevant functional assay(s) should be described in section 3.2.S.3. Results obtained on DP could be included, to demonstrate functionality. Furthermore, it is observed that in the Development History and Comparability section (3.2.S.2.6), the expressed protein size is evaluated by in vitro expression followed by Western blot. Results obtained by this method could be regarded as biological characterisation and should be included in section 3.2.S.3. The method needs further description and the results should be sufficiently characterized.

Impurities

Process-related and product-related impurities as well as potential contaminants are described in this section. Five batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches. It is noted that this section is incomplete and will be updated after PPQ completion.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the five DS batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are more product-related impurities, i.e. truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the DS specification in terms of RNA integrity. However, the characterisation of BNT162b2 DS is currently not found acceptable in relation to the CQA RNA integrity. Significant differences between batches manufactured by Process 1 and 2 are observed for this specific attribute. Even though two methods, namely agarose gel electrophoresis and capillary gel electrophoresis, have been applied to determine RNA integrity of BNT162b2 DS, no characterisation data on RNA integrity and truncated forms is presented and the potential safety risks associated with truncated RNA isoforms are not addressed. This is especially important considering that the current DS and DP acceptance criteria allows for up to 50% fragmented species. Therefore, the dossier should be updated with additional characterisation data and discussion on mRNA integrity, **this is considered a major objection.**

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 controlled by qPCR as defined in the DS specification, and the levels for all five batches are demonstrated to be well below the acceptance criteria. However, a drift towards higher level was observed for the third PPQ batch and therefore additional batch data are needed to conclude on the consistent removal of this impurity. Additional process-related impurities, including nucleoside triphosphates (NTPs) and capping structure, small molecules, and enzymes, are evaluated and assessed in Section 3.2.S.2.6 Risk Assessment of Potential Process Related Impurities. Taking section 3.2.S.2.6 into account, the process-related impurities are sufficiently described. Some uncertainty remains regarding the approach to determine the levels of T7 RNA polymerase and proteinase K.

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 drug substance.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

Table S. 4-1. Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Composition and Strength		
Clarity	Appearance (Clarity) ^a	≤ 6 NTU
Coloration	Appearance (Coloration) ^a	Not more intensely coloured than level 7 of the brown (B) colour standard
pH	Potentiometry ^a	7.0 ± 0.5
Content (RNA Concentration)	UV Spectroscopy	2.25 ± 0.25 mg/mL
Identity		
Identity of Encoded RNA Sequence	RT-PCR ^b	Identity confirmed
Purity		
RNA Integrity	Capillary Gel Electrophoresis	≥ 50% intact RNA
5'- Cap	RP-HPLC	≥ 50%
Poly(A) Tail	ddPCR	≥ 70%
Process Related Impurities		
Residual DNA Template	qPCR ^b	≤ 330 ng DNA/mg RNA
Product Related Impurities		
dsRNA	Immunoblot ^b	≤ 1000 pg dsRNA/μg RNA
Safety		
Bacterial Endotoxin	Endotoxin (LAL) ^a	≤ 12.5 EU/mL
Bioburden	Bioburden ^a	≤ 1 CFU/ 10 mL

a. Compendial

b. Assay not performed on stability.

Abbreviations: NTU = Nephelometric Turbidity Units; B = brown; RT-PCR = reverse transcription polymerase chain reaction; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA;

LAL = Limulus amoebocyte lysate; EU = endotoxin unit; CFU = colony forming unit

The proposed specification for drug substance is at large found acceptable with respect to the analyses chosen for routine release testing. The CQAs RNA integrity, 5'-cap, Poly(A) tail, residual DNA template and double stranded RNA (dsRNA) are all included in the release specification. However, the length of the poly(A) tails in BNT162b2 DS is important for RNA stability and translational efficiency and therefore should be included in DS release testing. It is also noted that no method references are included, this needs to be updated.

Potency testing is not included in the control of DS but instead is performed at the level of DP release. Considering the nature of this product, the approach is endorsed.

Analytical procedures and reference standards

Analytical procedures

All analytical methods used for testing of the drug substance are described in the dossier.

The following tests are performed in accordance with Ph Eur; 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).

A general comment which applies to all non-compendial analytical methods is that rather brief details are given. Some of the analytical methods are not presented in sufficient detail and often method descriptions are based on "examples" of procedures, controls and standards as well as on "typical" system operating parameters. This hampers a full understanding the operation or, sometimes, the scientific basis of the assay. Furthermore, since several of these assays are none standard and complex, this interferes with assessment of suitability. The lack of sufficient information on critical reagents, standards or equipment hinders regulatory control of critical aspects of the assays. Several concerns are raised for specific assays requesting additional information on critical procedures, reagents, standards and equipment.

It is claimed that the analytical methods were validated against the parameters presented in ICH Q2(R1). However, the validation summaries presented are far too brief to be able to conclude on suitability of the in-house analytical methods. The quality of BNT162b drug substance cannot be properly assessed, if the reliability of the analytical methods cannot be guaranteed.

Capillary gel electrophoresis (CGE) is used to determine the percent integrity of RNA in both drug substance (DS) and drug product (DP). The test sample is subjected to a denaturant containing formamide that unfolds the RNA and dissociates non-covalent complexes. When subjected to an electric field, the denatured RNA species migrate through the gel matrix, as a function of length and size, toward the anode. An intercalating dye binds to RNA and associated fragments during migration allowing for fluorescence detection. The intact RNA is separated from any fragmented species allowing for the quantitation of RNA integrity by determining the relative percent time corrected area for the intact (main) peak.

Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) is used to measure the relative amount of 5'- capped RNA species. Test samples are digested using RNase H followed by affinity purification and (RP-HPLC) with UV detection. After an annealing process to a biotinylated probe complementary to the last 26 bases of the 5' end of the RNA, samples are digested with RNase H, followed by streptavidin-matrix based affinity purification of the resultant duplexes from the much larger mRNA remnants. The short oligonucleotide capped, and uncapped species are eluted from the streptavidin-matrix, and relative quantification of the 5'-cap is accomplished by RP-HPLC analysis of the ensemble of RNA capped and un-capped molecules. The relative amount of capped species is determined by dividing the capped species signal by the total species signal.

The in-house analytical methods for CGE and RP-HPLC are at large well described and includes details on typical test conditions, operating parameters, representative electropherograms and chromatograms as well as information on system suitability testing.

An RT-PCR method is used to determine the identity of the encoded RNA sequence, a quantitative polymerase chain reaction (qPCR) analytical procedure is used to quantify the residual DNA template and an immunoblot analytical procedure is used to detect double stranded RNA (dsRNA) in BNT162b2 drug substance. All these assays are deemed suitable for their intended purpose and, in general, although brief, the descriptions provided are considered relevant. Several concerns regarding

additional details on method description, controls and in some cases further clarifications of criteria established to support method suitability are raised.

The ddPCR technology is proposed for the quantification of the poly(A) tail in the messenger ribonucleic acid (mRNA). The technical procedure is considered, in general, sufficiently described but the suitability of this method for the intended purpose needs additional clarifications. The rationale by which the method determines the percent poly(A) relative to the theoretical input (which is not clearly described) should be further addressed.

Release and stability testing can be performed at several testing sites. However, the method transfer plan or activities was not submitted in the RR. It should be noted that, if method transfer was / will be performed, the following information are requested. For the non-compendial tests, it should be confirmed that the validation acceptance criteria for the receiving sites will be the same as for the transferring site (which will be assessed during the RR). For the analytical methods where comparative analysis will be proposed, it should be confirmed that the acceptance criteria will be the same as for the intermediate precision validated at the transferring site (and assessed during RR).

Reference standard

The current reference standard is referred to as the Clinical Reference Material (CRM). It is stated that the CRM will be used for clinical supplies, process validation and initial commercial supplies. The CRM is prepared from the GMP BNT162b2 DS batch 20Y513C201. Release data is presented in the dossier. The intended storage condition is -20 ± 5 °C, but an alternative storage condition of -60 to -90 °C is also evaluated. A stability protocol is provided. There are several concerns regarding the reference standard, including the suitability of the batch chosen as CRM, if additional standards have been used during early development and issues related to the formal stability protocol. It should also be clarified for what release and stability testing methods the reference standard is used and will be used in future.

In future, a two-tiered system for future commercial reference material will be implemented. A PRM and an initial WRM will be established in 2021 for the drug substance reference material. The PRM will be the standard against which WRMs are qualified and the PRM will be intended to last the lifetime of the commercial product. The Applicant claims that further information on the selection, preparation, qualification and stability of the PRM and WRM will be provided in the future.

The use of a two-tiered system is encouraged. It is understood that the PRM and WRM is not yet established. The Applicant is reminded that the implementation of the two-tiered system should be applied for in a Type II variation application. Alternatively, information on the preparation, qualification and stability evaluation of the PRM and WRMs should be included in a PACMP.

Batch analysis

Batch results are presented for DS batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply, and stability.

In general, the results obtained using the commercial process (DS Process 2) demonstrate batch to batch consistency with a few exceptions. The results for RNA integrity are higher for batch PPQ3 (20Y513C501) as a volume adjustment was made for ATP and CTP volumes before manufacturing of this batch. Batch results should be presented for the two newly manufactured batches PPQ4 and PPQ5 to verify that the commercial manufacturing process consistently results in RNA integrity levels similar to levels achieved in process 1 batches.

Justification of specification

The rationale used to establish the acceptance criteria is described in detail and based a limited data set representative of BNT162b2 DS manufactured at the intended commercial scale and process. It is endorsed that the specification for BNT162b2 DS will be reassessed when more batches have been manufactured. However, from the available data, it appears that RNA integrity, dsRNA, Poly(A) tail and 5'-cap acceptance criteria are too wide and need to be tightened yet to better reflect data obtained from available lots used in clinical studies (and considered clinically qualified) and data from lots used for PPQ.

Container closure

The drug substance is stored in 12 L or 16.6 L single-use, flexible, disposable bags of ethylene vinyl acetate (EVA). Compliance with Ph. Eur. 3.1.7 *Ethylene-Vinyl Acetate Copolymer for Containers and Tubing for Parenteral Nutrition Preparations* is claimed. Schematic drawings of the bags are provided in the dossier but no specification or certificate of analysis for the container or the EVAM contact layer are included.

The information regarding container closure system is in general acceptable. However, the Applicant should verify compliance with Ph. Eur. 3.1.7 with a certificate of analysis for one representative batch of the EVAM contact layer.

A controlled extraction study has been performed on the EVA container film; all the compounds were observed below the Safety Concern Threshold of 1.5 µg/day TDI. Considering that the intended storage of the DS is -20 °C, a temperature which has a lower risk of leachables, it is reasonable that no specific leachable compounds have been selected for further studies. Nevertheless, a leachable study will be initiated to detect semi quantitate unexpected leachable compounds equal to or greater than 1.5 µg/day TDI. This approach can be accepted.

Stability

The initial proposed commercial shelf life of the drug substance is 6 months when stored at the intended storage condition of -20 ± 5°C in EVA bags. The initial shelf life is based on the currently available data from stability studies utilizing material from three clinical DS batches manufactured using Process 1 and two clinical DS batches (up to 3 months data presented) and three process validation batches manufactured by Process 2 (up to 1 month data presented).

It is claimed that the results of the comparability studies support that stability data generated using drug substance manufactured using Process 1 can be considered predictive of the drug substance manufactured by Process 2. This conclusion is not fully agreed with as detailed above in section S.2.6.

Based on the currently very limited stability data presented for process 2 batches (only 1-month data available for one batch) no conclusion can be drawn in relation to the proposed shelf life for the DS. Therefore, in order to support shelf life setting for drug substance updated reports from the ongoing stability studies on the primary batches (including data from the ongoing process validation batches) should be provided.

It is stated that sponsor will extend the assigned shelf life without notification providing the real time stability data at the intended storage condition is acceptable and within commercial specifications. This kind of extensions can be accepted for clinical trials but not after marketing authorisation approval. This statement should be removed from the dossier.

2.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The BNT162b2 drug product is supplied as a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The drug product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the drug product at pH 7.4 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution for a total volume of 2.25 mL, with each dose containing 30 µg of RNA in 0.3 mL. There is no manufacturing overage. The justification for the overfill is discussed, but the final volume exceeding the nominal volume is questioned.

The drug 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 composition of the drug product, including amounts per vial and function and quality standard applicable to each component, are given in Table P.1-1.

All ingredients, including process aids used in the manufacture, should be specified in the composition together with a footnote that they are processing aid removed during manufacturing. Therefore, ethanol and citrate buffer and the excipients present in the DS (HEPES and EDTA) should be added to the composition.

Table P.1-1. Composition of BNT162b2 drug product, multi-dose vial (225 µg/vial).

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.5	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	7.17	3.23 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.89	0.4 mg	0.05 mg
DSPC	In-house specification	Structural lipid	1.56	0.7 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	3.1 ^a	1.4 mg	0.2 mg
Sucrose	Ph. Eur.	Cryoprotectant	103 ^a	46 mg	6 mg
Sodium chloride	Ph. Eur.	Buffer component	6	2.7 mg	0.36 mg
Potassium chloride	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate ^b	Ph. Eur.	Buffer component	1.08	0.49 mg	0.07 mg
Monobasic potassium phosphate ^c	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Water for Injection	Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.

a. Values are rounded to maintain the same level of precision as the label claim, with trailing zeros not shown, where applicable. For example, 46 mg sucrose is rounded from 46.35 mg (103 mg/mL).

b. Dibasic sodium phosphate, dihydrate is named as disodium phosphate dihydrate in the Ph. Eur.

c. Monobasic potassium phosphate is named as potassium dihydrogen phosphate in the Ph. Eur.

Abbreviations:

ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide

DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine

q.s. = quantum satis (as much as may suffice)

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply to Ph. Eur. grade. 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 drug products. DSPC is used in several products approved in the EU (Marqibo, Doxil, Ambisome, Onpattro), though not by the same route of administration. Further justification that DSPC is not a novel excipient is requested.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Pharmaceutical development

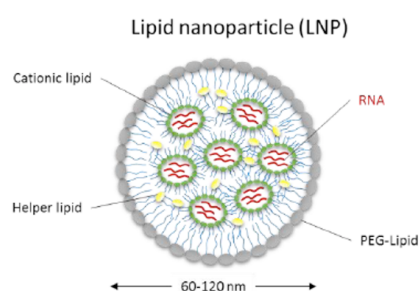
Formulation development

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 development of a robust LNP formulation platform was performed at Acuitas Therapeutics. Studies are comprehensively described and were performed with available drug substance, representative of the mRNA platform and included in the drug product.

The LNPs consists of four lipids, each has a functional or structural purpose. The ionizable cationic lipid ALC-0315 interact electrostatically with negatively charged nucleic acids and encapsulate the mRNA. The PEGylated lipid ALC-0159 is preferably inserted at the LNP surface as a steric barrier to interactions with surfaces or other LNPs to avoid aggregation during storage. The phospholipid DSPC and cholesterol are structural lipids providing a stable bilayer and enabling mobility of the lipid components in the LNP structure.

The formed RNA-containing LNPs are solid particles relatively homogeneous in size, largely spherical in shape and has a nearly neutral surface. Furthermore, the accumulated batch-data to date show a consistent manufacturing of lipid nanoparticles both with respect to size and polydispersity.



Critical quality attributes related to LNP formation and payload delivery are primarily LNP size, encapsulation efficiency, and in vivo potency (RNA integrity). Additionally, surface area is considered critical to avoid aggregation both during storage and with serum components in vivo. The ratio cationic lipid to RNA (N/P) is also critical for formation of LNP. An excess of cationic lipid is required and a ratio of about 6 is found reasonable.

The DP is stored frozen at the recommended storage temperature of -90 to -60°C. Stability studies are ongoing for the determination of DP shelf-life.

The same DP formulation composition has been used throughout the nonclinical and clinical studies and will also be used for the manufacturing of the pending full scale commercial PPQ-batches.

There are no formula overages in the drug product, only an overfill which has been acceptably justified ensuring that five doses can be removed from the multi-dose vial and delivered.

Screening studies were performed to confirm that the ALC-0315/ALC-0159/DSPC/CHOL at molar ratio 47.5/10/40.7/1.8 with a ratio of cationic lipid to RNA (N/P ratio) of 6.3 provide LNP with acceptable quality and stability. Physicochemical and biological properties were studied (density, viscosity, DSC characteristics). Moreover, size distribution and particle shape were studied showing a narrow distribution with a hydrodynamic radius and an almost spherical shape in the entire size distribution. The zeta potential was narrow and monomodal. The pegylated surface of the LNPs was studied showing consistence with the proposed LNP architecture: presence at the surface of PEG and hydrophilic head of ALC-0315. While the effort made by the applicant to provide sufficient development data in a very brief time is acknowledged, and taking into account that some additional heightened characterization information will be added, the formulation development lacks some characterisation studies showing the homogeneity of the suspension during storage at long-term or accelerated conditions, after freeze/thaw, or after dilution with 0.9% NaCl.

Manufacturing process development

The development history of the drug product is sufficiently described.

The initial LNP and drug product formulation processes were developed at Acuitas Therapeutics, followed by scale-up and manufacture at Polymun Scientific for clinical trial material and emergency supply. The process has been transferred to Pfizer commercial facilities in Kalamazoo, MI, USA, and Puurs, Belgium, for manufacture of later clinical materials (Puurs), emergency supply and commercial supply.

The DP analytical comparability evaluation employed release testing and extended characterization methods. It is agreed that comparability has been reasonable demonstrated between the clinical supply lots manufactured with the "classical" LNP process and the representative emergency supply lot manufactured with the "upscale" LNP process with only small differences noted.

It is stated in the dossier that the applicant has a plan for a comprehensive demonstration of comparability among clinical supplies and the commercial product including an assessment of the starting drug substance batches, raw materials (e.g. ALC-0315, DSPC and cholesterol) from different vendors, process designs and comprehensive characterization of the resulting product quality. Data for this section is pending and will be updated once the data has been generated, analyzed, and verified. Four commercial PPQ-batches will be manufactured in November and December 2020. The results for the comparability of the commercial PPQ-batches versus the clinical supply batches of DP is pending and will be provided for assessment during the procedure.

In summary, no final conclusion on comparability can be drawn until all comparability data among clinical supplies and the commercial product (PPQ-batches) will be provided for assessment.

Critical Quality Attributes include appearance, visible particulates, subvisible particles, pH, osmolality, extractable volume, lipid identities and contents, RNA identity and content, LPN size and polydispersity, RNA encapsulation, RNA integrity, 5'-cap, poly(A) tail, in vitro expression, endotoxins, sterility, container closure integrity. Even though the risk assessment was not explained in detail, no issue is raised on that point since the DP specification contains the expected parameters.

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies based on Cause and Effect Matrices (C&E) assessment, Failure Modes and Effects Analysis (FMEA), design of experiments (DOE), using scale-

down models of individual unit operations, were / will be performed. It is noted that some results of process characterisation studies are pending. The overall documentation related to criticality assignment and NOR/PAR establishment will be assessed when completed. In addition, it is highlighted that for the process characterisation studies already presented, the level of information was not sufficient to allow assessment. Therefore, the PARs are not considered acceptable at this stage.

The lipid nanoparticle (LNP) formation is one critical manufacturing step. The process development is described and physicochemical properties (e.g. LNP size, polydispersity, RNA encapsulation, lipid to RNA ratio (N/P) as well as LNP topology by X-ray scattering) has been evaluated during upscale. The provided results are comparable. The tested parameters are considered relevant, covering the critical attributes size, shape, encapsulation and lipid to RNA molar ration.

The in-process hold times, dilution and mixing of DS parameters, and lipid weight and organic phase mixing parameters will be studied during PPQ. For buffer exchange and concentration step, residual ethanol and citrate should be studied during PPQ and process validation. Process characterisation studies were satisfactorily provided for DS thawing, sterile filtration, aseptic filling, stoppering, sealing and capping, and freezing steps. However, PPQ data will be needed to verify the filling weight of BNT162b2 filled at the commercial filling lines. Moreover, no development data showing homogeneity of LNP or RNA concentration in the vials during filling process was provided. Drug product robustness to freezing and warming during storage was studied and confirmed that BNT162b1 quality was not impacted by different thawing processes, but this will have to be confirmed for BNT162b2 DP.

Overall control strategy was presented but some parameter 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.

The analytical testing strategy of drug 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. Leachables studies are planned to be set up the applicant should commit to provide the updated results from the leachables study for assessment.

Microbiological attributes:

Sterility and endotoxin testing is performed at Drug Product (DP) release. A rapid sterility test may be utilized. CCI will be verified by dye ingress testing or head-space analysis. These tests were demonstrated to be able to detect CCI failure.

Compatibility

The drug product is frozen, and after thawing, the solution/suspension must be diluted with sterile 0.9% sodium chloride solution. The studies described have been performed to assess physicochemical stability of the DP 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 DP are ongoing as part of the stability program in section P.8.

Results presented support physicochemical stability of DP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures and compatibility with dosing components (syringes and needles) for up to 6 hours. Furthermore, a microbiological in-use hold time study was performed by a challenge test including five compendial micro-organisms. No significant growth ($>0.5\log_{10}$ from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted DP in 0.9% sodium chloride solution. However, while the representativity of 0.05 mg/mL concentration against the 0.1 mg/mL concentration is accepted, there was no confirmation that the analytical methods are valid at this dilution, and the in-use specifications should be the same as the shelf-life specifications. It is noted, however, that this section may be updated as additional studies are completed.

Compatibility of drug product is at large acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

Table P.3-1 lists the sites that have responsibilities in the production of BNT162b2 drug product and their specified functions.

Table P.3-1. Sites and responsibilities for BNT162b2 drug product manufacture

Site	Responsibility
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium	LNP fabrication and bulk drug product formulation Fill and finish Primary packaging Secondary packaging Release and stability testing (Composition, Adventitious Agents) Batch release by Qualified Person in EEA [European Economic Area]
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC ^a 1 Burtt Road Andover, MA 01810 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Adventitious Agents)
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	Release and stability testing (Composition and Strength, Identity, Potency, Purity, Adventitious Agents)
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	Release and stability testing (Identity, Composition)
Hospira Zagreb Ltd. ^b Prudnička cesta 60 10291 Prigorje Brdovečko Croatia	Release testing (Sterility)
SGS Lab Simon SA Vieux Chemin du Poète 10 Wavre, 1301 Belgium	Release testing (Sterility)
BioNTech Manufacturing GmbH Kupferbergterrasse 17-19 55116 Mainz Germany	Batch release by Qualified Person in EEA [European Economic Area]

a. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD.

b. Hospira is a wholly owned subsidiary of Pfizer Inc.

The DP is manufactured tested and batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium. Batch release can also be done at BioNTech Manufacturing GmbH, Mainz, Germany. Several testing sites are listed, in addition to Pfizer, Puurs, Belgium. Some clarifications are requested for GMP activities of sites located in Europe (**MO**). Moreover, as Mutual Recognition Agreement is not in force for human vaccines, the provided documentation for sites located in the USA is not considered sufficient (**MO**).

The manufacturing process includes lipid nanoparticle (LNP) fabrication and bulk drug product formulation followed by fill and finish. The target drug product batch size is 139 L (approximately 309,000 vials). The batch formula is provided but lacks process aids.

LNP fabrication and bulk drug product formulation

The frozen drug substance (mRNA) is thawed and diluted in water for injection to a target concentration of 2.0 mg/mL. The lipids are diluted in ethanol. To form the LNPs the aqueous phase with mRNA and the organic phase with the lipids are fed into one or more parallel T-mixers with pre-

set flow rates to get 3:1 volume ratio. The LNP bulk is then first buffer exchanged with citrate buffer to remove ethanol from the suspension then with phosphate-buffered saline (PBS) at pH 7.4, suitable for intramuscular administration. Sucrose is added as cryoprotectant, the concentration is adjusted, and the solution mixed until homogenous. Hold times during the bulk drug product formulation process are established.

Sterile filtration and aseptic filling

The bulk drug product is sterile filtered into a holding vessel using two sequential redundant sterilizing grade filters. Integrity of these filters are controlled by pre- and post-use integrity testing. A sample is taken for bioburden prior to filtration. The holding vessel is aseptically connected to the filling line and then sterile filtered bulk drug product is aseptically filled into sterile vials and capped. Vials are 100% inspected for defects either through automated visual inspection or manual visual inspection. Inspected vials are individually labelled and packed. All hold times following sterile filtration will be within the validated media fill times, ensuring acceptable microbial control during the drug product manufacturing process.

Controls of critical steps and intermediates

Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Residual ethanol is not controlled in-process or in the final drug product specification. Data provided demonstrates that ethanol is sufficiently removed in the final drug product. Absence of test is therefore considered acceptable.

The lipid nanoparticle (LNP) formation is one critical manufacturing step and some additional information is requested regarding this step such as that a drawing of the T-mixer should be provided as well as the number T-mixers defined.

Process validation and/or evaluation

No full commercial scale batches are included in section 3.2.P.3.5 and the applicant states that "Data for this section is pending and will be updated once the data has been generated, analysed, and verified."

However, it is stated in the dossier that four commercial PPQ-batches will be manufactured in November and December 2020. These batches will be executed according to defined protocols and evaluated with predetermined acceptance criteria. Furthermore, these batches will be used both to demonstrate the comparability of the commercial PPQ-batches versus the clinical supply batches as well as for process validation of the manufacturing process of the drug product. In addition, validation data on process hold-times, shipping validation and verification of in-process test methods are incomplete. **Since all these validation data are pending, no final conclusion on process validation in section 3.2.P.3.5 can be drawn until these data are provided for assessment.**

Media fills have been performed 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 drug product (maximum filling time is 112 hours) and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process.

Acceptable information has been provided for filter validation on the 0.2 µm-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 0.2 µm-filters are appropriate for sterile filtration of the drug product. However, the applicant should clarify if the 0.2 µm-filter used for bioburden reduction is identical with the 0.2 µm-filters used for sterile filtration.

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved drug product within EU. Additional information is provided separately in Section A.3.

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. However, appropriate documentation for processing aids (ethanol and citrate buffer) and for drug substance buffer (HEPES and EDTA) should be provided.

Product specification, analytical procedures, batch analysis

The release and stability testing specifications for BNT162b2 drug product are provided in Table P.5-1.

Table P.5-1. BNT162b2 drug product specifications.

Quality Attribute	Analytical Procedure ^a	Acceptance Criteria
Composition and Strength		
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) ^b	Essentially free from visible particulates
Subvisible Particles	Subvisible Particulate Matter ^{b, c}	Particles $\geq 10 \mu\text{m}$: ≤ 6000 per container ^{b, c} Particles $\geq 25 \mu\text{m}$: ≤ 600 per container ^{b, c}
pH	Potentiometry ^b	6.9 – 7.9
Osmolality	Osmometry ^{b, d, e}	425 - 625 mOsmol/kg
LNP Size	Dynamic Light Scattering (DLS)	40 to 180 nm
LNP Polydispersity	Dynamic Light Scattering (DLS)	≤ 0.3
RNA Encapsulation	Fluorescence assay	$\geq 80\%$
RNA content	Fluorescence assay	$0.50 \pm 0.13 \text{ mg/mL}$
ALC-0315 content	HPLC-CAD	4.50 to 9.25 mg/mL
ALC-0159 content	HPLC-CAD	0.55 to 1.20 mg/mL
DSPC content	HPLC-CAD	0.90 to 2.05 mg/mL
Cholesterol content	HPLC-CAD	1.80 to 3.90 mg/mL
Container content for injections	Volume of injections in containers ^{e, f}	Not less than the sum of the nominal volumes of 5 doses
Identity		
Lipid identities	HPLC-CAD ^g	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR ^g	Identity confirmed
Potency		
In Vitro Expression	Cell-based flow cytometry	$\geq 30\%$ Cells Positive
Purity		
RNA Integrity	Capillary Gel Electrophoresis	$\geq 50\%$ intact RNA
Adventitious Agents		
Bacterial Endotoxin	Endotoxin (LAL) ^b	$\leq 12.5 \text{ EU/mL}$
Sterility	Sterility ^b	No Growth Detected
Container Closure Integrity	Dye incursion ^g	Pass

a. All assays performed on stability unless otherwise noted.

b. Compendial

c. USP<787> (obscuration method), and aligned with upcoming (Jan 2021) revision of Ph. Eur. 2.9.19

d. USP<785>; also in accordance with Ph Eur. 2.2.35, with minor difference in instrument calibration

e. Assay not performed on stability.

f. Procedure is aligned with Test for Extractable Volume of Parenteral Preparations.

g. Tested at release and on stability for stability batches only

Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; FACS = fluorescence activated cell sorter; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amoebocyte lysate; EU = endotoxin unit

Specification and justification of specifications

The specifications document for drug product in section 3.2.P.5.1 includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmometry, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at DP release, all other analytical procedures are conducted at release and stability studies for drug 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, but this remains to be confirmed.

Test method numbers are missing and should be given to all analytical procedures used in the specifications for release and end-of-shelf-life and should consequently be inserted in the drug product specifications document and to the descriptions and validations of analytical procedures.

LNP size for drug product is measured by dynamic light scattering (DLS) and the efficacy of the drug product depends on the size of the LNP. The proposed acceptance criteria of 40 to 180 nm seem wide

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compared to clinical batch data that is found in the range of 59-74 nm for the small scale clinical batches ("classical LNP process) and 68-71 nm for the emergency supply ("upscale" LNP process). The acceptance criteria should therefore be tightened to be in line with what has been qualified in the clinical studies or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product.

Potency: In-vitro expression is a cell-based flow cytometry assay. The assay was implemented recently and the proposed acceptance criteria of $\geq 30\%$ cells positive seem wide compared to the limited batch release data available to date, i.e. emergency supply lots that is in the range of 63-65%. In addition, some data are presented for the small-scale clinical batches used in comparability testing, where data are found in the range of 50-71% (Table 3.2.P.2.3-5 in the dossier). The proposed acceptance criteria need to be thoroughly justified and tightened in line with the levels qualified in clinical studies or clinically qualified by other means. This justification should include the applicant's total current knowledge of the drug product.

RNA encapsulation of drug product is measured by a fluorescence assay where free and total RNA are determined and the difference between the total and free RNA corresponds to RNA encapsulation. Encapsulation is used to ensure delivery of the RNA and improve the chances of transfection. The proposed acceptance criteria of $\geq 80\%$ seem wide compared to clinical batch data that is found in the range of 92-94%. The proposed acceptance criteria for RNA encapsulation should therefore be tightened based on clinical qualification or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product.

The proposed acceptance criteria of $\geq 50\%$ intact RNA for RNA integrity as measured by capillary gel electrophoresis seem wide compared to clinical batch data that is found in the range of 69-81%. The proposed acceptance criteria for RNA integrity should therefore be tightened based on clinical qualification or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product. Additionally, it should also be clarified if the emergency lots EE8492 and EE8493, both with results for RNA integrity of 55%, have actually been used in the clinical trials or not. In this context, it is also unclear whether there is a decrease in RNA integrity during the manufacturing of DP or not and a consequential need for a more stringent DS specification. The applicant should therefore discuss, and present comparative results for DS and DP, on RNA integrity. Sections S.4.1 and P.5.1 in the dossier should be aligned and updated accordingly. **(MO)**

The proposed acceptance criteria for LNP polydispersity as measured by DLS are wide and should be tightened in line with batch results for clinical batches, i.e. NMT 0.2 (0.22 observed on stability).

The proposed acceptance criteria for appearance, subvisible particles, pH, osmolality, volume of injection in containers, identity of encoded RNA sequence, RNA content, bacterial endotoxin, sterility and container closure integrity are all found acceptable.

Lipid content: Both safety and efficacy are dependent on the total amount of lipid relative to the RNA DS. A consistent molar ratio of lipid/RNA is expected in the DP vial, driven by the encapsulation process. Absolute lipid content may vary but composition (relative molar %) of the four lipids remains consistent. The acceptance criteria ranges have been calculated from worst-case low and high RNA content. No batches manufactured to date have exhibited results at or below the low RNA content estimate while the high RNA content level has been justified by development batches manufactured at worst-case high RNA contents. Although the absolute range of each lipid appears somewhat broad, the acceptance criteria are found acceptable. However, to further strengthen the control strategy given that a fixed molar ratio of cationic lipid and RNA is critical for LNP formation, acceptance criteria for the molar ratio N/P should be included in the specification unless further justified.

A separate test for in vitro release is not included in the specification. This is considered acceptable since test for potency is included by a cell-based method.

Analytical procedures

Some of the analytical procedures are common to both DS and DP. Several analytical procedures are specific to DP and are detailed and validation results are presented.

The compendial methods have been verified for use in accordance to the appropriate Ph. Eur. chapters.

It is claimed that all non-compendial methods were validated against the parameters given in ICH Q2. However, the validation summaries presented are far too brief to be able to conclude on the suitability of the analytical method. More comprehensive validation summaries of all non-compendial methods, for example in the form of short validation reports should be provided. The validation summaries should include all relevant calculations, acceptance criteria, description of and results obtained for individual samples. Chromatograms and dose response curves should be included, where applicable. The dossier should be updated accordingly.

Furthermore, in all of the in-house analytical methods used in the release of DP, method descriptions are based on "examples" of procedures, controls and standards as well as on "typical" system operating parameters. These terms raise uncertainties regarding the developmental stage, and the control of critical steps of these assays. The analytical methods used in the control of DP are expected to be finalized. The applicant is requested to confirm this and to update the relevant parts of the dossier with unequivocal method descriptions and additional details, if needed. The applicant should also confirm that any significant changes in analytical procedures will be applied for in a variation application.

In addition, it is stated in the dossier that a complete description of the rapid sterility test is pending. Therefore, method description and validation summary of the rapid sterility test should be provided during the procedure.

Potency: Cell based flow cytometry is used to confirm the in vitro expression of SARS-CoV-2 spike protein encoded by the RNA in BNT162b2 drug product (DP). Although the principle and method procedure are, at largely described, additional details are requested on critical reagents (such as antibodies), drug product control samples, equipment, assay suitability, gating strategy as well as further justification of the use of HEK293 cells in the assay.

Batch analysis

Batch analysis data have been provided including DP batches used in toxicology studies, clinical trials, emergency supply and stability. All these batches have been manufactured with the "classical" LNP process (nonclinical, clinical supply lots) or the "upscale" LNP process (emergency supply) and comparability has been reasonably demonstrated between the clinical supply lots and the emergency supply lot with only small differences noted. All DP batches manufactured and presented met the acceptance criteria in the DP specification. However, no DP batches at the intended full commercial scale have been manufactured to date.

Characterisation of impurities

The impurity profile of the DP is based on the impurity profile of the materials that are used for the manufacturing as well as the lipid impurities.

There are four process-related impurities identified for the DP; ethanol, citrate, HEPES and EDTA. Removal of ethanol will be demonstrated during process validation against the ICH Q3C limit (5000

ppm, class 3 solvents). EDTA, citrate and HEPES have been shown through safety risk assessment and theoretical worst-case calculations to be significantly below established safety limits. This is found acceptable.

The lipids are controlled via the acceptance criteria in their specifications. However, no information is provided on the lipid-related impurities originating from the degradation of the lipid nanoparticles and such data needs to be provided.

The applicant plans to update the dossier with further evaluations of lipid-related impurities and states that for section 3.2.P.5.5 "Data for this section is pending and will be updated once the data has been generated, analysed, and verified". Until these data are available for assessment, no final conclusions can be drawn on section 3.2.P.5.5.

A summary of risk assessment on elemental impurities in line with the ICH Q3D is missing. A summary of this risk assessment based on the general principles outlined in Section 5.1 of ICH Q3D should be submitted.

In summary, no final conclusion on the section 3.2.P.5.5 can be drawn until all data on the characterization of impurities will be provided for assessment.

Reference standard

The current reference standard for the BNT162b2 drug product is the clinical batch EE8493, stability data is being acquired. The applicant intends to establish a primary (PRS) and a working reference standard (WRS). A question is raised on the preparation, qualification and stability of PRS and WRS.

Stability of the product

The proposed initial shelf-life for drug product is 6 months when stored at the recommended storage condition of -90 to -60°C.

The applicant has provided stability results up to 4 months at -80 to -60°C of one clinical batch and up to 3 months of a non-clinical batch of drug product. Additionally, up to 3 months results at -80 to -60°C are also provided for supportive stability studies for two clinical lots of drug product.

The applicant has also initiated stability studies on two emergency supply lots (only release data exists to date) and has plans to initiate stability studies on the future PPQ-batches.

In addition, stability data has 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.

Data is presented in P.2.5 for the container closure include extractables and leachables, container integrity, and for functional tests for the bromobutyl stopper (penetrability, fragmentation, and self-sealing). A question is raised regarding the self-sealing test for the bromobutyl stopper after freezing and thawing.

All stability results for the clinical and non-clinical batches as well as for the supportive stability studies stored at -80 to -60°C complies with the clinical acceptance criteria in place at the time of testing. Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality.

At accelerated conditions of +5°C-storage and up to 4 months testing of a clinical batch of drug product, LNP polydispersity and RNA integrity were out of specification at the 3 and 4 month-points.

As discussed, and concluded in section 3.2.P.2.3, it is agreed that comparability has been reasonable demonstrated between the clinical supply lots manufactured with the "classical" LNP process and the representative emergency supply lot manufactured with the "upscale" LNP process. However, the applicant has a plan for a comprehensive demonstration of comparability among clinical supplies and the full commercial scale product but data for this section is pending. Four commercial PPQ-batches will be manufactured in November and December 2020. In summary, no final conclusion on comparability can be drawn until all comparability data among clinical supplies and the commercial product (PPQ-batches) of drug product will be provided for assessment. In addition, the claimed shelf-life is not yet acceptable since the batches are not representative of commercial supply (manufacturer, scale, drug substance process), the batches used represent less than 1% of the commercial scale, and only very limited data is available.

Photostability testing as well as temperature cycling studies are planned, and results are pending to date. While normally this data should be provided before the end of the RR procedure, it is acknowledged that the outer container (carton box) will provide protection from light; this information should be clearly stated in the SmPC/PIL.

Furthermore, it should be confirmed that future extensions of the assigned DP shelf life will be applied for in formal variation applications. The following statement should be removed for Module 3.2.P.8.1 of the dossier; "The sponsor will extend the assigned shelf life without notification providing the real time stability data at the intended storage condition is acceptable and within commercial specifications."

Post-approval stability protocol and stability commitment

A minimum of one batch of drug product will be added to the on-going post-approval stability program annually. The annual post-approval stability protocol has been provided and found acceptable although this protocol is part of GMP and therefore not assessed in this report. However, the applicant should confirm that they commit to continue all the ongoing stability studies at long-term conditions until completion.

Concluding remarks on the proposed shelf-life and storage conditions

The proposed initial shelf-life for the drug product is 6 months at the recommended storage temperature of -90 to -60°C. In order to support the suggested shelf-life for drug product, updated reports from the ongoing stability studies should be provided.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

Adventitious agents safety evaluation has been provided for the DS manufacturing site [Andover] and for the DP manufacturing site [Puurs]. Information regarding the DP manufacturing site [BNT & Rentschler] is pending.

Proteinase K used in DS manufacturing and LB broth used in the establishment of the pST4-1525 MCB and WCB are the only materials of animal origin used in the manufacturing 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, deemed minimal.

No information is provided regarding viral safety of these materials. Considering the stringent conditions routinely used in the heparin production, the risk for viral contamination is considered negligible for this material. Additional clarifications are requested for pyrophosphatase, T7 polymerase and RNase inhibitor, spermidine, DNase I and excipients ALC-0315, ALC-0159, DSPC and Cholesterol.

No information is included in A.2 on the control of other non-viral adventitious agents and only sterility testing performed at the level of DP is named. However, sufficient details on the aseptic validation filling and media fills have been provided in P.3 Manufacture. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process, as described in section S.2.4. Therefore, based on the information existing in other parts of the dossier and pending new information regarding the BNT & Rentschler manufacturing site as well as new information requested on the control of materials, the overall risk for contamination is considered minimal at this point and no additional concerns are raised.

GMO

N/A

Novel excipients

Two novel excipients are included in the drug product, the cationic lipid ALC-0315 the PEGylated lipid ALC-0159. No final conclusion can be drawn until all data are provided. Some questions with regards to batch size and validation of analytical methods are raised at this point. Additional information on chemical synthesis, quality control of starting material, specification limits and retest period will be provided for assessment during the procedure.

2.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance

Where data is submitted, the dossier is overall of acceptable quality. However, a substantial amount of information is pending, due to the very short time frame of product development and will be submitted in the subsequent submission(s). Information on the manufacturing process and process controls for the manufacturing site Andover is provided, while the corresponding information for site BNT Mainz & Rentschler is pending.

Based on the significant differences observed between batches manufactured by DS Process 1 and 2 for the CQA mRNA integrity, a MO is raised regarding comparability, characterisation and clinical qualification of the proposed acceptance criteria of $\geq 50\%$ intact RNA. Whilst some testing results of biological activity/functionality has been submitted in support of comparability and potency testing is part of the DP release specifications, biological characterisation of the active substance is limited, and additional data and discussion is requested to address functionality.

The reference standard was poorly characterised, and the final two-tiered system is not yet in place.

The proposed initial shelf-life for the drug substance is 6 months at the recommended storage temperature of -20°C . In order to support the proposed shelf-life for drug product, updated reports from the ongoing stability studies should be provided.

Drug product

The drug product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The drug 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 drug substance, representative of the mRNA platform and included in the drug 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 drug product formulation followed by fill and finish, and the process has at large been acceptably described.

However, no drug product batches at the intended full commercial scale have been manufactured to date. It is described in the dossier that four commercial PPQ-batches will be manufactured in November and December 2020. These batches will be used both to demonstrate the comparability of the commercial PPQ-batches versus the clinical supply batches as well as for process validation of the manufacturing process of the drug product. **Therefore, no final conclusion on drug product comparability, process validation, and shelf life can be drawn until additional data will be provided for assessment.**

The specifications document for drug product includes a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several questions are raised concerning tightening of acceptance criteria for LNP size, polydispersity, potency, RNA integrity and RNA encapsulation to be in line with what has been qualified in the clinical studies or clinically qualified by other means.

The proposed initial shelf-life for the drug product is 6 months at the recommended storage temperature of -90 to -60°C. In order to support the suggested shelf-life for drug product, updated reports from the ongoing stability studies should be provided.

Conclusion

Three major objections are identified that would preclude a marketing authorisation: The first MO relates to the GMP status of the DS and DP manufacturing sites. Comparability between clinical and commercial material has not yet been demonstrated, which is addressed in MO 2. In particular, significant differences between batches manufactured by DS Process 1 and 2 are observed for the CQA mRNA integrity. Characterisation of truncated forms, more comprehensive comparability data, results on additional batches and impact on safety and efficacy is requested. The third MO concerns omission of data on DP manufactured at the commercial site. Batch results at release, data on comparability of commercial batches with clinical batches and additional stability data is required.

In addition, several deficiencies have been noted which should be appropriately addressed by the applicant before a positive CHMP opinion can be granted.

2.2. Non-clinical aspects

2.2.1. 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 characterization 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 with BNT162b2 have been conducted due to the nature of the RNA-based vaccine product, which is according to applicable guidelines.

Mechanism of action

The SARS-Cov-2 virus infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, especially, as recently suggested, the angiotensin converting enzyme 2 (ACE2). 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 immunization with 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 its receptor-binding domain (RBD) interaction with host cell receptors but also by opsonization mediated virus clearance. In addition, the immunization 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 structural elements of the vector backbones of the BNT162b2 are optimized for prolonged and strong translation of the antigen-encoding RNA. The potency of the RNA vaccine is further optimized 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. 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.

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.

The RNA is formulated with functional and structural lipids forming lipid nano particles (LNPs), which protect the RNA from degradation and enable transfection of the RNA into host cells after IM injection. 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.

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. Regarding the results obtained from the Western Blot, a semi quantitative analysis of the results should be provided to improve the readability of the protein expression and in the analysis of the blot, some missing scientific information and explanations should be added by the applicant **(OC)**. 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 localization 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. No study report for this data set could be found and should be provided **(OC)**. 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 nano molar 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 immunization with the P2 S encoding BNT162b2. Regarding the Structural and Biophysical Characterization, the applicant is asked to provide a) A schematic description of the V8 and V9 variants, so as to identify the exact position of optimized codons in the sequence, as well as the position of added cytosines nucleotides. The exact position of these optimized codons inside the modRNA sequence should be provided. b) The exactly detailed mRNA structure of BNT162b2, including coding and non-coding sequences. c) A comparison in the V8 and V9 codon sequences, highlighting their differences and mΨU residues. d) An estimation of mΨU content in both V8 and V9 sequences and discuss on the potential difference in immunogenicity between these two sequences. E) A comparison on the protein expression obtain from both variants (V8 and V9) to ensure that the expected protein is expressed in non-clinical models **(OC)**.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates.

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-CoV2- RBD or S1 was analyzed 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 characterize the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virustype 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. Concerning study R-20-0085 on the immunogenicity of the LNP formulated modRNA encoding the viral S protein (V9), the applicant is asked to a) justify the absence of IgG2A and IgG1 characterization for RBD; b) justify why the results were not expressed in titers that would also allowed comparisons across experiments. Indeed, comparison with pVNT experiments expressing results in titers could help to determine the levels of neutralizing and non-neutralizing antibodies present in the sera **(OC)**. Immunization 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. 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 titers 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. Regarding Study VR-VTR-10671 : BNT162b2 (V9) Immunogenicity and Evaluation of Protection against SARS-CoV-2 Challenge in Rhesus Macaques, the applicant needs to a) precise for the Luminex data how the reference curve for has been constructed, what does represent the arbitrary U/ml used and how it is referring to the serum dilution factor; b) define the criteria for choosing a 10-30% infection rate of Vero cells; c) Methods to quantify antibody production in the different experiments differ and consequently cross-comparison between experiments is hardly impossible. Indeed, it is important to distinguish neutralizing antibodies from non-neutralizing antibodies. 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. The applicant needs to provide an estimation of the non-neutralizing antibodies in the whole antibody response. d) It is important to notice that on figure 6 of study report, neither panel A nor panel B highlight the consumption of IgG S1 binding antibodies after challenge nor the increase due to B memories response following the challenge: this would need to be further justified by the Applicant **(OC)**.

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-α 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 served 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 intra tracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21. 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). Considering that the time between the first and second vaccine dose may have a significant impact on the immunological response, the applicant is asked to provide the rationale for the chosen prime-boost interval (21 days) (**OC**). At the time of challenge, SARS-CoV-2 neutralizing titers ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralizing titers 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. The data from the individual animals should be provided for the RT-qPCR test for presence of SARS-CoV-2 RNA (**OC**).

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, immunized 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 immunized animals. The CT score signal was at the same level as the control at Day 10/EOP and is of unclear significance due to the presence in one animal before challenge. No radiographic evidence of vaccine-elicited enhanced disease was observed. Histopathological examination of lung tissues is ongoing and will be submitted as an addendum (**OC**). Overall, the challenge study is suboptimal as it comes with a number of uncertainties. The limitations can be listed regarding the model: absence of sars-cov2-clinical signs in control and challenged NHP, use of juveniles NHP, lack of females NHP, one out of three age-matched saline control-immunized ($n=3$) male rhesus macaques not responding to challenge (no viral RNA neither in the BAL and nasal swab), low numbers of animals with a low statistical significance, questionable selection of titer of the viral challenge ($1.05 \cdot 10^6$ PFU). Moreover, some important data are missing to date like the absence of cytokines measurement in the NHP BAL. The applicant is asked to discuss all these limitations and should provide further scientific information on the NHP model relevance. Although the model is considered adequate to demonstrate immunogenicity, and viral clearance, it is considered insufficient to demonstrate efficacy against the disease (**OC**).

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2. This is accepted.

Safety pharmacology programme

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 accepted.

Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is accepted.

2.2.2. 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 a LNP-formulated surrogate luciferase RNA in mice. No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

No validated methods of analysis to support the non-clinical PK/biodistribution studies have been submitted. However, the applicant claims to have used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients without providing such data **(OC)**.

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. No other organs besides the liver were investigated and therefore distribution to other organs cannot be excluded. The clinical administration route is IM the PK study was performed with a different administration route (IV) **(OC)**.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial $t_{1/2}$ 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 $t_{1/2}$ 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 time. 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 is asked to comment on the differences in the kinetics of the two novel excipients as well as on the relatively long liver clearance of ALC-0315 **(OC)**.

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 not study distribution of the modRNA used in the vaccine candidate BNT162b2, but instead, in a non-GLP study, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2. Since several LNP formulations were tested in the study it is not completely clear which of the LNP formulation is used in the clinical version of BNT162b2 **(OC)**.

The 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. The biodistribution method has not been validated or qualified and no discussion on its sensitivity has been included **(OC)**.

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 gGGT levels.

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 where 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. The applicant is asked to clarify issues regarding the data and discuss the possible clinical relevance of the transiently increased IL-6 levels **(OC)**. 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.

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. Theoretical metabolites were arrived at via examination of the excipient molecules and consideration of commonly observed biotransformations (hydroxylation, *N*-dealkylation, hydrolysis, glucuronidation, sulfation, oxidation and combinations thereof). Given that the acetamides have been reported to be carcinogenic in animals, including liver tumors, potentially based on genotoxic mechanism, the applicant is asked to provide a discussion on the distribution and metabolism of the ALC-0159 focusing on the acetamide moiety (**OC** raised in toxicology section).

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.

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-0315 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.2.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies (one full study submitted, one intermittent study submitted) and one DART/EFD rat study (not yet submitted beyond a study plan). The test substance is BNT162b2 (variant 8 and the clinically relevant variant 9), 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 novel (ALC-0315 and ALC-0159).

General toxicity: The two general/repeat-dose toxicity studies involved i.m. exposure of Han Wistar rats to BNT162b2 for a total of 17d (three exposures; 1ggr/w) followed by three weeks of recovery.

One study used variant 8 of BNT162b2 (dose 100ug) and one study used variant 9 (30ug). Overall, the study designs only included a single experimental group each with a variant of BNT162b2, with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. This somewhat limits the risk assessment but is acceptable. No test substance-linked mortality or clinical signs were observed (except a slight increase [$<1^{\circ}\text{C}$] 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 within 24h after 1st exposure (-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 lymph nodes at 100ug. Overall, there were signs of a significant immune response which is likely linked to – and expected to a certain degree for – the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis 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 and periportal vacuolation at d17 (partially or fully reversed during recovery) which may be related to hepatic clearance of the PEGylated lipid in the LNP. Only some organ and tissue samples from the main organs were used for BNT162b2 V8 histopathology (adrenal gland, brain, epididymis, heart, kidney, liver, lungs, lymph nodes, ovary, pituitary gland, prostate, spleen, testicle, thymus, thyroid). Other tissues/structures (nasal body cavity, clitoral gland, dorsal root ganglion, larynx, mandibular lymph node, tibial nerve, preputial gland, ureter, Zymbal's gland) were preserved for additional histopathology if needed. The interim data for 30ug BNT162b2 V9 did not include histopathology data and no specification of what tissues are to be examined/stored.

Immunogenicity: Treatment of rats with 100ug BNT162b2 V8 generated SARS-CoV-2 S-binding IgG antibodies against the S1 fragment and the RBD (based on ELISA and pseudovirus neutralization test on blood samples).

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 very strong increase ($>100\%$) in large unclassified cells [LUC; 295.5-319.5% for V8, not specified for V9], neutrophils [606-680% for V8, not specified for V9], eosinophils [419-509% for V8, not specified for V9], basophils [105-147% for V8, not specified for V9] and fibrinogen [160-205% for V8, not specified for V9]. The changes were reversible (assessed for V8). No effects on coagulation were observed for a V8 and a slight increase in mainly males with 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 gGT ($>200\%$) and increased gGT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate

increases in ALT and ALP levels, possible indicative of liver effects. There were no changes in cytokine levels (IFN γ , TNF α , IL-1 β , IL-6, IL-10) after 100ug V8 exposure. 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 has been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential. That being said, the novel lipids possess an acetamide moiety which is classified as possible human carcinogen (IARC Group 2B) with debated genotoxic mechanism, which should be discussed further (**OC**).

DART: No results have yet been submitted nor has a discussion been provided on choice of animal model (rat) or experimental design (**OC**).

Local tolerance: No dedicated local tolerance studies available but assessment included in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly light to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The interim data for 30ug BNT162b2 V9 exposure indicated similar effects.

2.2.4. Ecotoxicity/environmental risk assessment

As the active substance is a vaccine product (which additionally is based on naturally degradable mRNA and lipids), no ERA is considered necessary.

2.2.5. Discussion on non-clinical aspects

Pharmacology: The proposed medical 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). Applicant should provide a more detailed clarification of the mode of action of BNT162b2, e.g. which cells types will take up the LNP, translate the modRNA and express the S-protein on the surface. Moreover, which cell types/organs will be targeted by the immune defence system, when the vaccine is in action. Further information on the potential activity/mode of action of the two novel excipients should be provided (**OC**).

Regarding the structural and biophysical characterization of the modRNA, some information is missing (e.g. a schematic description and comparison of both vaccine variants including the position of added cytosines nucleotides and optimized codons, coding and non-coding sequences, m Ψ U content, an assessment of sequence structure relation to immunogenicity)(see **OC for details**). Regarding the results obtained from the Western Blot in the in-vitro studies, a semi quantitative analysis of the results should be provided and in the analysis of the blot, some missing scientific information and explanations should be added by the applicant (**OC**). It can be noted that an overview of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided. 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 IgG, 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 but a more in depth discussion on the suitability of these pharmacological animal models has not been provided (e.g. susceptibility for SARS-CoV-2 infection; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains) and the relevance of the immunogenicity data for the clinic (e.g. only single

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immunisation 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 (**OC**). 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. Nevertheless, no further discussion was provided regarding the possibility of autoimmune responses induced by the ModRNA. The Applicant is invited to further discuss the risk that the mRNA vaccine can trigger potential autoimmune responses and how they plan to possibly evaluate their occurrence (**OC**).

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).

There are some issues with study R-20-0085 regarding the immunogenicity of the LNP formulated modRNA encoding the viral S protein (V9; e.g. regarding the absence of IgG2A and IgG1 characterization of RBD, experimental design that would allow an effective titer comparison between experiment) (see **OC for details**). There are also some issues with the study on multiplex analysis of cytokine release from murine Splenocytes Day 28 after Immunization with BNT162b2 (the use of "5" as compared to "1 ug" BNT162b2 for the Luminex analysis in the Pharmacology written summary, page 18 (last paragraph) as compared to in the report R-20-0085) (**OC**). Moreover, it is noted that high levels of the Th1 cytokines IFN γ and IL-2 in multiplex immunoassays were detected after re-stimulation with the S but not RBD overlapping peptide mix, although RBD is part of the S protein. This should also be clarified (**OC**).

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. The reasoning behind this can be followed. The assumption that the immune response to SARS-CoV-2 infection provides some measure of protection from disease upon subsequent exposure to the virus, appears plausible. There were a number of specific questions regarding the NHP proof of concept study (study VR-VTR-1067) which could be considered demonstrate immunogenicity and viral clearance in NHP but insufficient to fully demonstrate efficacy against the disease (issues to consider were e.g. on the report itself, the animal model relevance, technical aspects, endpoints, immunological aspects) (**OC**).

The applicant needs to a) precise for the Luminex data how the reference curve for has been constructed, what does represent the arbitrary U/ml used and how it is referring to the serum dilution factor; b) define the criteria for choosing a 10-30% infection rate of Vero cells; c) Methods to quantify antibody production in the different experiments differ and consequently cross-comparison between experiments is hardly impossible. Indeed, it is important to distinguish neutralizing antibodies from non-neutralizing antibodies. 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. The applicant needs to provide an estimation of the non-neutralizing antibodies in the whole antibody response (**OC**). d) It is important to notice that on figure 6 of study report, neither panel A nor panel B highlight the consumption of IgG S1 binding antibodies after challenge nor the increase due to B memory response following the challenge: this would need to be further justified by the Applicant (**OC**). The report VR-MQR-10211, on S1-binding rhesus macaque serum IgG levels detected by a direct binding Luminex immunoassay, was not provided. This should be submitted (**OC**).

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFN γ producing T cell responses, including a high frequency of CD4+ T cells that produced IFN γ , 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 plausible, however, there was no reference to what to expect from a typical Th2 biased response to enable a comparison of the current data. Nevertheless, 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. However, the potential importance of T-cell effector cells for a putative protection against SARS-CoV-2 infection after BNT162b2 (V9) immunization was not further investigated or discussed.

When immunized 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), nasal 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. The size of the study prevents any firm conclusion on these observations. A histopathological examination of lung tissues is ongoing and a submission ASAP as an addendum is awaited **(OC)**. Furthermore, the data from the individual monkeys should be provided for the RT-qPCR test for presence of SARS-CoV-2 RNA **(OC)**.

In the NHP pharmacology study (Study VR-VTR-10671), rhesus macaques were immunized on days 0 and 21. 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). Considering that the time between the first and second vaccine dose may have a significant impact on the immunological response, the applicant is asked to provide the rationale for the chosen prime-boost interval (21 days). (Graham et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7385486/> Corbett et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7449230/>) **(OC)**. The Spike protein of SARS-CoV-2 undergo mutations, and it thus critically important to investigate the biological significance of these variants in relation to the development of Spike-based covid-19 vaccine candidates. For example, Korber et al. present evidence that there are now more SARS-CoV-2 viruses circulating in the human population globally that have the G614 form of the Spike protein versus the D614 form that was originally identified from the first human cases in Wuhan, China. Further, Li et al., states that as of May 6, 2020, 329 naturally occurring variants in Spike protein have been reported in the public domain. The applicant is asked to discuss how the chosen Spike antigen variant in BNT162b2 relates to the Spike variants currently on the dominant SARS-CoV-2 viruses circulating in the human population. (Korber et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7332439/> Li et al., 2020: <https://doi.org/10.1016/j.cell.2020.07.012>) **(OC)**. The rhesus macaques were challenged with the SARS-CoV-2 USA-WA1/2020 isolate. To our knowledge, this strain does not contain the D614G mutation. This mutation is reported to rapidly accumulate in the circulating SARS-CoV-2 strains and may increase the infectivity several-fold compared to the original Wuhan-1 strain. The applicant is asked to discuss the relevance of the NHP challenge study results in relation to the strain used for challenge and the strains circulating in the human population **(OC)**.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing IgGs and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters (to be confirmed by histopathology), provide some support for the vaccination approach. It can be noted that in the primary proof-of-concept study, the use of juvenile rhesus monkeys with no or only mild clinical symptoms for the preclinical efficacy testing has

limitations in its value as a disease animal model for human Covid-19 (which is a clearly age stratified disease, mostly affecting the elderly). In addition, the low number of animals of the male sex only that were studied only for a short time period weakens the conclusiveness of the study. However, due to species differences in the immune system between animal model species and humans, the final call on whether this candidate vaccine will work sufficiently well in humans will entirely rely on the clinical outcome.

Pharmacokinetic (regarding the two novel LNP excipients): The applicant is requested to provide qualification data for LC-MS/MS method used to quantify the two novel LNP lipids in the non-clinical PK study **(OC)**. The Applicant is also asked to justify the choice of an IV study instead of an IM study, which would have a more clinical relevance. The difference observed in terms of PK absorption should be discussed **(OC)**.

It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0159, ie the one that does not contain any PEG, although PEG is known to be used to increase half-life of many recombinants. The Applicant will have to justify this observation, as well as to discuss the difference of kinetics profile between the two lipids. The Applicant is also requested to estimate the delay of the clearance of the ALC-0315 from the liver, as this could have an impact on the safety profile **(OC)**.

Biodistribution: As expected for an RNA, the expression of the surrogate luciferase reporter RNA was transient and decreased over time. It is acknowledged that the biodistribution of the mRNA mostly will be dependent on the composition of LNP and the applicant has provided data that differences in LNP formulation affects the biodistribution of the luciferase modRNA and luciferase protein expression. The Applicant mentions that the LNP-formulated luciferase-encoding modRNA tested in this study have the exact same lipid composition than BNT162b2. It is however not clear to understand which of the three tested LNP formulation is present in the drug product, BNT162b2 variant V9. The Applicant should comment **(OC)**.

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. It can be noted that there is no information on the similarities of the mRNA modifications of the non-coding regions between the luciferase modRNA used in the study and the modRNA used in BNT162b2. The applicant is asked to provide more information on the luciferase reporter RNA, in particular, whether the untranslated sequences are similar to that of the BNT162b2 modRNA and therefore at least the stability of the mRNAs are somewhat comparable. **(OC)**

The biodistribution of the vaccine has been evaluated in mice, using 2 µg mRNA (encoding for luciferase). In humans and in the repeat-dose study in rat using the V9 version, 30 µg (per administration) was used. It is not clear if this difference in RNA concentration results differences in the amount of LNP used. The applicant is therefore asked to clarify if there were differences in the amount of LNP used in the biodistribution study and the repeat-dose study /clinical trials and if so, discuss how this could affect the distribution and safety evaluation observed in the clinic compared to non-clinical data **(OC)**.

The bioluminescence method used to determine the surrogate luciferase modRNA biodistribution has not been validated or qualified and no discussion on its sensitivity has been included. Only three females were investigated which is considered a low number. Moreover, only one dose level (given as

single injection) was tested (compared to two injections given clinically). The sensitivity of the method and dose proportionality effects have therefore not been determined.

The applicant has only discussed distribution at the injection site and to the liver. To the untrained eye it is not clear that the bioluminescence signal is solely liver specific. Although the signal appears to be in the liver region, from the data submitted it cannot be excluded that the bioluminescence signal could include distribution to other organs located in proximity of the liver.

Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain. The observed extra-hepatic distribution of modified RNAs have been detected at much lower levels compared to the liver when measured with techniques detecting nucleic acids (for example branched DNA analysis). This raises the concern if the sensitivity of the bioluminescence method is sufficient to detect potentially weaker biodistribution to sites besides the liver and injection sites?

The vaccine is intended to be given to patients twice with a booster dose after 22 days. The booster dose scheme could increase the risk for inflammatory reactions at sites of expression and therefore a wide biodistribution profile might not be optimal from a safety perspective. The applicant is therefore asked to provide more information regarding the biodistribution assay and should discuss the sensitivity of the biodistribution method. The choice of using a non-validated/non-qualified bioluminescence method to determine the biodistribution of a surrogate luciferase protein instead of choosing to detect the actual modRNA used in the vaccine candidate BNT162b2 should be justified **(OC)**. Moreover, the applicant is asked to consider the possibility of a wider biodistribution pattern than observed and discuss the possible safety consequences of a wider biodistribution profile of BNT162b2. **(OC)**

Results from the Luminex-based multiplex assay revealed that immunisation with LNP formulated luciferase modRNA transiently increased levels of MCP-1, IL-6, IP-10, at 6 hours post-immunization. These results in mice suggest that the LNP can activate the innate immune system of mice, by the synthesis of pro-inflammatory cytokines. As the effect was transient, this effect could be considered as an adjuvant-like effect. Overall, on the basis of above, the LNP formulation is expected to have not only a role to protect modRNA from nucleases degradation, and facilitating cellular transfection, but also adjuvant like effects.

In view of potential acute immunotoxicity mediated by LNPs, does the Applicant possess data on other timepoints (earlier than 6h or beyond) regarding the cytokines measurements? **(OC)**

The Applicant is also asked to discuss the absence of an in vitro hPBMC stimulation assay in healthy donors to assess reactogenicity **(OC)**.

Extrapolating to clinics, the Applicant is requested to discuss the level of IL-6 cytokine induced by LNPs, considering that asymptomatic but infected subjects candidate to vaccination, could display higher IL-6 levels during early phase infection **(OC)**.

Toxicology: The first "V8"-repeat-dose toxicity rat study has some documentation issues that possible would have to be followed up regarding its GLP status (a GLP inspection has been initiated) and thereby increasing the uncertainty of the interpretation of the results **(OC)**. That being said, as the toxicological outcomes from the V8 and V9-studies are overall similar (and the two studies were conducted at different sites), the V8-results are considered to be useful for risk assessment. There is also some uncertainty regarding which production process (two possible) was used for the test substance in the V9 study (also dependent on the quality assessment which has yet to start).

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. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. It is unclear if or how much of that immune response is attributable to the LNP components (which are included in the formulation as excipients). There is some pharmacokinetic data that indicates that the LNP has the potential to induce a transient immune response, but it can also be noted that most exogenous biomolecules tend to generate some degree of transient immune response, so such observations would not be unexpected.

While no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate, with no deeper discussion on the choice of animal models [OC]), immunogenicity tests on blood samples in the V8 repeat-dose toxicity study indicate that rats generate SARS-CoV-2 antibodies, partly supporting the choice of 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 lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30g (V9). While an immune response is expected from V8 and V9, the strong reaction of the injection site and immune system in rat is difficult to interpret/risk assess as the vaccine candidate(s) are derived from a novel vaccine platform. There is also the possibility, which is difficult to assess non-clinically or effectively in-silico, that the generated antibodies may react with endogenous proteins. An absence of dose-response designs in the studies increases the difficulty to interpret the effects.

As the pharmacokinetic distribution study in rat was limited (mainly giving data on liver), the distribution (and its effects) has to be inferred indirectly from the toxicological studies. There is some uncertainty in this regard as not all tissues have been investigated in the V8 study and histopathological details are unknown for the V9 study and it is recommended to study as many tissues as possible (the following tissues were not studied: nasal body cavity, clitoral gland, dorsal root ganglion, larynx, mandibular lymph node, tibial nerve, preputial gland, ureter, Zymbal's gland). 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 gGT levels at >200% and activity, minor-moderate increase in levels of ALT and ALP) which may be linked to the LNP. The gGT changes were not observed with 30ug V9, which may be due to variant differences and/or a lower dose. Considering that vaccines are expected to generate little or no toxicity (beyond local tolerance and immune response effects) and that BNT162b2 derives from a novel vaccine platform in the context of a pandemic, further discussion on these effects and a possible mention in the SmPC is required (see **OC for specific details**). DART data remains to be submitted and the choice of animal model and experimental design to be justified (**OC**).

With regard to the characterization of the novel LNP components, these are not considered primarily as adjuvant substances. While some degree of LNP-specific immune response cannot be ruled out (as demonstrated in the *in vivo* biodistribution study in Balb-C mice by pro-inflammatory cytokines induction [MCP-1, MIP-1 β , TNF- α , IFN- γ , IL-6, IP-10] at 6 h post immunization – see study R-20-0072), no further experimental toxicological studies are considered necessary as the use of the whole formulation (RNA + LNP) in the repeat-dose toxicity and DART studies is sufficient to qualify the novel excipient lipids in combination that the overall effects are also being assessed in the clinical trials. That being said, as the lipids contain an acetamide moiety which has been linked to carcinogenicity in

animals, including liver tumors, potentially related to genotoxicity, and liver distribution and functional effects have been observed in rat, an extended discussion of these lipids is requested (**OC**).

It is unclear at this stage of the rolling review how these effects are depicted in the SmPC.

2.2.6. Conclusion on non-clinical aspects

Based on the provided data so far there are no non-clinical major objections. The applicant will need to sufficiently address the other concerns raised to be granted MAA from a non-clinical perspective. Other non-clinical elements in further rolling review cycles are expected to define the safety profile of the vaccine.

2.3. Clinical aspects

N/A

2.4. Risk management plan

N/A

2.5. Pharmacovigilance system

N/A

3. SCIENTIFIC OVERVIEW AND DISCUSSION on responses to questions raised in previous cycle(s)

N/A

4. Benefit risk assessment

N/A

5. CHMP list of questions

5.1. Quality aspects

Major objections

GMP

1. GMP status for DS and DP manufacturing sites is currently not acceptably demonstrated:
 - a. A statement on GMP compliance issued by EU supervisory authority of the DS and DP manufacturing and testing sites Wyeth BioPharma Division, Andover, United States and Pfizer Inc, Chesterfield, United States should be available by adoption of the CHMP opinion.
 - b. The MIA for Pfizer Puurs is limited to the formulation and filling only. It should be clarified if authorisation will be extended to all operations listed in 3.2.P.3.1, including LNP manufacturing. Moreover, GMP certificate or a statement of GMP compliance issued by the Supervisory authority of BioNTech Manufacturing GmbH, Mainz, Germany should cover batch certification of the DP.

Drug substance and Drug product

2. Comparability between clinical and commercial material has not yet been demonstrated, which raises uncertainties about consistency of product quality and hence uncertainties as regards product safety and efficacy of the commercial product. Significant differences between batches manufactured by DS Process 1 and 2 are observed for the CQA mRNA integrity. In addition, the characterisation of BNT162b2 DS is currently not found acceptable in relation to this quality attribute. This is especially important considering that the current DS and DP acceptance criteria allows for up to 50% fragmented species. Therefore, the dossier should be updated with additional characterisation data on mRNA integrity in sections 3.2.S.2.6 (comparability) and 3.2.S.3 of the dossier.
 - a. Truncated and modified RNA species should be regarded as product-related impurities. Even though two methods, namely agarose gel electrophoresis and capillary gel electrophoresis (CGE), have been applied to determine RNA integrity of BNT162b2 DS, no characterisation data on truncated forms is presented. Results obtained on RNA integrity by CGE and agarose gels should be included in the characterisation section (3.2.S.3). The truncated forms should be sufficiently characterised, i.e. they should be described, and it should be discussed if the fragmented species are expected to be similar between batches. In addition, the possibility of translated proteins other than the intended spike protein (S1S2), resulting from truncated and/or modified mRNA species should be addressed and relevant protein characterization data for predominant species should be provided, if available.
 - b. Upon changing to DS Process 2, a decrease in RNA integrity was observed (only numerical values provided). Concerning this difference in RNA integrity between Process 1 and Process 2 DS batches the Applicant is requested to provide capillary electropherograms together with an evaluation of any batch differences in peak patterns. The potential safety risks associated with truncated RNA isoforms should be thoroughly discussed with reference to the batches used, clinical experience and possibly literature data. The quantitative and qualitative differences observed between Process 1 and 2 should be discussed with respect to their impact on safety and efficacy.
 - c. For Process 2, the CTP and ATP volumes were adjusted before the manufacture of DS batch PPQ3 to align better with RNA integrity results from Process 1. Additional batch data (from PPQ4 and PPQ5) should be provided to confirm that the optimised Process 2 allows for reaching RNA integrity levels consistent with the Process 1 batches.

- d. After contact with the applicant it was confirmed that DP batches manufactured from early Process 2 batches, with lower RNA integrity, have been recently introduced in clinical trials. However, as the cut-off date for the clinical Interim Analysis (IA) was changed, the IA doesn't include data from subjects dosed with Process 2 material, and the Company does not expect to have Process 2 included in the Final Analysis dataset. Therefore, the proposed acceptance criteria of $\geq 50\%$ intact RNA for RNA integrity is considered too wide compared to clinical batch data, 69-81%. The proposed release and shelf-life acceptance criteria for the DP should therefore be tightened based on the clinical data included in the dossier or clinically qualified by other means.
 - e. Release data provided for some of the DP batches indicates a possible decrease in mRNA integrity during the manufacturing of DP. The applicant should therefore discuss possible root causes, and present comparative results for DS and DP, on RNA integrity. A consequential need for a more stringent DS specification should be considered. Sections S.4.1 and P.5.1 in the dossier should be aligned and updated accordingly.
2. Drug product batches manufactured at the commercial facility (whole manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, drug substance from process 2) were not presented. Process validation (PPQ) for commercial scale batches are already initiated and validation data should be provided. Batch results for at least 2 commercial scale batches representative of the commercial process should be presented. Comparability of commercial batches with clinical batches should be demonstrated and the data should be provided. The claimed shelf-life and storage condition are not yet acceptable since no stability data is available for batches from the commercial manufacturing site and scale and shelf-life is based on very small scale (development) batches (less than 1% of the commercial scale), not representative of the commercial batches (manufacturing site, scale, process for the drug substance). Additional stability data (6 months at long-term storage condition) should be presented.

Other concerns

Drug substance

The applicant plans to update a number of sections along the dossier and states the following: "Data for this section is pending and will be updated once the data has been generated, analysed, and verified". Until these data are available for assessment, no final conclusions can be drawn on the concerned sections.

General information (S.1)

3. The proposed mechanism of action should be presented in S.1 General Information.

Description of manufacturing process and process controls (S.2.2)

4. Information on the final batch volume should be provided. The Applicant should state either the total batch volume or the approximate number of DS containers generated from one batch. Section 3.2.S.2.2 should be updated accordingly.

5. It is noted that some parameters and ranges may be updated after PPQ and additional characterization studies are completed. These updates could have an impact on overall assessment of the manufacturing process description, leading to additional issues. However, the following issues have already been identified and should be addressed:
 - a. It should be indicated that the incubation time during GTP/N1-methylpseudo UTP bolus feeds is a global time for the 11 feeds
 - b. The strategy for UFDF membrane lifetime validation is to perform concurrent validation of the membranes at commercial scale. This is found acceptable, provided that the Applicant will include control of the feed flow rates, transmembrane pressure and membrane surface area in section 3.2.S.2.2. The dossier should be updated accordingly.
 - c. The transfers of the UFDF pool into a single PE flexible container before and/or after 0.45/0.2 µm filtration should be clarified and should appear in the DS process flow diagram.
 - d. The DS filling volume range in the EVA flexible containers should be defined in line with the volumes validated for shipping.

Control of materials (S.2.3)

6. Representative CoAs or full specifications should be provided for starting and non-compendial raw materials used in the manufacturing of BNT162b2 DS. It is expected that information regarding the microbiological control is included. Additionally, all raw materials should be demonstrated to be free from contaminating RNases, unless otherwise justified.
7. It is noted that for starting and raw materials used at Andover, additional material testing will be performed and provided when available. Where relevant, the applicant should consider in house testing for the functional activity of starting and critical raw materials such as the enzymes used in the manufacturing process. The information should also be completed with the analytical methods.
8. As the 5'-cap structure is complex, its synthesis should be described. The impurities and by-products generated during its synthesis should be discussed.

Linear DNA template

9. Additional details on relevant characteristics and origin of the E. coli strain DH10B as well as source and an overall description of generation (flow chart of the successive steps) of the plasmid used as template for the production of Drug Substance should be provided.
10. Release testing of plasmid MCB and WCB should be completed with a percentage of the expected sequence rather than "comparable to the reference sequence". Moreover 100 % homology is requested for the coding sequence; for the other parts of the plasmid any mutation should be assessed.
11. The specification for the future WCBs should be completed with the percentage of viable cells with an appropriate acceptance limit. Moreover, an acceptance limit for viable cell concentration should be set, and a percentage of the expected sequence (% homology) for DNA sequencing as requested for plasmid MCB and current WCB should be proposed. Finally, the analytical methods should be indicated.
12. The cell bank stability protocol (including test parameters and corresponding acceptance criteria) should be provided. Otherwise, the performance of the WCB should be checked during the

manufacture of each batch of plasmid DNA, for example by following the trends in bacterial growth and plasmid yield.

13. It is recommended that cell banks be stored in two or more separate locations to minimize the risks of their total loss as a result of a catastrophic event. It is indicated that Pfizer facility at 875 Chesterfield Parkway West, Chesterfield is the only proposed storage site for MCB and WCB. A clarification whether any risk amelioration strategies are in place to avoid the loss of cell banks should be requested.
14. Information should be provided regarding the reference material used in the restriction map analysis and DNA sequencing determination for MCB and WCB used for plasmid DNA template production.
15. The manufacturing process to obtain the linear DNA template should be completed with the following information:
 - a. The quantity of linear DNA template obtained in each batch should be stated
 - b. The chemical agent used for chemical lysis of the cells should be mentioned and its clearance should be demonstrated to be sufficient.
 - c. The mention "or equivalent" for the restriction enzyme should be deleted.
 - d. The Applicant should confirm that implementation of changes in the manufacture of the linear DNA template will be applied for in a variation application.
16. The specification for the linear DNA template should be revised with narrower limits for purity and process-related impurities taking into account the batch analysis results. A high level of DNA impurities could impact the activity of the T7 polymerase during the Transcription phase of the DS production.
17. Appropriate descriptions of all analytical methods used in the release control of the linear DNA template as well as summaries of the results obtained in the method validation/qualification studies should be provided.
18. The reference material for plasmid identity testing should be described. (Rapp Q10)
19. The stability of the linear DNA template and the stability of the filtered circular plasmid DNA intermediate should be addressed. A shelf life for the linearized DNA template should be established and a stability protocol covering the proposed storage period should be included. Relevant available data should be provided to support this proposal.

Control of critical steps and intermediates (S.2.4)

20. It is stated that OOS result for in-process controls would trigger an evaluation of the deviation to determine if the batch could be further manufactured. It should be confirmed that OOS results will lead to batch rejection.

Process validation and/or evaluation (S.2.5)

21. Several validation studies and full PPQ data are still pending for the manufacturing process at Wyeth BioPharma, Andover. Therefore, additional information is needed:

- a. Results for PPQ4 and PPQ5 batches should be provided to confirm the consistency of the DS manufacturing process after the change of ATP and CTP volumes in the IVT vessel at PPQ3 and onwards. The description of deviations and investigation conclusions should be provided, as well as the evaluation of removal of impurities for the five PPQ batches.
 - b. A time-plan for the submission additional process validation data should be provided before marketing authorisation approval.
22. Residual DNA template is present at higher level in PPQ3 batch (211 ng DNA / mg RNA) than in PPQ1 and PPQ2 batches (10 and 23 ng/mg); the robustness of DNase I digestion step should be further investigated.

Manufacturing process development (S.2.6)

23. It is noted that the ranges studied for addition volumes for CTP and ATP as stated in 3.2.S.2.6 are 81.0-143.8 and 90.0-135.1 mg/L respectively and that the acceptable ranges proposed are 85.4-143.8 and 85.4-135.1 mg/L. It seems as if the lower acceptable range of 85.4 mg/L proposed for ATP volume have not been studied, this needs to be clarified. In addition, it needs to be justified why the lower end of the ranges for both CTP and ATP volumes remained unchanged although the target ranges were increased (from 90 to 135.1 and 107.9 mg/L respectively), to avoid that these nucleotides will be limiting in order to increase the percentage of the RNA integrity. These ranges need to be further justified and clarified and the dossier updated accordingly.
24. In the In vitro transcription (IVT) step, the magnesium dependent T7 RNA polymerase assembles ribonucleotide building blocks. Since magnesium can be chelated by pyrophosphate released by the addition of each ribonucleotide pyrophosphatase is important to maintain sufficient levels of free magnesium. The Applicant states that added volumes of these two enzymes have been identified as non-CPPs as they are most likely to impact yield only. This conclusion is not entirely agreed upon.
- a. It needs to be further justified why these parameters are not classified as CPPs.
 - b. Regardless of the classification as non-CPPs or CPPs it is strongly recommended to include an appropriate control of the added volumes of the enzymes T7 polymerase and pyrophosphatase in sections 3.2.S.2.2 and 3.2.S.2.4 of the dossier.
 - c. In addition, it needs to be clarified if the actual volumes loaded are calculated based on enzyme activity as stated in the certificates of the actual batch of the enzymes that are used. (See also question in section 3.2.S.2.3 above).
25. The Applicant should provide data on the T7 RNA polymerase and proteinase K levels in additional commercial scale DS batches, once testing is complete. In addition, the Applicant should briefly describe that the methods applied to determine the concentrations of these two enzymes in the BNT162b2 DS samples and confirm that these methods are fit for purpose.
26. Differences in the poly(A)tail pattern were observed when comparing the Process 1 and Process 2 DS batches. The differences in the extent of cytidine monophosphate incorporation and transcriptional slippage should be further investigated and the possible impact on efficacy and safety should be discussed. The only Process 2 DS included in the comparison was manufactured prior to the adjustment of CTP and ATP volumes. Results obtained on the PPQ batches, manufactured after adjustment (PPQ 3, 4 and 5) should also be presented and discussed.

27. The level of information in the dossier presenting the available process characterisation studies is not sufficient to allow assessment: the results of the studies should be presented, preferably summarised in figures or tables.
28. An overall control strategy was presented but some parameter 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 submission of the final data set of the control strategy should be provided.

Characterisation (S.3)

29. In the Development History and Comparability section (3.2.S.2.6), the expressed protein size is evaluated by in vitro expression followed by Western blot. Results obtained by this method could be regarded as biological characterisation and should be included in section 3.2.S.3. The method needs further description and the results should be sufficiently characterized.
 - a. A brief method description including conditions for protein expression, gel separation, and western blot assay should be provided.
 - b. The expected protein size should be stated and supported by theoretical calculations.
 - c. The identities of the two distinct bands should be explained. If possible, the identities of the bands should be confirmed and characterized by LC-MS/MS.
 - d. The Applicant should provide data on protein expression in terms of percentage of successfully transduced HEK293 cells using the lipofectamine transfection system.
30. Even though biological characterisation might not be possible to perform on DS, the strategy to determine potency and relevant functional assay(s) should be described in section 3.2.S.3. Results obtained on DP could be included, to demonstrated functionality.
31. NGS technology has been used as an orthogonal method to confirm primary sequence but details are missing about the results of this analysis in terms of coverage of the target genome. A brief description of the NGS method, and the results obtained with it should be provided.
32. As regards 5' end of the RNA, relative abundance of each species (capped, non-capped and/or incompletely capped) is given as major (>50%) for the expected 5'-cap structure, minor (5 to 50%) and trace (<5%) for other species. However, a more precise quantification of each uncapped or incompletely capped species should be provided. Moreover, the potential contribution of uncapped or incompletely capped structures to the potency of the BNT162b2 DS should be discussed.
33. The Applicant should discuss the relationship between 5'-cap heterogeneity and dsRNA production. A risk assessment should be provided. This should be also taken into account in the justification of DS specification.
34. It should be addressed whether, under expected storage conditions, individual base modifications occur (e.g. depurination, oxidation). Based on this discussion it may be necessary to review the impurity methods and specifications for appropriateness to detect relevant degradation under long-term conditions.

Control of drug substance, Specifications (S.4.1)

35. The proposed commercial drug substance specifications, the method descriptions and the method validation summaries should be updated to include in-house method identification numbers for the non-compendial methods. The information is required in order to provide a clear link between the specification and the descriptions and validations of analytical procedures used for routine testing. Furthermore, for the compendial methods references to relevant parts of the Ph Eur should be included. Section 3.2.S.4.1, 3.2.S.4.2 and 3.2.S.4.3 of the dossier should be updated accordingly.

Control of drug substance, Analytical procedures (S.4.2)

36. In all the in-house analytical methods used in the release of DS, method descriptions are based on "examples" of procedures, controls and standards as well as on "typical" system operating parameters. These terms raise uncertainties regarding the developmental stage, and the control of critical steps of these assays. The analytical methods used in the control of DS are expected to be finalized. The applicant is requested to confirm this and to update the relevant parts of the dossier with unequivocal method descriptions, including relevant lists of materials and additional details, if needed. The applicant should also confirm that any significant changes in analytical procedures will be applied for in a variation application.
37. Regarding the RT-PCR method for determination of DS and DP identity:
- Information regarding the positive control used in the should be provided.
 - The proposed assay acceptance criteria for the qualitative RT-PCR-based assay used for determination of DS identity requires a Ct value for the positive PCR control of NMT than 32 simultaneous with a Ct value for the negative controls of NLT 32. These criteria are not considered relevant to support method suitability. More stringent acceptance criteria should be established and supported by relevant data.
 - The mRNA extraction step needed for determination of the identity of BNT162b2 DP should be included in the description of the RT-PCR-based assay and this step should be appropriately described and addressed in the method validation procedure. This question relates to the DP part of the dossier.
38. Regarding the ddPCR-based method for determination of poly(A) tails in the mRNA DS:
- Information regarding the internal control used in the should be provided.
 - From the limited description of the ddPCR-based assay for quantification of poly(A) tails it seems that the cDNA generated using a poly(T) primer is used both as a template for further amplification of the (poly(A) positive mRNA)-derived cDNA and also as the theoretical input based on which the final calculation of the Poly(A) tails is made. This strategy is not understood. The suitability of this approach and the rationale by which the method is able to determine the percent poly(A) tails in the mRNA DS relative to the input (which should be clearly defined) needs to be better described.
 - With respect to the storage conditions of the cDNA prior ddPCR, storage at room temperature, however with no hold time defined, is mentioned in the method description, but a storage time of 3 days at -20°C is examined in the validation studies with respect to method robustness. These discrepancies should be clarified. Information on the qualified lot of linearized plasmid

standard used in the qPCR-based method to quantify the residual DNA template in BNT162 b2 DS should be provided.

39. Information on the qualified lot of linearized plasmid standard used in the qPCR-based method to quantify the residual DNA template in BNT162 b2 DS should be provided.
40. With respect to the immunoblot analytical method used for determination of dsRNA in BNT162b2 drug substance:
 - a. Additional information regarding the critical reagents (such as antibodies), standards and equipment used as well as representative dot blots and standard curves should be highlighted in the dossier. The robustness of the method should be appropriately demonstrated in the validation exercise, if different reagents, e.g. different clones or different vendors for the antibodies, are envisaged.
 - b. An incubation time of >16h is defined for the primary antibody incubation step. An upper limit should be defined as well. Unless otherwise justified, all variable incubation times described in the method should be considered in the validation exercise, in order to demonstrate the robustness of the assay.
41. For the capillary gel electrophoresis method, it should be specified how the peaks are integrated to allow quantitation of the RNA integrity. An integrated electropherogram should be provided as an example.

Control of drug substance, Validation of analytical procedures (S.4.3)

42. The information in the dossier does not support that any of the in-house analytical procedures applied for drug substance has been properly validated in line with ICH Q2. The validation summaries provided are far too brief and important details are missing. The Applicant should submit more comprehensive validation summaries of all non-compendial methods, for example in the form of short validation reports. The validation summaries should include all relevant calculations, acceptance criteria, description of and results obtained for individual samples. Chromatograms and dose response curves should be included, where applicable. Module 3.2.S.4.3 of the dossier should be updated accordingly.
43. The method transfer plan or activities should be addressed. It should be noted that, if method transfer was / will be performed, the following information should be provided. For the non-compendial tests, it should be confirmed that the validation acceptance criteria for the receiving sites will be the same as for the transferring site (which will be assessed during the RR). For the analytical methods for which comparative analysis will be proposed, it should be confirmed that the acceptance criteria will be the same as for the intermediate precision validated at the transferring site (and assessed during RR).

Control of drug substance, Batch analyses (S.4.4)

44. Batch results should be presented for the two newly manufactured batches PPQ4 and PPQ5 to be able to assess process consistency. This is considered specifically important to verify that the volume adjustments made for ATP and CTP volumes before manufacturing of PPQ3 (20Y513C501) consistently provides reproducible results, in particular with RNA integrity levels similar to levels achieved in process 1 batches.

Control of drug substance, Justification of specifications (S.4.5)

45. The length of the poly(A) tails in BNT162b2 DS is important for RNA stability and translational efficiency and this test should therefore be included in DS release specification.
46. The proposed acceptance criteria for the percentage of 5'- Cap ($\geq 50\%$), dsRNA ($< 1000 \text{ pg}/\mu\text{g}$ mRNA) and Poly(A) tail ($\geq 70\%$) are not considered justified and should be tightened to better reflect the data presented for the DS material used in the manufacturing of the clinical and PPQ batches. In addition, batch release results from two newly manufactured batches PPQ4 and PPQ5 should be included in the reassessment of the acceptance criteria.

Reference standards (S.5)

47. It should be clarified for what release and stability testing methods the reference standard is used and will be used in future. The function of the reference standard should be briefly stated for each assay, i.e. result evaluation/normalisation, sample compliance, assay control etc. The information could be provided preferentially in a tabulated form.
48. It is noted that the CRM is derived from a Process 2 DS batch that was established in September 2020. It should be explained if another reference standard was used to perform release tests on Process 1 DS batches. All initial reference materials should be listed.
49. The CRM is derived from an early Process 2 batch which has a slightly lower RNA integrity than the clinical batches and possibly also to future batches, due to target value optimisation. The Applicant should justify the suitability and address potential risks of using this material as a reference standard.
50. Neither the storage condition, nor the shelf-life is established for the CRM. The Applicant should explain if the reference standard is used in any of the methods included in the formal stability protocol. If this is the case, the Applicant should explain how compliance with the acceptance criteria can be guaranteed.
51. Since the Applicant intends to establish primary and working reference materials, information on the preparation, qualification and stability evaluation of the PRM and WRMs should be included in a PACMP. Otherwise it should be confirmed that a variation application will be submitted in connection with the introduction of these standards.

Container closure system (S.6)

52. The following additional information should be included in Module 3.2.S-6 of the dossier.
 - a. A certificate of analysis of one representative batch of the EVAM contact layer demonstrating compliance with Ph. Eur. 3.1.7.
 - b. A specification for the container closure system including dimensions (currently only schematic drawings are included).
53. A commitment to submit for assessment any unexpected leachable compound from EVA container closure system reproducibly observed above $1.5 \mu\text{g}/\text{day}$ TDI should be provided.

Stability (S.7)

54. Process 1 batch is not considered representative to process 2 batches. The only parameters studied for process 1 batch are RNA integrity and RNA content and the cGE method for RNA integrity was changed. Therefore, based on the currently very limited stability data presented for process 2 batches (only 1-month data available for one batch) no conclusion can be drawn in relation to the proposed shelf life for the DS. Thus, in order to support shelf life setting for drug substance updated reports from the ongoing stability studies on the primary batches (including data from the ongoing process validation batches) should be provided.
55. It should be confirmed that future extensions of the assigned DS shelf life will be applied for in formal variation applications. The following statement should be removed for Module 3.2.S.7.1 of the dossier; *"The sponsor will extend the assigned shelf life without notification providing the real time stability data at the intended storage condition is acceptable and within commercial specifications."*

Drug product

The applicant plans to update a number of sections along the dossier and states the following: "Data for this section is pending and will be updated once the data has been generated, analysed, and verified". Until these data are available for assessment, no final conclusions can be drawn on the concerned sections.

P.1 Description and composition of the drug product (P.1)

56. All ingredients, including process aids used in the manufacture, should be specified in the composition together with a footnote that they are removed during manufacturing. Therefore, ethanol and components of citrate buffer should be added to the composition. Moreover, HEPES and EDTA (excipients used in the drug substance buffer) should also be added to the composition table. Section P.1 should be updated accordingly. All these ingredients should be mentioned in the SmPC and PIL.
57. While the final volume of drug product after reconstitution (2.25 ml) exceeds the vial nominal capacity (2 ml), it is expected that during clinical trials it was demonstrated that the method of preparation is feasible and is robust in ensuring efficient mixing and uniformity of the solution. This issue should be addressed and if needed, appropriate instructions for use (IFU) should be given in the SmPC and PIL.

Pharmaceutical development (P.2)

58. Controlled extraction studies have been performed on the bromobutyl rubber stopper. Leachables studies are planned to be set up to support the proposed DP shelf-life of 24 months, the T0 will be provided later on during the procedure. The applicant should commit to provide the updated results from the leachables study for assessment.
59. It is noted that some additional heightened characterization information will be added in the formulation development file. However, the awaited data were not detailed. Formulation development should be completed with characterisation studies showing the homogeneity of the

suspension during storage at long term or accelerated conditions, after freeze/thaw, or after dilution with 0.9% NaCl should be studied.

60. Development data showing homogeneity of LNP or RNA concentration in the vials during filling process should be provided.
61. Overall control strategy was presented but some parameter 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 submission of the final data set of the control strategy should be provided.
62. The compatibility studies of the diluted suspension in the vial and in syringes were performed with DP diluted to 0.05 mg/mL while dilution for administration is intended to be 0.1 mg/mL: it should be confirmed that the analytical methods are valid at this dilution. Moreover, the specifications applied for RNA content and RNA integrity (+/- 20% of T0) are not acceptable; in use specifications should be the same as the shelf-life specifications. It is noted, however, that this section may be updated as additional studies are completed. The applicant still needs to define in P.8 and the SmPC/PIL the in-use shelf-life and storage conditions after dilution and first use, in line with available data.

Manufacture (P.3)

63. The batch formula should be completed with process aids.
64. The lipid nanoparticle (LNP) formation is one critical manufacturing step and some additional information is requested regarding this step.
 - a. The range number of DS bags and DS batches to be thawed should be stated.
 - b. According to pharmaceutical development (Section P.2.3.4) 2-8 parallel T-mixer may be used depending on the batch size and manufacturers equipment. In the description of manufacturing process (Section P.3.3) it is stated that "one or more" T-mixer(s) are used. The number of T-mixers should be defined in Section P.3.3 and the dossier should be updated accordingly.
 - c. A drawing of the T-mixer including further details should be provided, e.g. geometry and dimensions.
3. It is noted that some parameters and ranges may be updated after PPQ and additional characterization studies completed. These updates could have an impact on overall assessment of the manufacturing process description, leading to additional issues. From the first assessment, the manufacturing process description should already be completed with the following information:
 - a. The environment grades should be indicated for each step;
 - b. holding times will be assessed when complementary data will be available.
4. The applicant should clarify if the 0.2 µm-filter used for bioburden reduction is identical with the 0.2 µm-filters used for sterile filtration.
5. It is stated that OOS result for in-process controls would trigger an evaluation of the deviation to determine if the batch could be further manufactured. It should be confirmed that OOS results for acceptance criteria will lead to batch rejection.

6. The validation protocol should be completed with the minimum number of consecutive batches at commercial scale to be included in the PPQ validation process, which should not be less than 3 batches. DS thaw parameters should be studied. Each thawing method (controlled room temperature thaw or controlled thaw) should be validated on at least one batch. Moreover, the mixing speed during dilution of DS should be added in the list of studied parameters.
7. For PPQ, to validate the TFF efficiency, residual ethanol and citrate should be measured with appropriate limits. During aseptic filling, a homogeneity test of the filled vials should be added with appropriate sampling and acceptance criteria. Finally, some acceptance criteria are "report results" with limits to be developed after sufficient manufacturing experience. This is not endorsed and acceptance criteria should be fixed before PPQ validation.
8. Acceptance criteria for quality attributes that are requested to be narrowed in the DP specification should be narrowed as well in the process validation protocol.
9. It should be confirmed that the Kleenpak Capsule with Supor EKV Membrane will be the one used for routine DP manufacturing at Puurs. If other filters are used, the extractables / leachables should be studied before use.

Control of excipients (P.4)

10. It should be confirmed that cholesterol will be controlled in line with Ph. Eur. monograph Cholesterol for parenteral use (2397) for future batches and not Ph. Eur. monograph Cholesterol (0993).
11. Additional test for microbial contamination should be included for all compendial excipients, except for water for injection. Further, where relevant, a test for bacterial endotoxins should be added unless otherwise justified.
12. Appropriate documentation for the processing aid excipients ethanol and citrate buffer and the excipients for drug substance buffer HEPES and EDTA is missing and should be provided.
13. DSPC is used in several medicinal products approved in EU and administered intravenously. According to the guideline on excipients in the dossier (EMA/CHMP/QWP/396951/2006), an excipient used by a new route of administration may be considered as a novel excipient. Therefore, further discussion should be provided to justify why DSPC administered intramuscularly is not considered as a novel excipient and how data from intravenous administration can support safety of the excipient for this drug product.
14. Specifications for DSPC should include a test for purity of stearic acid, identity of phosphorus, and the assay specification (90.0-110.0%) should be tightened in line with batch results from the supplier.
15. For cholesterol and DSPC, the analytical methods for residual solvents and microbial purity should be described in detail (e.g. detailed chromatographic conditions for GC, sample and standards

preparation, detailed calculation formulae for the GC method and respectively the actual method of preparation and count for microbial purity).

16. Unless otherwise justified, controls for the absence of RNase should be included in the specification for excipients, especially Water for Injections.

Control of drug product (P.5)

17. In all of the in-house analytical methods used in the release of DP, method descriptions are based on "examples" of procedures, controls and standards as well as on "typical" system operating parameters. These terms raise uncertainties regarding the developmental stage, and the control of critical steps of these assays. The analytical methods used in the control of DP are expected to be finalized. The applicant is requested to confirm this and to update the relevant parts of the dossier with unequivocal method descriptions and additional details, if needed. The applicant should also confirm that any significant changes in analytical procedures will be applied for in a variation application.
18. The information in the dossier does not support that any of the in-house analytical procedures applied for DP has been properly validated in line with ICH Q2. The validation summaries provided are far too brief and important details are missing. The Applicant should submit more comprehensive validation summaries of all non-compendial methods, for example in the form of short validation reports. The validation summaries should include all relevant calculations, acceptance criteria, description of and results obtained for individual samples. Chromatograms and dose response curves should be included, where applicable. Module 3.2.P.5.3 of the dossier should be updated accordingly.
19. With the exception of osmometry, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at DP release, all other analytical procedures are conducted at release and stability studies for drug product. It is stated by the applicant in section 3.2.P.5.6 that the acceptance criteria used for stability during shelf life will be the same as the acceptance criteria used for lot release. This is found acceptable, however, the applicant should confirm that the same acceptance criteria are valid both at release and end-of-shelf-life for the drug product. The specifications document in 3.2.P.5.1 could preferably be updated to include a separate column for the end-of-shelf-life specifications.
20. Test method numbers are missing and should be given to all analytical procedures used in the specifications for release and end-of-shelf-life and should consequently be inserted in the drug product specifications document and to the descriptions and validations of analytical procedures. Sections 3.2.P.5.1, 3.2.P.5.2 and 3.2.P.5.3 should be updated accordingly.
21. LNP size for drug product is measured by dynamic light scattering (DLS) and the efficacy of the drug product depends on the size of the LNP. The proposed acceptance criteria of 40 to 180 nm seem wide compared to clinical batch data that is found in the range of 59-74 nm for the small scale clinical batches ("classical LNP process") and 68-71 nm for the emergency supply ("upscale")

LNP process). The acceptance criteria should therefore be tightened to be in line with what has been qualified in the clinical studies or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product.

22. The mRNA extraction step needed for determination of the identity of BNT162b2 DP should be included in the description of the RT-PCR-based assay and this step should be appropriately addressed in the method validation procedure.
23. With respect to the cell-based flow cytometry method used to confirm the in vitro expression of SARS-CoV-2 spike protein encoded by the RNA in BNT162b2 DP:
 - a. Information regarding critical reagents (such as antibodies), drug product control samples and equipment used should be provided in the dossier. The robustness of the method should be appropriately demonstrated in the validation exercise, if different reagents, e.g. different clones or different vendors for the antibodies or different instruments, are envisaged.
 - b. It is stated that exact shapes and locations of gates are expected to be different between instruments and that gates will be shaped and sized to select for the relevant cell populations. The gating strategy should be established, clearly defined and a description of the rationale for establishing the gating strategy should be provided. Possible changes observed between different equipment should be appropriately cross-validated.
 - c. Complete examples of results (including the three population: P1, P2 and P3) should be provided for NC, DPC and TS samples
 - d. In the table defining assay acceptance criteria, a limit of >30% is established for results obtained using drug product control samples. In order to unequivocally demonstrate the suitability of this method, the lower limit strategy should be replaced by a target/interval value. A value of, or close to, 30% is considered too low for the demonstration of method suitability and should be updated based on relevant data.
 - e. The relevance of the results obtained in the in vitro expression test using a HEK293 cell line for the in vivo intended targeted cell population should be further discussed and, ideally, substantiated with characterization data, unless otherwise justified. Additionally, information on characterisation of the HEK293 cell line used, including specifications should be provided.
 - f. The cell culture and transfection steps included in the potency method should be appropriately considered in the method validation strategy. For example, substantial variation in the culture parameters (such as passage number and seeding densities) are allowed for HEK293 cells used in determining DP in vitro expression. Unless otherwise justified, these possible variations should be addressed in the validation exercise when investigating assay robustness
 - g. High variability is claimed in the comparability exercise in P.2.2; in method validation it is noted that variability (% RSD) decreases significantly with sample size (%RSD is 18% for 150ng (sample size per method) and 7.1% for 250ng). It should be discussed if the method is optimized for the intended use and this should be confirmed with comparability results with commercial scale batches.

24. In-vitro expression is a cell-based flow cytometry assay. The assay was implemented recently and the proposed acceptance criteria of $\geq 30\%$ cells positive seem wide compared to the limited batch release data available to date, i.e. emergency supply lots that is in the range of 63-65%. In addition, some data are presented for the small-scale clinical batches used in comparability testing, where data are found in the range of 50-71% (Table 3.2.P.2.3-5 in the dossier). The proposed acceptance criteria need to be thoroughly justified and tightened in line with the levels qualified in clinical studies or clinically qualified by other means. This justification should include the applicant's total current knowledge of the drug product.
25. The proposed acceptance criteria of $\geq 80\%$ for RNA encapsulation seem wide compared to clinical batch data that is found in the range of 92-94%. The proposed acceptance criteria for RNA encapsulation should therefore be tightened based on clinical qualification or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product.
26. The specification range of each lipid appears somewhat broad, but the acceptance criteria are found acceptable. However, to further strengthen the control strategy given that a fixed molar ratio of cationic lipid and RNA is critical for LNP formation, acceptance criteria for the molar ratio N/P should be included in the specification unless further justified.
27. The method description and validation summary of the rapid sterility test should be provided during the procedure.
28. A specification should be included for free lipids or the applicant should justify that the control strategy is sufficient in this regard. In addition, no information and discussion are provided on the lipid-related impurities originating from the degradation of the lipid nanoparticles and such data needs to be provided.
29. A risk assessment with respect to the potential presence of elemental impurities in the drug product based on the general principles outlined in Section 5.1 of ICH Q3D should be performed. 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.
30. The specification for LNP polydispersity index should be tightened in line with batch results for clinical batches, i.e. NMT 0.2 (0.22 observed on stability).
31. Detailed description of analytical methods should be provided in P.5.2; these details should be in line with the validation data:
 - a. for all methods, a list of materials needed for analysis
 - b. for the DLS method for particle size and polydispersity, further details of the instrument and the sample size

- c. for the fluorescence assay method: the surfactant and its concentration, sample and standard concentration and the range of the calibration curve.
 - d. for the CAD method, the sample diluent.
 - e. for the potency in vitro by cell based flow cytometry: the Drug Product Control (DPC) (e.g. qualification), for the flow cytometer acquisition: complete examples of results (including the three population: P1, P2 and P3) should be provided for NC, DPC and TS samples, and Assay and Sample acceptance criteria rationale should be explained and justified.
 - f. for the RT-PCR method: criteria for the selection of primers used for the test.
32. Validation data for the CGE (RNA integrity) is referred to the drug substance section S.4.3. However, as the active substance is formulated (RNA is encapsulated in the LNP formula), the appropriate validation parameters for the drug product (specificity, accuracy, sensitivity, robustness) should be addressed.
33. Method transfer plan was not submitted in the RR but is requested to be discussed in the next submission. For the non-compendial tests, it should be confirmed that the validation acceptance criteria for the receiving sites will be the same as for the transferring site (which will be assessed during the RR). For the analytical methods where comparative analysis will be proposed, it should be confirmed that the acceptance criteria will be the same as for the intermediate precision validated at the transferring site (and assessed during RR).

Reference standards or materials (P.6)

34. It should be clarified for what release and stability testing methods the reference standard (including the CRM) is used today and will be used in the future. The function of the reference standard should be briefly stated for each assay, i.e. results of evaluation/normalisation, sample compliance, assay control etc. This information could be provided preferentially in a tabulated form.
35. Since the Applicant intends to establish primary and working reference standards, information on the preparation, qualification and stability of the PRS and WRSs should be provided.

Stability (P.8)

36. The proposed initial shelf-life for the drug product is 6 months at the recommended storage temperature of -90 to -60°C. In order to support the suggested shelf-life for drug product updated reports from the ongoing stability studies should be provided.
37. It should be confirmed that future extensions of the assigned DP shelf life will be applied for in formal variation applications. The following statement should be removed for Module 3.2.P.8.1 of the dossier; "The sponsor will extend the assigned shelf life without notification providing the

real time stability data at the intended storage condition is acceptable and within commercial specifications.”

38. Results on photostability testing as well as temperature cycling studies are pending to date and needs to be provided for assessment.
39. The applicant should confirm that they commit to continue all the ongoing stability studies at long-term conditions until completion.
40. It should be confirmed that the specifications for the bromobutyl stopper include the tests in the Ph Eur 3.2.9, including the self-sealing test, and that the self-sealing test is still acceptable after the stopper exposure to freezing (down to -90°C) and thawing, since the vial is a multi-dose container intended for 5 doses.
41. The applicant needs to clearly define in P.8 and in the future SmPC/PIL in line with available data and practical needs:
 - a. the shelf-life under recommended, refrigerated, and ambient conditions
 - b. the in-use shelf-life and storage conditions after dilution with saline and after first use
 - c. a storage condition to keep the vial in outer carton and protect from light, before and after dilution (since multi-dose container).

Appendices (3.2.A)

Viral safety

42. Regarding the Pyrophosphatase, T7 polymerase and RNase inhibitor, spermidine and DNase I provide a certificate stating that no product of biological origin has been used during the manufacture (production and purification) or provide adequate virological documentation, with regard to viruses and unconventional transmissible agents (NCTA or prions, compliance with EMEA/410/01 Rev.3 requirements) where applicable, for each of the components concerned.
43. Regarding the four lipid excipients: ALC-0315, ALC-0159, DSPC and Cholesterol provide a certificate stating that no product of biological origin has been used during the manufacture (production and purification) or provide adequate virological documentation, with regard to viruses and unconventional transmissible agents (NCTA or prions, compliance with EMEA/410/01 Rev.3 requirements) where applicable, for each of the components concerned.

Novel excipient – ALC-0315

Based on the limited information no final conclusion can be drawn on chemical synthesis, quality control of starting material, specification limits for impurities and retest period.

44. The commercial batch size should be provided.
45. The specification limit for assay (85-115%) is considered wide and should, if possible, be tightened. The specification limit should be re-evaluated as more batch data are available and

then specification limits for impurities are set, i.e. the mass balance should be taken into account.

46. The method description should include the GC chromatography parameters.
47. A brief summary of validation of the GC method is provided. Extended information in form of a short validation report including relevant data, chromatograms and calculations should be submitted.
48. It should be confirmed that the packaging materials are conform to Ph Eur or EU regulation 10/2011 amended.

Novel excipient – ALC-0159

Based on the limited information no final conclusion can be drawn on chemical synthesis, quality control of starting material, specification limits for assay impurities and retest period.

49. The synthesis scheme is illegible, a readable scheme should be provided.
50. The commercial batch size should be provided.
51. The method description should include the GC chromatography parameters.
52. A brief summary of validation of the GC method is provided. Extended information in form of a short validation report including relevant data, chromatograms and calculations should be submitted.
53. A test for molecular weight and polydispersity should be included unless otherwise justified.
54. It should be confirmed that the packaging materials are conform to Ph Eur or EU regulation 10/2011 amended.

5.2. Non-clinical aspects

Major objections

None

Other concerns

Pharmacology

1. Applicant should provide a more detailed clarification of the mode of action of BNT162b2, e.g. which cells types will take up the LNP, translate the modRNA and express the S-protein on the surface. Moreover, which cell types/organs will be targeted by the immune defence system, when the vaccine is in action. Further information on the potential activity/mode of action of the two novel excipients should be provided. ([confidential information deleted])

2. In study 20-0211, regarding the results obtained from the Western Blot, a semi quantitative analysis of the results to improve the readability of the protein expression should be provided and in the analysis of the blot, some missing scientific information and explanations should be added by the applicant (*[confidential information deleted]*):
 - a. The presence of the two bands for BNT162b2 ARN (at 100 KDa and 190 KDa respectively)
 - b. The 76.5 kDa bands are not observed in both BNT162b2 nor in S1 control lanes, and the full S protein at 141.14 kDa is also not observed in BNT162b2 lane.
 - c. The lack of an important expression for the S1 protein ctrl at 76.5 Kda
3. Regarding the structural and biophysical characterization, the applicant is asked to provide (*[confidential information deleted]*):
 - a. A schematic description of both variants, (V8 and V9) so as to identify the exact position of optimized codons in the sequence and including coding and non-coding sequences...
 - b. A comparison between the V8 and V9 codon sequences, highlighting their differences on mΨU and cytosine residues. The exact position of these optimized codons inside the modRNA sequence should be provided
 - c. An estimation of mΨU relative content in both V8 and V9 sequences and a discussion on the potential difference in immunogenicity between these two variants. Changes in cytosine and mΨU content can significantly change the modRNAs immunogenicity.
 - d. A comparison on the protein expression obtain from both variants (V8 and V9) to ensure that the expected protein is expressed in non-clinical models.
4. The modRNA contains a substitution of 1-methyl-pseudouridine for uridine. This substitution decreases recognition of the vaccine RNA by innate immune sensors, such as toll-like receptors (TLRs) 7 and 8, resulting in decreased innate immune activation and increased protein translation. Vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity. Nevertheless, no further discussion was provided regarding the risk of autoimmune responses induced by the modRNA. The Applicant is invited to further discuss the possibility that the mRNA vaccine can trigger potential autoimmune responses and how do it plan to possibly evaluate their occurrence (*[confidential information deleted]*).
5. The applicant is requested to provide a more extended discussion on the choice and relevance of the pharmacological animal models (also with regard to the choice of the rat as a toxicological animal model) and chosen endpoint in the pharmacological-immunological assessment (e.g. lack of assessment of long-term memory responses, no assessment of old age-dependent effects) (*[confidential information deleted]*).
6. Concerning study R-20-0085 on the immunogenicity in mice of the LNP formulated modRNA encoding the viral S protein (V9):
 - a. The applicant is asked to justify the absence of IgG2A and IgG1 characterization for RBD (*[confidential information deleted]*);
 - b. The applicant is asked to justify why the results were not expressed in titers that would also allowed comparisons across experiments. Indeed, comparison with pVNT experiments expressing results in titers could help to determine the levels of neutralizing and non-neutralizing antibodies present in the sera (*[confidential information deleted]*).
 - c. In the study report R-20-0085 section 4.5.3.1 a discrepancy was found between text (1, 5 or 10 ug/animal) and table of treatment schedule (0.2, 1 and 5 ug); the Applicant should clarify which is the correct piece of information (*[confidential information deleted]*).

- d. Concerning the *Multiplex analysis of cytokine release from murine Splenocytes Day 28 after Immunization with BNT162b2*, it is referred to *immunization with "5"* as compared to *"1 ug"* BNT162b2 for the Luminex analysis in the Pharmacology written summary, page 18 (last paragraph) as compared to in the report R-20-0085, respectively, this discrepancy could be clarified. Moreover, it is noted that high levels of the Th1 cytokines IFN γ and IL-2 in multiplex immunoassays were detected after re-stimulation with the S but not RBD overlapping peptide mix, although RBD is part of the S protein. This could be further clarified or commented ([*confidential information deleted*]).
7. Regarding Study VR-VTR-10671: BNT162b2 (V9) Immunogenicity and Evaluation of Protection against SARS-CoV-2 Challenge in Rhesus Macaques ([*confidential information deleted*]):
 - a. The applicant needs to precise for the Luminex data how the reference curve has been constructed, what does represent the arbitrary U/ml used and how it is referring to the serum dilution factor;
 - b. The applicant is asked to define the criteria for choosing a 10-30% infection rate of Vero cells
 - c. Methods to quantify antibody production in the different experiments differ and consequently cross-comparison between experiments is difficult. Indeed, it is important to distinguish neutralizing antibodies from non-neutralizing antibodies. 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. The applicant needs to provide an estimation of the non-neutralizing antibodies in the whole antibody response.
 - d. It is important to notice that on figure 6 of study report, neither panel A nor panel B highlight the consumption of IgG S1 binding antibodies after challenge nor the increase due to B memories response following the challenge: this would need to be further discussed by the Applicant
 8. The report VR-MQR-10211, on S1-binding rhesus macaque serum IgG levels detected by a direct binding Luminex immunoassay, was not provided. This should be submitted ([*confidential information deleted*]).
 9. The data from the individual animals should be provided for the *RT-qPCR test for presence of SARS-CoV-2 RNA after SARS-CoV-2 Challenge in BNT162b2 (V9) immunized nonhuman primates* ([*confidential information deleted*]).
 10. In the NHP pharmacology and in the toxicology studies the control group is immunized with PBS and not with a mRNA in LNP expressing a non-correlated antigen. The Applicant is invited to further discuss the potential effect of the formulated mRNA on the immune response and toxicity ([*confidential information deleted*]).
 11. The Spike protein of SARS-CoV-2 undergo mutations, and it thus critically important to investigate the biological significance of these variants in relation to the development of Spike-based covid-19 vaccine candidates. For example, Korber et al. 2020 present evidence that there are now more SARS-CoV-2 viruses circulating in the human population globally that have the G614 form of the Spike protein versus the D614 form that was originally identified from the first human cases in Wuhan, China. Further, Li et al., states that as of May 6, 2020, 329 naturally occurring variants in Spike protein have been reported in the public domain. The applicant is asked to discuss how the chosen Spike antigen variant in BNT162b2 relates to the Spike variants currently on the dominant SARS-CoV-2 viruses circulating in the human population ([*confidential information deleted*]).

References: Korber et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7332439/> Li et al., 2020: <https://doi.org/10.1016/j.cell.2020.07.012>

12. The rhesus macaques were challenged with the SARS-CoV-2 USA-WA1/2020 isolate. To our knowledge, this strain does not contain the D614G mutation. This mutation is reported to rapidly accumulate in the circulating SARS-CoV-2 strains and may increase the infectivity several-fold compared to the original Wuhan-1 strain. The applicant is asked to discuss the relevance of the NHP challenge study results in relation to the strain used for challenge and the strains circulating in the human population (*[confidential information deleted]*).
13. Overall, the challenge study appears questionable in its design and hardly supports the robustness of the immunological response. The above limitations can be listed regarding the model:
 - a) Absence of clinical signs in control and challenged NHP,
 - b) Use of juveniles NHP,
 - c) Lack of females NHP,
 - d) One out of three age-matched saline control-immunized (n=3) male rhesus macaques not responding to challenge (no viral RNA neither in the BAL and nasal swab),
 - e) Low numbers of animals with a low statistical significance
 - f) Questionable selection of titer of the viral challenge ($1.05 \cdot 10^6$ PFU)
 - g) In the NHP pharmacology study (Study VR-VTR-10671), rhesus macaques were immunized on days 0 and 21. 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). Considering that the time between the first and second vaccine dose may have a significant impact on the immunological response, the applicant is asked to provide the rationale for the chosen prime-boost interval (21 days) (*[confidential information deleted]*). References: Graham et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7385486/> Corbett et al., 2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7449230/>

Moreover, some important data are missing to date:

- h) Lung histopathology and immunochemistry, mentioned by the Applicant as ongoing, should be provided.
- i) Absence of cytokines measurement in the NHP BAL

The applicant is asked to discuss all these limitations and should provide further scientific information on the NHP model relevance. Although the model is considered adequate to demonstrate immunogenicity, and viral clearance, it is considered insufficient to demonstrate efficacy against the disease (*[confidential information deleted]*).

Pharmacokinetics

1. Quantification of ALC-0315 and ALC-0159 in plasma, liver homogenates, urine, and faeces homogenates was conducted by LC-MS/MS in an in vivo PK study (PF-07302048_06Jul20_072424). No validation data for the LC-MS/MS method in the non-GLP IV PK study in rats (Study PF-07302048_06Jul20_072424) had been presented. The Applicant is requested to provide qualification data for this method (*[confidential information deleted]*).

2. The Applicant is asked to justify the choice of an IV study instead of an IM study in the non-GLP IV PK study in rats (Study PF-07302048_06Jul20_072424), which would have a more clinical relevance. The difference observed in terms of PK absorption should be discussed (*[confidential information deleted]*).
3. It's worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0159, ie the one that does not contain any PEG, although PEG is known to be used to increase half-life of many recombinants. The Applicant will have to justify this observation, as well as to discuss the difference of kinetics profile between the two lipids. The Applicant is also requested to estimate the delay of the clearance of the ALC-0315 from the liver, as this could have an impact on the safety profile (*[confidential information deleted]*)
4. The Applicant mentions that the LNP-formulated luciferase-encoding modRNA tested in this study have the exact same lipid composition than BNT162b2. It is however not clear to understand which of the three tested LNP formulation is present in the drug product, BNT162b2 variant V9. The Applicant should comment. (*[confidential information deleted]*)
5. There are uncertainties regarding the biodistribution study performed with the surrogate luciferase reporter RNA. The applicant is therefore asked to provide more information regarding the biodistribution assay:
 - a) The applicant is asked to justify and discuss the choice of using a non-validated/non-qualified bioluminescence method to determine the biodistribution of a reporter luciferase protein instead of detecting the actual BNT162b2 modRNA. The justification should include a discussion on the sensitivity of the method. (*[confidential information deleted]*)
 - b) It can be noted that there is no information on the similarities of the mRNA modifications of the non-coding regions between the luciferase modRNA used in the study and the modRNA used in BNT162b2. The applicant is asked to provide more information on the luciferase reporter RNA, and in particular, whether the untranslated sequences are similar to that of the BNT162b2 modRNA and therefore at least the stability of the mRNAs are somewhat comparable. (*[confidential information deleted]*)
 - c) The biodistribution of the vaccine has been evaluated in mice, using 2 µg mRNA (encoding for luciferase). In humans and in the repeat-dose study in rat using the V9 version, 30 µg (per administration) was used. It is not clear if this difference in RNA concentration results differences in the amount of LNP used. The applicant is therefore asked to clarify if there were differences in the amount of LNP used in the biodistribution study and the repeat-dose study /clinical trials and if so, discuss how this could affect the distribution and safety evaluation observed in the clinic compared to non-clinical data. (*[confidential information deleted]*)
 - d) The applicant is asked to consider the possibility of a broader biodistribution pattern than observed and discuss the possible safety consequences of a wider biodistribution profile of BNT162b2. (*[confidential information deleted]*)
6. Luminex-based multiplex assay:

- a) In view of potential acute immunotoxicity mediated by LNPs, does the Applicant possess data on other timepoints (earlier than 6h or beyond) regarding the cytokines measurements? (*[confidential information deleted]*)
- b) The Applicant is asked to discuss the absence of an in vitro hPBMC stimulation assay on healthy donors to assess reactogenicity. (*[confidential information deleted]*)
- c) Extrapolating to clinics, the Applicant is requested to discuss the level of IL-6 cytokines induced by LNPs considering that asymptomatic but infected subjects candidate to vaccination, could display higher IL-6 levels during early phase infection. (*[confidential information deleted]*)

Toxicology

- 7. Further discussion is requested on how the immunological response to the vaccine observed in rats, the species used in the toxicological studies, compares to that observed in Rhesus monkeys, the species used in the virus challenge study and, if possible, humans (*[confidential information deleted]*).
- 8. The qualitative and quantitative composition of the lipids constituting the LNP are not specified in the final study report #38166. It is thus not possible to check the composition of LNP; this point appears crucial as it is expected that the toxicity associated with modRNA formulated in LNP formulations is expected to be driven primarily by the LNP composition: This will have to be specified (*[confidential information deleted]*).
- 9. Both the "V8" and "V9" repeat-dose toxicity rat studies indicate functional hepatic and/or biliary effects (enlarged liver, vacuolation, increased gGT, ALT and ALP) which may or may not be linked to the LNP and which requires further discussion (*[confidential information deleted]*).
 - a. The applicant is requested to provide a discussion on the clinical relevance of these findings, and the need for a notation in the SmPC (*[confidential information deleted]*).
 - b. The discussion should include the mechanism underlying the elevated plasma activity of liver/biliary enzymes and its potential relation to LNP lipids (*[confidential information deleted]*).
 - c. The discussion should also include the findings of vacuolation of hepatocytes (minimal to mild) that was present in the portal regions of liver for all BNT162b2 (V8)-dosed animals (19 of 20 animals) at the end of the dosing phase (*[confidential information deleted]*):
 - d. Confirm that the same LNPs composition was used amongst all treated groups (from a qualitative and quantitative point of view);
 - e. Explain and discuss the difference in vacuolation occurrence between sexes for all treated groups as well as the absence of vacuoles in the V9 study;
 - f. Justify the occurrence of vacuolation in hepatocytes, while this effect is usually seen with phagocytes and not hepatocytes;
 - g. Discuss the short delay of occurrence as well as the mechanism underlying these vacuoles at the time of sacrifice (i.e. only 3 IM weekly injections) (i.e. *Development of anti-PEG antibodies? adaptive response with or without functional change? imaging to*

determine if vacuoles contain PEG?). Of note, the accumulation in the liver was mainly observed with ALS-0315 that does not contain PEG, in contrast of ALC-0159 which does contain PEG 2000. Discuss their potential toxicity from a non-clinical and clinical point of view.

- h. In light of the *in vivo* PK study, showing persistence of ALC-315 inside liver (slow elimination kinetics inside liver) and considering the presence of PEG in the formulation of ALC-0159, the Applicant is requested to document more in depth the role/implication of ALC-0159 and ALC-315 in the occurrence of vacuolation of peri-portal hepatocytes ([confidential information deleted]).
10. The Applicant will also have to detail and further document the elevated serum levels of the cytokines IFN-gamma, TNF-alpha, IL-1beta, IL-6, and IL-10 that were noted in the control group of study #38166 ([confidential information deleted]).
11. Complement (C) activation-related pseudoallergy (CARPA) can be a serious side effect of liposomal drugs, biologicals, and many other modern therapeutic and diagnostic agents. The Applicant is asked to discuss the absence of quantitative and targeted assays of C3c and C4 proteins ([confidential information deleted]).
12. The applicant is requested to provide an extended discussion on the distribution and metabolism of the novel excipient lipids (ALC-0315 and ALC-0159), their potential genotoxicity of the acetamide moiety in the lipids (which is classified as possible human carcinogen (IARC Group 2B) with debated genotoxic mechanism) in the context of the rat liver observations ([confidential information deleted]).
13. Some toxicological studies remain to be submitted: the full report for the #20GR142 study and the interim and full report for the DART study.
 - a. The Applicant is also asked to provide at the next NC roll of submission, a detailed timeline for availability of preliminary data ([confidential information deleted]).
 - b. With regard to the DART study, a justification of the study design is requested to determine the value of this study for evaluation of the developmental risk in humans. Primarily the choice of the rat as relevant animal species (rodent placental antibody transfer during the latter part of gestation is not considered similar to human antibody transfer during the third trimester of gestation) and the design of the dose regimen (whether this will lead to sufficient antibody transfer during lactation, which is equivalent to the third trimester exposure in humans) will need attention ([confidential information deleted]).
14. In terms of GLP compliance, concerns have been raised by the assessors during the review of the non-clinical report amendment of the study #38166 ([confidential information deleted]).

About the test items and formulations:

Page 26: The test item EE4 (G7) is designed as: LNP formulated modRNA encoding the RBD subunit of SARS-CoV-2 S protein ("BNT162b - 2"): what is the difference with b1 designed by the same terminology. b2 is not supported to code the full-length spike S glycoprotein?

BNT162b - 2 is also associated with another name in the pathology report page 1563 ("LNP modRNA Sp2"). Is it the same test item? The applicant is asked to clarify the different terminologies used for the test item EE4.

Information about stabilities of the test items during 6 hours at room temperature is not documented, whereas the test items were administrated 6 hours after thawing at room temperature. Could you provide evidence that the test items are stable for 6 hours at RT.

Calculation of dose concentrations to be administrated to animals are difficult to be understood for Group7 (BNT162b2 as test item), if 200µl per animal is administrated, the total concentration seems to be 110µg and not 100ug as stated. The applicant should clarify.

About the management of the study:

A mistake in the conclusion page 61 concerning the sex of animal No.179 having eschar has been observed. It seems to be a male, and not a female as stated. And this presence of eschar was not found in the table for individual clinical signs page 152 for this female No.179. Same comment for male No.162 (reddened skin reported page 62) not found page 138. The applicant should explain these discrepancies and correct these issues.

The final report had been amended justified by changes qualified as minor or/and corrections following sponsor comments. Some corrections could be considered as not minor but major, because they put into relief real mistakes in the issuance of the final report: "eschar formation was incorrectly described with occurrence on test days 14 and 15 instead of on test day 14 only" ; "on haematology and coagulation the finding of an increased number of eosinophils in groups 4, 5 and 7 was missing" ; "on clinical chemistry the directions of changes for albumin and globulin levels were incorrectly stated as an increase in albumin and a decrease in globulin plasma levels instead of a decrease in albumin and an increase in globulin plasma levels"; "the incorrect test item 'BNT162b1' instead of 'BNT162a1' was stated for Group 3".

5.3. Clinical aspects

N/A

5.4. Risk management plan

N/A

5.5. Pharmacovigilance system

N/A

5.6. New active substance status

N/A

6. Recommended conditions for future marketing authorisation and product information in case of a positive benefit risk assessment

N/A

7. Appendices (as appropriate)

N/A

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**Response to CBER Comments Received on 20 November 2020
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REGARDING THE MANUFACTURE AND TESTING FACILITIES:

QUERY 1

In amendment 119 (submitted on October 21, 2020) Table 1 - EUA and Commercial Supply Chain Manufacturing Nodes, facilities are listed for use in “US and EU markets” (for initial EUA and EUA supply-chain expansion) and “US and/or EU markets” (for commercial/EUA). Please identify the facilities and manufacturing nodes for the production of emergency supply for the US market.

RESPONSE 1

A simplified version of the table provided in amendment 119 (submitted on October 21, 2020) is provided in Table 1 and includes facilities and manufacturing nodes for the production of emergency supply for the US market.

Table 1. Emergency Supply Chain Manufacturing Nodes

Emergency Supply						
Drug Substance	Pfizer Andover			BNT Mainz, and Rentschler, Germany (Purification)		
DS Testing	Pfizer ⁵ Andover, ^{1,2} Chesterfield ²			BNT Mainz, BNT IMFS ⁴ , Rentschler, Germany		
LNP, DP	Polymun	Pfizer Puurs	Pfizer Kalamazoo	Polymun	DermaPharm	Pfizer Puurs
Fill/Finish	Pfizer Puurs (Lines WSL5, FC2, VC2)		Pfizer Kalamazoo (Lines 8,18)	Pfizer Puurs (Line WSL5, FC2, VC2)		
DP Release and stability Testing	Pfizer Andover, ² Chesterfield, ² Puurs ³		Pfizer Andover, ² Chesterfield, ² Kalamazoo ³	Pfizer Andover, ² Chesterfield, ² Puurs ³		

1 Microbial tests: endotoxin, bioburden.

2 Release and Stability testing for Identity, Composition, Strength, Product Purity and/or Process Related Impurities.

3 Microbial tests: endotoxin, sterility. Back-up sterility test sites may be employed.

4 Poly(A) tail and 5'-Cap (Composition) tests may be performed for EUA supplies at Pfizer Andover or Pfizer Chesterfield.

5 Double stranded RNA (Product Related Impurity) Test may be performed for EUA supplies at BNT IMFS.

Literature References

None

SUPPORTING DOCUMENTATION

None

QUERY 2

For each DP manufacturing node, please specify the number of GMP commercial scale DP lots for which data will be available, and submitted for review, at the time of EUA. For DP manufacturing nodes for which GMP commercial scale DP lot data will not be available at the time of initial EUA, please provide an updated time table for submission of these data. Please note that data from at least three GMP commercial-scale DP lots will be required from a DP manufacturing node prior to initial authorization to distribute EUA supplies from that node.

RESPONSE 2

Six lots have been provided to the IND to date as listed in Table 2.

Table 2. Lots Submitted to IND for Emergency Use

Lot	DS Manufacturing Site	LNP Production Site	Fill/Finish Site
EE8492	Pfizer Andover	Polymun Scientific	Pfizer, Puurs
EE8493	Pfizer Andover		
EJ0553	Pfizer Andover		
EJ1685 ^a	BioNTech; Rentschler		
EJ1686 ^a	BioNTech; Rentschler		
EK1768	Pfizer Andover		

a. IVE data for lots EJ1685 and EJ1686 are provided in [3.2.R BNT162b2 Comparability Report](#).

Lots manufactured but pending submission to the IND for Emergency Use are provided in Table 3

Table 3. Manufactured Lots Intended for Emergency Supply^a

Lot	DOM	DS Manufacturing Site	LNP Production Site	Fill/Finish Site	Anticipated CoA Availability
Andover/Kalamazoo/Kalamazoo					
EH9899	7-Oct-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	30-Nov-2020
EK5730	22-Oct-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	30-Nov-2020
EK9231	04-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	30-Nov-2020
EL1283	11-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	14-Dec-2020
EL1284	17-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	15-Dec-2020
EL3246	19-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	29-Dec-2020
BioNTech;Rentschler/Polymun/Puurs					
EL0141	29-Oct-2020	BNT;RNT	Polymun ^b	Puurs (WSL5)	7-Dec-2020
EK4241	12-Nov-2020	BNT;RNT	Polymun ^b	Puurs (WSL5)	15-Dec-2020

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Table 3. Manufactured Lots Intended for Emergency Supply^a

Lot	DOM	DS Manufacturing Site	LNP Production Site	Fill/Finish Site	Anticipated CoA Availability
BioNTech;Rentschler/DermaPharm/Puurs					
EL0140	29-Oct-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020
EL0142	29-Oct-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020
EK4237	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020
EK4243	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020
EK4244	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	14-Dec-2020
EK4245	12-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	16-Dec-2020
BioNTech;Rentschler/Puurs/Puurs					
EL0725	30-Oct-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020
EL0739	03-Nov-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020
EL1484	04-Nov-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020
EJ6795	12-Nov-2020	Andover	Puurs	Puurs (FC2)	14-Dec-2020

a: All lots are currently pending release.

b: Data from 6 GMP commercial-scale Polymun DP lots have already been submitted, thus complying with the 3 lot requirement to distribute EUA supplies from that node.

Abbreviations: BNT = BioNTech; RNT = Rentschler

Note: Final lot release by the Quality Unit occurs after CoA availability.

Literature References

None

SUPPORTING DOCUMENTATION**New or Replaced Supporting Documentation**[3.2.R BNT162b2 Comparability Report](#), Replaced**Previously submitted supporting documentation**

None

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QUERY 3

Please note that data from all PPQ studies at all manufacturing nodes must be completed prior to submission of a BLA.

RESPONSE 3

The sponsor acknowledges that data from all PPQ studies at all manufacturing nodes must be completed prior to submission of a BLA.

Literature References

None

SUPPORTING DOCUMENTATION

None

QUERY 4

In the absence of adequate PPQ data for drug product manufactured at multiple sites, it will be necessary for you to submit final COAs for lots to be distributed under EUA at least 48 hours prior to lot distribution. Please submit a plan and schedule for lot distribution under EUA.

RESPONSE 4

Pfizer plans to submit batches of available Certificates of Analyses (CoAs) twice a week (e.g. on Mondays and Thursdays). This schedule may be increased prior to December 11 to facilitate release of initial supplies and in accordance with the requirements laid out in Question 2. Lots will continue to be manufactured in support of emergency supply and submitted to the IND at least 48 hours prior to lot distribution.

Table 4. Anticipated Distribution Dates

Lot	DOM	DS Manufacturing Site	LNP Production Site	Fill/Finish Site	Anticipated CoA Availability	Anticipated Distribution Date
Andover/Kalamazoo/Kalamazoo						
EH9899	7-Oct-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	30-Nov-2020	Authorization Date
EK5730	22-Oct-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	30-Nov-2020	Authorization Date
EK9231	04-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	30-Nov-2020	Authorization Date
EL1283	11-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	14-Dec-2020	Dec 16-2020
EL1284	17-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 18)	15-Dec-2020	Dec 19-2020
EL3246	19-Nov-2020	Andover	Kalamazoo	Kalamazoo (Line 8)	29-Dec-2020	Dec 31-2020
Andover/Polymun/Puurs						
EE8492	05-Aug-2020	Andover	Polymun	Puurs (WSL5)	Data provided	N/A ^a
EE8493	05-Aug-2020	Andover	Polymun	Puurs (WSL5)	Data provided	N/A ^a
EJ0553	25-Sep-2020	Andover	Polymun	Puurs (WSL5)	Data provided	Authorization Date
EK1768	16-Oct 2020	Andover	Polymun	Puurs (WSL5)	IVE Results pending	Authorization Date
BioNTech;Rentschler/Polymun/Puurs						
EJ1685	05-Oct-2020	BNT;RNT	Polymun	Puurs (WSL5)	Data provided	Authorization Date
EJ1686	07-Oct-2020	BNT;RNT	Polymun	Puurs (WSL5)	Data provided	Authorization Date
EL0141	29-Oct-2020	BNT;RNT	Polymun	Puurs (WSL5)	7-Dec-2020	Authorization Date
EK4241	12-Nov-2020	BNT;RNT	Polymun	Puurs (WSL5)	15-Dec-2020	Dec 19-2020

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Table 4. Anticipated Distribution Dates

Lot	DOM	DS Manufacturing Site	LNP Production Site	Fill/Finish Site	Anticipated CoA Availability	Anticipated Distribution Date
BioNTech;Rentschler/DermaPharm/Puurs						
EL0140	29-Oct-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020	Authorization Date
EL0142	29-Oct-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020	Authorization Date
EK4237	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020	Authorization Date
EK4244	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	7-Dec-2020	Authorization Date
EK4243	5-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	14-Dec-2020	20-Dec-2020
EK4245	12-Nov-2020	BNT;RNT	DermaPharm	Puurs (WSL5)	16-Dec-2020	30-Dec-2020
BioNTech;Rentschler/Puurs/Puurs						
EL0725	30-Oct-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020	Authorization Date
EL0739	03-Nov-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020	Authorization Date
EL1484	04-Nov-2020	BNT;RNT	Puurs	Puurs (FC2)	7-Dec-2020	Authorization Date
EJ6795	12-Nov-2020	Andover	Puurs	Puurs (FC2)	14-Dec-2020	30-Dec-2020

a. Not intended for distribution under Emergency Use in the United States due to differences in applied label

Abbreviations: BNT = BioNTech; RNT = Rentschler

Literature References

None

SUPPORTING DOCUMENTATION

None

QUERY 5

For lots with observable LMS, please describe the percent range of the LMS peak area detected by CGE.

AND

QUERY 6

Please state the percentage of DP lots that have the LMS peak and provide a list of all impacted DP lots, including information on the DP manufacturing site as well as the associated DS lots and lipid lots/sources used for DP manufacture.

RESPONSE to 5 and 6

[Table 5](#) is a list of drug product lots with results from capillary gel electrophoresis (CGE) including the percent late migrating species. The RNA integrity assay reports the % time-corrected area of the main peak, with all other peaks (RNA fragments preceding main peak and LMS RNA species trailing main peak) influencing the reported % RNA integrity value. Most lots (14 out of 20) have some level of late migrating species reported.

The release specification for RNA integrity controls both RNA fragments and LMS since both of these species lead to lower RNA integrity. The release specification limit has been tightened to $\geq 55\%$ to ensure the integrity of RNA is maintained through the point of use. For lots that meet release specification acceptance criteria, LMS ranged up to 16%. A representative electropherogram of a recent lot with 9% late migrating species is presented in Figure 1.

Figure 1. CGE Electropherogram of DP Lot EJ1685

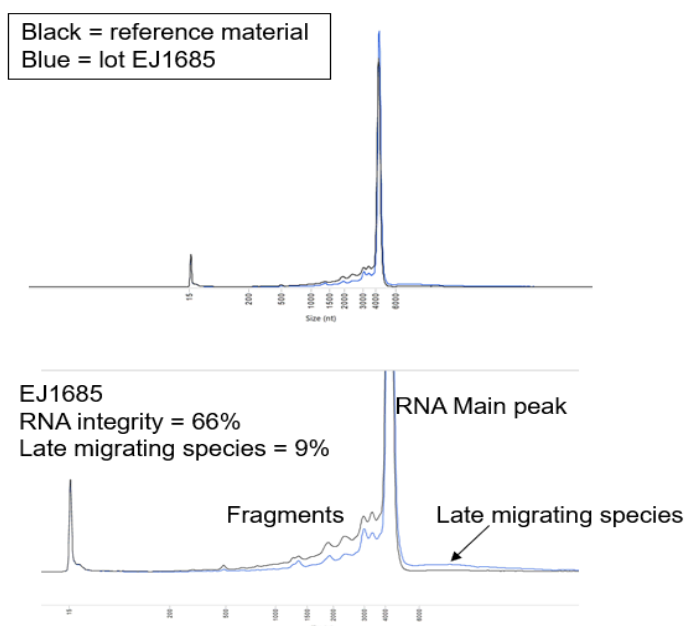


Table 5. Lot Genealogy with RNA Integrity and LMS Levels

LNP Site	DP Lot #	F/F Site	LMS	RNA Integrity	ALC-0315 Mfr	ALC-0315 Lot #	ALC-0159 Mfr	ALC-0159 Lot #	DSPC Mfr	DSPC Lot #	Cholesterol Mfr	Cholesterol Lot #
PLY	EE8492	Puurs	< QL ^c	55%	Avanti	GALC03 15-12	Avanti	GALC01 59-12	Lipoid	556500-219039 5-01	Wilshire ^b	P60349
PLY	EE8493	Puurs	< QL ^c	55%	Avanti	GALC03 15-13	Avanti	GALC01 59-12	Lipoid	556500-219039 5-01	Wilshire ^b	P90390
KZO	EJ0701	KZO	17%	52% ^a	Croda	DTP/465 /1	Avanti	ALC015 9-105	Avanti	DSPCII S-112	Avanti	SCHOLB-105
DMP	EJ0724	Puurs	< QL ^c	71%	Avanti	GALC03 15-14	Avanti	ALC015 9-105	Avanti	DSPCII S-111	Avanti	SCHOLB-105
PLY	EJ0553	Puurs	< QL ^c	68%	Avanti	GALC03 15-12/ GALC03 15-13	Avanti	GALC01 59-12	Lipoid	556500-219039 5-01	Wilshire ^b	P90390
KZO	EH9899	KZO	< QL ^c	59%	Croda	DTP/465 /3	Avanti	ALC015 9-105	Avanti	DSPCII S-112	Avanti	SCHOLB-105
PLY	EK1768	Puurs	< QL ^c	60%	Croda	1755889	Avanti	ALC015 9-104	Lipoid	556500-220042 1-01	Wilshire ^b	P90390
PLY	EJ1685	Puurs	9%	66%	Croda	DTP/465 /3	Avanti	GALC01 59-12	Lipoid	556500-2180372 -01 556500-2200421 -01	Wilshire ^b	P90390
PLY	EJ1686	Puurs	6%	69%	Croda	DTP/465 /3	Avanti	GALC01 59-12/ ALC015 9-104	Lipoid	556500-2200421 -01	Wilshire ^b	P90390
DMP	EJ1688	Puurs	10%	63%	Croda	1755889	Avanti	ALC015 9-105	Avanti	DSPCII S-111	Avanti	SCHOLB-105
PLY	EK4176	Puurs	10%	65%	Croda	1760275	Avanti	ALC015 9-104	Lipoid	556500-220042	Wilshire ^b	P90390

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Table 5. Lot Genealogy with RNA Integrity and LMS Levels

LNP Site	DP Lot #	F/F Site	LMS	RNA Integrity	ALC-0315 Mfr	ALC-0315 Lot #	ALC-0159 Mfr	ALC-0159 Lot #	DSPC Mfr	DSPC Lot #	Cholesterol Mfr	Cholesterol Lot #
DMP	EK4175	Puurs	16%	58%	Croda	1760275	Avanti	ALC015 9-106	Avanti	1-01 DSPCII S-111	Avanti	SCHOLB-105
DMP	EJ1691	Puurs	24%	51% ^a	Croda	1760275	Avanti	ALC015 9-106	Avanti	DSPCII S-111	Avanti	SCHOLB-105
KZO	EK5730	KZO	10%	62%	Croda	DTP/465 /3	Avanti	ALC015 9-105	Avanti	DSPCII S-112	Avanti	SCHOLB-105
DMP	EL0140	Puurs	6%	69%	Croda	1755889	Avanti	ALC015 9-106	Avanti	DSPCII S-111	Avanti	SCHOLS-129
PLY	EL0142	Puurs	6%	69%	Croda	1755889	Avanti	ALC015 9-106	Avanti	DSPCII S-111	Avanti	SCHOLS-129
PLY	EL0141	Puurs	5%	67%	Croda	1755889	Avanti	ALC015 9-104	Lipoid	556500-220042 1-01	Wilshire ^b	P90390
Puurs	EL0725	Puurs	9%	63%	Croda	DTP/465 /3	Avanti	ALC015 9-106	Avanti	DSPCII S-112	Avanti	SCHOLS-129
DMP	EK4237	Puurs	9%	64%	Croda	1755889 and 1760275	Avanti	ALC015 9-107	Avanti	DSPCII S-111	Avanti	SCHOLS-129
Puurs	EL0739	Puurs	6%	67%	Croda	DTP/465 /3	Avanti	ALC015 9-106	Avanti	DSPCII S-112	Avanti	SCHOLB-105

a. does not meet the tightened DP RNA Integrity release specification, not intended for emergency supply

b. Wilshire is now Evonik.

c. QL=quantitation limit (3%).

QL= quantitation limit, DMP = Dermapharm, PLY = Polymun, KZO = Kalamazoo, LMS = late migrating species, LNP = lipid nanoparticle, F/F = fill/finish

QUERY 7

Your investigation regarding the identity of the LMS is based on the evaluation of one DP engineering lot (EG5411). Please provide similar data for other impacted DP lots. In addition, please provide data to support that the presence of LMS peak will have no impact on the stability profile of DP.

RESPONSE 7

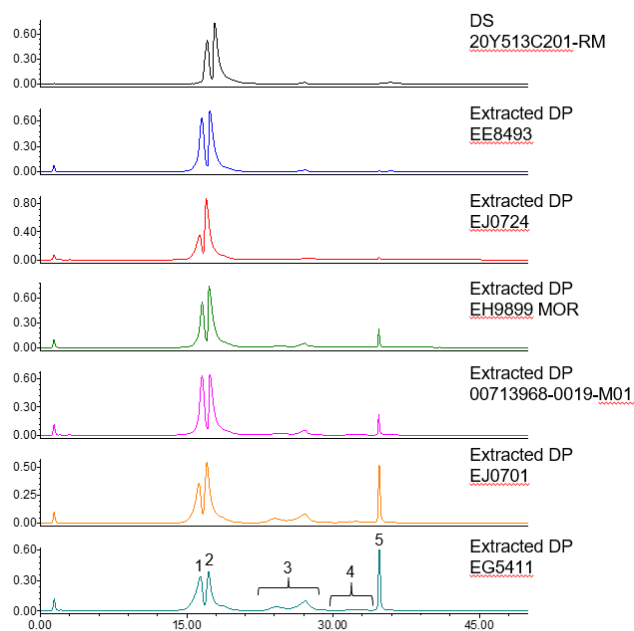
Characterization of additional DP lots are summarized below.

Table 6. Characterization of LMS in DP Lots in addition to EG5411

Characterization Method	Lots (release LMS result)	Conclusion
IP-RP-HPLC (Figure 2)	EE8493 (< QL), EJ0724 (< QL), 00713968-0019-M01 (6%), EJ0701 (17%)	Similar to EG5411, the same late-eluting peaks in IP-RP-HPLC are observed at elevated levels in DP lots with elevated LMS
Nucleoside and nucleotide analysis by LC/MS/MS (Figure 3, Table 3, Table 4)	EE8493 (<QL), EJ0553 (<QL), EJ0724 (<QL), 00713968-019-M01 (6%), EJ0701(17%), EH9978 (35%)	Similar to EG5411, for all tested lots with or without reportable levels of LMS, up to 35%, the expected nucleosides and nucleobases are present, with no detectable modifications greater than 0.01% (reportable limit), besides the intended single 3'-O-methylated 7-methylguanosine and 2'-O-methylated adenosine in the 5'-Cap structure

00713968-019-M01 is a small scale development lot. EH9978 is an early engineering lot. Other DP lots are described in Table 1. QL= quantitation limit (3%)

In addition to the characterization data presented in P.2 on engineering lot EG5411, additional data has been collected by the orthogonal ion-pairing RP-HPLC (IP-RP-HPLC) method presented in P.2 on other representative lots ([Figure 2](#)). Similar to EG5411, the lots that have late migrating species by CGE (EJ0701 and 00713968-0019-M01, a small scale development lot with 6% late migrating species) also contain elevated levels of the same late-eluting peaks, as compared to the lots without reported late migrating species (EE8493, EJ0724). As summarized in P.2, the late eluting peaks from IP-RP-HPLC were characterized by UV multi-angle light scattering (MALS) detection, denaturing agarose gel electrophoresis (AGE), and mass spectrometry (MS). The late eluting peaks were characterized as RNA of the expected size that is conformationally folded or reversibly aggregated RNA and is not denatured in the sample preparation of the CGE method.

Figure 2. Ion Pairing RP-HPLC of RNA Extracted from Drug Product Lots

DS 20Y513C201-RM is the DS reference material. EH9899 MOR is an in-process sample for the DP lot EH9899. 00713968-019-M01 is a small-scale development lot. Other DP lots are described in Table 1. Based on characterization of the collected IP-RP-HPLC fractions, peak 1 contains fragments, peak 2 contains mostly intact RNA, while peaks 3-5 are correlated with LMS.

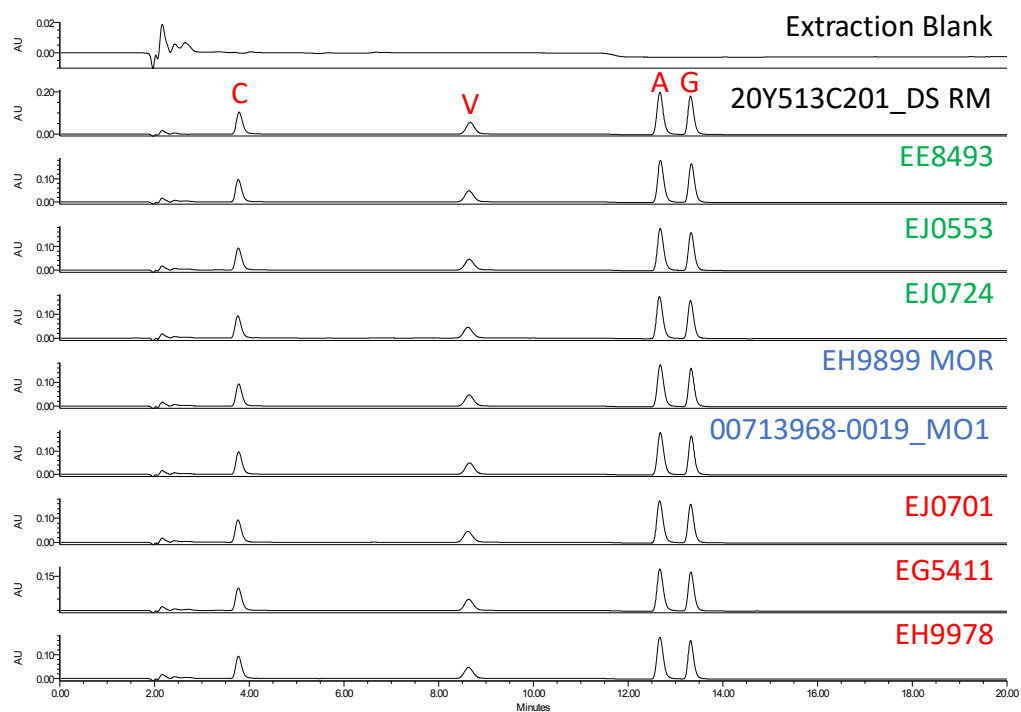
In addition to analysis of additional lots by IP-RP-HPLC, nucleoside analysis by LC-UV with online tandem mass spectrometry (MS/MS) was performed on additional lots that have elevated levels of late migrating species, EH9978 and EJ0701, for further confirmation that these lots consist of RNA without detectable modification. Lot EH9978 is an early engineering lot (similar to EG5411) with high levels of LMS (35%); EH9978 does not meet the RNA integrity specification but was used for characterization purposes. Nucleoside analysis involved digestion of DS control and extracted RNA from DP lots with nuclease P1 and venom phosphodiesterase at low and high pH, respectively, and then alkaline phosphatase to remove the phosphate group. The resulting nucleosides were separated by reversed-phase ultrahigh performance liquid chromatography with UV detection at A260 nm using an extended gradient in case of potential modified residues (Figure 3). Each nucleoside displays an elution position and well resolved peak that is consistent between all DP lots and the DS control. The observed accurate monoisotopic masses for each respective peak were consistent with the theoretical masses of the four expected nucleosides from BNT162b2 mRNA (Table 7). The corresponding observed masses of the predominant fragment ions representing the four nucleobases also agreed with the theoretical masses indicating no base modifications (Table 8). These data confirm that like EG5411, a lot with higher levels of late migrating species, that the expected nucleosides and nucleobases are present, with no detectable modifications greater than 0.01% (reportable limit), besides the intended single 3'-O-methylated 7-methylguanosine and 2'-O-methylated adenosine in the 5'-Cap structure (the relative abundances of 2'-O-methylated adenosine in 5'-Cap structure range from 0.24 to 0.42% in the DP lots, similar to DS at 0.37%).

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Figure 3. Analysis of Nucleosides in Additional BNT162b2 DP Lots by LC-UV-MS/MS (A260 nm)



BNT162b2 nucleosides: cytidine (C); N1-methylpseudouridine (V); adenosine (A); guanosine (G)

Table 7. Accurate Mass Assignments of Nucleosides for Additional BNT162b2 DP Lots via LC-UV/MS

Nucleoside	Theoretical Mass	DS Reference Material	DP Lots						Engineering Run DP Lots	
		20Y513C201	EE8493	EJ0553	EJ0724	EH9899 MOR	00713968-0019 MOI	EJ0701	EG5411	EH9978
Cytidine (C)	244.0928	244.0925	244.0926	244.0926	244.0926	244.0927	244.0926	244.0925	244.0925	244.0925
N1-methylpseudouridine (V)	259.0925	259.0922	259.0922	259.0921	259.0922	259.0922	259.0923	259.0923	259.0922	259.0923
Adenosine (A)	268.1040	268.1036	268.1036	268.1036	268.1036	268.1037	268.1036	268.1037	268.1037	268.1036
Guanosine (G)	284.0989	284.0988	284.0986	284.0988	284.0987	284.0988	284.0988	284.0988	284.0988	284.0988

Observed masses (monoisotopic) agree with theoretical masses to within 5 ppm, which is consistent with the accuracy and precision of contemporary mass spectrometers

Table 8. Accurate Mass Assignments of Nucleobases for Additional BNT162b2 DP Lots via LC-UV-MS/MS

Nucleobase (derived from respective diagnostic fragment ions)	Theoretical Mass	DS Reference Material	DP Lots						Engineering Run DP Lots	
		20Y513C201	EE8493	EJ0553	EJ0724	EH9899 MOR	00713968-0019 MOI	EJ0701	EG5411	EH9978
Cytosine (C)	112.0511	112.0505	112.0502	112.0503	112.0502	112.0502	112.0503	112.0504	112.0503	112.0504
N1-methylpseudouridine (V)	139.0508	139.0500	139.0499	139.0501	139.0501	139.0500	139.0500	139.0500	139.0500	139.0501
Adenine (A)	136.0623	136.0617	136.0615	136.0615	136.0617	136.0618	136.0615	136.0616	136.0616	136.0616
Guanine (G)	152.0572	152.0564	152.0564	152.0564	152.0564	152.0564	152.0565	152.0565	152.0565	152.0566

Observed masses (monoisotopic) agree with theoretical masses to within 10 ppm, which is consistent with the accuracy and precision of MS/MS in contemporary mass spectrometers

Taken together, these data confirm that the late migrating species observed in additional lots is the same as the EG5411 late migrating species used for detailed characterization, and the additional MS characterization of enzymatically digested RNA confirm the presence of expected nucleosides in additional lots with LMS. The LMS has been characterized as conformationally folded or reversibly aggregated RNA that is not denatured in the CGE method. Lots that are within the RNA integrity specification have comparable in vitro expression as previously shown in P.2, Enhanced Characterization. The CGE method controls both LMS and fragments with a specification limit on the intact RNA species (RNA integrity).

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The vaccine drug product is stored at a temperature of -70 °C. Emergency supply DP lots are currently or will be enrolled in formal stability studies (Table 9) . Formal results of these studies will be provided as they become available.

Table 9. Representative Stability Study Design

Study Condition	Storage Temperature	Time Points	Analytical Procedures
Long Term	-90 to -60 °C	0, 1M, 3M, 6M, 9M, 12M, 18M, 24M	• Appearance • Potentiometry • Dynamic Light Scattering (LNP Size Polydispersity) • Fluorescence Assay (RNA Encapsulation, Content) • HPLC-CAD (Lipid Content) • Cell-based Flow Cytometry (In vitro expression) • Capillary Gel Electrophoresis (RNA Integrity) • Subvisible Particles • Container Closure Integrity Test • Endotoxin • Sterility
Accelerated	-60 to -30 °C	0, 1M, 3M, 6M, 9M, 12M, 18M, 24M	
Accelerated	-20 ± 5 °C	0, 1M, 3M, 6M, 9M, 12M, 18M, 24M	
Accelerated	5 ± 3 °C	0, 1M, 3M, 6M	
Thermal Stress	25 ± 2 °C / 60 ± 5 % RH	0, 1W, 2W, 1M	

Current stability data that provide insight on impact of LMS on stability are available from dilution and administration (DAI) simulation studies. Two BNT162b2 DP lots that contain 9-10 % LMS at release (EJ1685 and EJ1688) were evaluated to demonstrate the product has an acceptable RNA integrity at the time of dosing. The DP lots were removed from -70 °C storage, thawed and held in refrigerated storage (2-8 °C) conditions for at least 5 days plus an additional 2 hours at elevated ambient temperatures (30 °C/75% RH). The DP was then diluted to 0.1 mg/mL with normal saline in the vial and held in contact with either the dosing needles and syringes or in the vial for 6 hours at elevated ambient temperatures (30 °C/75% RH). These conditions cover the maximum allowable storage and handling conditions at the point of use. In addition, the diluted DP was held for 24 hours at elevated ambient temperatures (30 °C/75% RH) in a vial to demonstrate the DP meets the specification beyond the allowable conditions.

RNA integrity was acceptable through the allowed administration time period. The RNA integrity data are presented in [Table 10](#).

Additional data on complete DAI study results from two other lots are provided below ([Table 11](#) and [Table 12](#)). Similar stability behavior of the RNA integrity level was observed, all results met acceptance criteria and showed acceptable product quality.

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In conclusion, the stability profile of the drug product with LMS has been evaluated to confirm acceptable storage and handling through the vaccine point of use, and will continue to be monitored in stability studies. The RNA integrity attribute is a stability indicating assay including for lots that contain LMS, and all lots showed similar stability behavior. The specification for RNA integrity controls both fragment and LMS since both species would lead to lower RNA integrity level. Vials that were thawed for 5 days followed by dilution in saline and a hold at room temperature for up to 6 hours were acceptable; the additional hold of a diluted vial in saline up to 24 hours also met specification including in vitro expression.

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Table 10. RNA Integrity Test Results for the Study Performed with Lots# EJ1685^a and EJ1688^a (0.1 mg/mL in 0.9% Sodium Chloride)

Test		Acceptance Criteria	T0 (5 days 2-8°C and 2 hours at 30 °C)	30 °C/75% RH				
			Vial	3 Hours	3 Hours	6 Hours	6 Hours	24 Hours
				Vial	Polycarbonate Syringe	Vial	Polycarbonate Syringe	Vial
Lot # EJ1685								
RNA Integrity	Fragment Analyzer (CGE)	T0 Vial ± 20% (≥ 50% Intact RNA)	64.8%	64.7%	64.9%	65.1%	64.0%	63.1%
		Report LMS result	9.7%	9.8%	9.8%	10.1%	10.0%	10.9%
Lot # EJ1688								
RNA Integrity	Fragment Analyzer (CGE)	T0 Vial ± 20% (≥ 50% Intact RNA)	61.4%	59.5%	59.8%	58.4%	58.2%	55.8%
		Report LMS result	11.0%	11.2%	11.9%	12.7%	13.0%	14.4%

a. All vials used in this study were held for ≥5 days at 2-8 °C plus 2 hours at 30 °C prior to dilution

Abbreviations: CGE = capillary gel electrophoresis; LNP = lipid nanoparticle

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Table 11. Analytical Test Results for the Study Performed with Lot# EH9899^a (0.1 mg/mL in 0.9% Sodium Chloride)

Test		Acceptance Criteria	T0 (5 days 2-8°C and 2 hours at 30 °C)	30 °C/75% RH				
			Vial	3 Hours	3 Hours	6 Hours	6 Hours	24 Hours
				Vial	Polycarbonate Syringe	Vial	Polycarbonate Syringe	Vial
Appearance	Visual	White to off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension
	Particulate Matter	Essentially Free of Visible Particles (EFVP)	EFVP	EFVP	EFVP	EFVP	EFVP	EFVP
RNA Content	RiboGreen	T0 Vial ± 20%	0.12 mg/mL	0.12 mg/mL	0.12 mg/mL	0.11 mg/mL	0.12 mg/mL	0.12 mg/mL
RNA Integrity	Fragment Analyzer (CGE)	T0 Vial ± 20% (≥50% Intact RNA)	55.4%	54.2%	54.9%	53.8%	53.3%	50.2%
		Report LMS result	10.0%	11.5%	10.9%	11.4%	11.7%	14.6%
RNA Encapsulation	RiboGreen	≥ 80%	95%	94%	94%	94%	95%	95%
LNP Size	Dynamic Light Scattering	40 to 180 nm	67 nm	67 nm	70 nm	70 nm	69 nm	69 nm
LNP Polydispersity	Dynamic Light Scattering	≤ 0.3	0.16	0.16	0.19	0.19	0.18	0.17
In-Vitro Expression	Cell-based Flow Cytometry	≥ 30% positive cells	86%	76%	69%	79%	77%	69%

a. All vials used in this study were held for ≥5 days at 2-8 °C plus 2 hours at 30 °C prior to dilution
 Abbreviations: CGE = capillary gel electrophoresis; LNP = lipid nanoparticle

Table 12. Analytical Test Results for the Study Performed with Lot# EJ0553^a (0.1 mg/mL in 0.9% Sodium Chloride)

Test		Acceptance Criteria	T0 (5 days 2-8°C and 2 hours at 30 °C)	30 °C/75% RH				
				3 Hours	3 Hours	6 Hours	6 Hours	24 Hours
				Vial	Polycarbonate Syringe	Vial	Polycarbonate Syringe	Vial
Appearance	Visual	White to off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension	Off-white suspension
	Particulate Matter	Essentially Free of Visible Particles (EFVP)	EFVP	EFVP	EFVP	EFVP	EFVP	EFVP
RNA Content	RiboGreen	T0 Vial ± 20%	0.10 mg/mL	0.11 mg/mL	0.10 mg/mL	0.10 mg/mL	0.11 mg/mL	0.11 mg/mL
RNA Integrity	Fragment Analyzer (CGE)	T0 Vial ± 20% (≥ 50% Intact RNA)	67.2%	67%	66.3%	66.1%	65.6%	64.2%
		Report LMS result	2.5%	2.3%	2.7%	2.6%	2.4%	2.8%
RNA Encapsulation	RiboGreen	≥ 80%	93%	92%	92%	92%	94%	93%
LNP Size	Dynamic Light Scattering	40 to 180 nm	69 nm	69 nm	74 nm	70 nm	68 nm	76 nm
LNP Polydispersity	Dynamic Light Scattering	≤ 0.3	0.18	0.17	0.18	0.17	0.15	0.19
In-Vitro Expression	Cell-based Flow Cytometry	≥ 30% positive cells	79%	63%	75%	74%	71%	82%

a. All vials used in this study were held for ≥5 days at 2-8 °C plus 2 hours at 30 °C prior to dilution

Abbreviations: CGE = capillary gel electrophoresis; LNP = lipid nanoparticle

REGARDING THE INTRINSIC PARTICLES OBSERVED DURING VISUAL INSPECTION, PLEASE PROVIDE THE FOLLOWING INFORMATION:

QUERY 8

Please clarify the percentage of DP lots that contain the intrinsic visible particles and whether particles occurred only in the most recent DP lots. Please comment on the possible contributing factors that may lead to the formation of these particles.

RESPONSE 8

[Table 13](#) (see Query 9) presents information for drug product lots and includes the inspection method and the percentage of vials that were rejected due to particles during inspection. As can be seen, in 29 out of 33 lots filled and inspected at the Pfizer Puurs and Pfizer Kalamazoo sites including early lots produced, a small number of vials were detected during visual inspection and rejected from the lot due to particles (min 0.01% - max 3.68%). In Pfizer's experience with suspension vaccine products, these rejection rates are not uncommon. The particles specifically from EJ0553, EG5411 (bulk DP lot EG5477, Pfizer Puurs) and EH9899 (bulk DP lot EH9783 Pfizer Kalamazoo) were characterized and identified as product related and most likely comprised of lipids and cholesterol components, as assessed by FTIR spectra. When a vial with particles was diluted with 1.8 mL of sterile 0.9% sodium chloride, Inj., mixed and the resulting solution drawn into a syringe, the particles appeared to disperse.

No specific factors have been identified as definitively correlating with nor directly contributing to the formation of these intrinsic particles. Particles have been observed to a varying degree across many lots spanning multiple manufacturing sites, including four sites of LNP production and two fill finish sites, as listed in [Table 13](#) and across different lipid sources (vendors and batches) as listed in [Table 14](#). Particles have been observed in the sterile holding vessel post-sterile filtration and before aseptic filling. Particles are light in density and have a tendency to float. Because sterile bulk drug product flows from the bottom of the vessel to the filling line, floating particles tend to be observed more frequently in vials filled towards the end of the filling process.

Literature References

None

SUPPORTING DOCUMENTATION

None

QUERY 9

For all lots that contain the visible intrinsic particles, please submit data on the percentage of vials that contain the intrinsic particles (for example, through data obtained from the 100% automated/manual inspection).

RESPONSE 9

Previously submitted Section P.2 Pharmaceutical Development, Table P.2-17 Drug Product Lot Genealogy and Usage is amended below as [Table 13](#) with the inspection method (100% manual or 100% automated) and the percentage of vials that were rejected due to particles during inspection. Information is presented for lots where fill finish was conducted at either Pfizer Puurs or Pfizer Kalamazoo which are the fill finish sites intended for manufacture of emergency supply and includes lots that are not intended for emergency supply (but are manufactured at the same sites using the essentially the same process). Vials that are rejected due to particles during 100% visual inspection are not reintroduced into the batch and are discarded. The acceptance quality limit (AQL) sampling procedure assesses the robustness of the inspection method, as a statistically determined number of vials that passed the inspection method are reinspected manually. The appearance method and label reflect that after dilution, in the rare case particles are observed prior to administration, the product should not be administered.

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Table 13. Lot Genealogy and Vials Rejected During Visual Inspection for Particles

DP Lot Number (DP Name)	Fill Volume (mL)	Drug Product (DP)		Date of Manufacture	Manufacturing Scale (vials)	Drug Substance Site of Manufacture	Inspection method	% vials rejected during inspection due to particles
		LNP Site (Process)	Fill/Finish Site					
CTM10.4 BCV40720-P/ ED3938	0.2	Polymun Scientific (Classical)	Pfizer Puurs (S2F2)	16 Jul 2020	19,010	BioNTech	100% Manual Visual Inspection	0.06%
CTM11 BCV40820-P/ EE3813	0.2	Polymun Scientific (Classical)	Pfizer Puurs (S2F2)	29 Jul 2020	30,193	BioNTech	100% Manual Visual Inspection	0.02%
CTM12 BCV4/L05 EE8492	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	05 Aug 2020	67,665	Pfizer Andover	100% automated inspection at IL7	0.41%
CTM13 BCV4/L06 EE8493	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	05 Aug 2020	68,445	Pfizer Andover	100% automated inspection at IL7	0.06%
CTM14 BCV4/L07 EJ0553	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	25 Sep 2020	164,580	Pfizer Andover	100% automated inspection at IL7	0.34%
BCV4/L08 EJ1685	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	05 Oct 2020	159,315	BioNTech; Rentschler	100% automated inspection at IL7	0.16%
BCV4/L09 EJ1686 (BNT162b2)	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	07 Oct 2020	147,615	BioNTech; Rentschler	100% automated inspection at IL7	0.04%
BCV4/L10 EK1768 (BNT162b2)	0.45	Polymun Scientific (Upscale)	Pfizer Puurs (WSL5)	16 Oct 2020	141,960	Pfizer Andover	100% automated inspection at IL7	0.30%
EG5411	0.45	Pfizer Puurs	Pfizer Puurs (FC2)	3 Sep 2020	201,258	Pfizer Andover	100% automated inspection at Innoscan	0.29%
EJ0701	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 18)	26 Sep 2020	200,265	Pfizer Andover	100% Manual Visual Inspection	0%
EH9978	0.45	Pfizer Puurs	Pfizer Puurs (FC2)	23 Sept 2020	304,869	Pfizer Andover	100% automated inspection at Innoscan	1.30%

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Table 13. Lot Genealogy and Vials Rejected During Visual Inspection for Particles

DP Lot Number (DP Name)	Fill Volume (mL)	Drug Product (DP)		Date of Manufacture	Manufacturing Scale (vials)	Drug Substance Site of Manufacture	Inspection method	% vials rejected during inspection due to particles
		LNP Site (Process)	Fill/Finish Site					
EJ0724	0.45	Dermapharm	Pfizer Puurs (WSL5)	29 Sep 2020	39,195	BioNTech; Rentschler	100% automated inspection at IL7	0.01%
EH9899	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 8)	7 Oct 2020	179,400	Pfizer Andover	100% automated inspection	0.01%
EJ1688	0.45	Dermapharm	Pfizer Puurs (WSL5)	12 Oct 2020	150,345	BioNTech; Rentschler	100% automated inspection at IL7	0.06%
EK4176	0.45	Polymun	Pfizer Puurs (WSL5)	16 Oct 2020	131,625	BioNTech; Rentschler	100% automated inspection at IL7	0.03%
EK4175	0.45	Dermapharm	Pfizer Puurs (WSL5)	12 Oct 2020	145,275	BioNTech; Rentschler	100% automated inspection at IL7	0.09%
EJ1691	0.45	Dermapharm	Pfizer Puurs (WSL5)	16 Oct 2020	133,575	BioNTech Rentschler	100% automated inspection at IL7	1.17%
EK2808	0.45	Puurs	Pfizer Puurs (VC2)	19 Oct 2020	48,945	BioNTech Rentschler	100% automated inspection at Innoscan	0.57%
EK5730	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 8)	22 Oct 2020	191,295	Pfizer Andover	100% automated inspection	0.09%
EL0140	0.45	Dermapharm	Pfizer Puurs (WSL5)	29 Oct 2020	155,610	BioNTech; Rentschler	100% automated inspection at IL7	0.52%
EL0142	0.45	Dermapharm	Pfizer Puurs (WSL5)	29 Oct 2020	138,060	BioNTech; Rentschler	100% automated inspection at IL7	0.81%
EL0141	0.45	Polymun	Pfizer Puurs (WSL5)	29 Oct 2020	156,195	BioNTech; Rentschler	100% automated inspection at IL7	0.15%
EL0725	0.45	Puurs	Pfizer Puurs (FC2)	30 Oct 2020	272,073	BioNTech; Rentschler	100% automated inspection at Innoscan	1.20%
EK9231	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 18)	4 Nov 2020	230,685	Pfizer Andover	100% automated inspection	0.02%
EK4237	0.45	Dermapharm	Pfizer Puurs (WSL5)	5 Nov 2020	140,985	BioNTech; Rentschler	100% automated inspection at IL7	3.68%
EL0739	0.45	Puurs	Pfizer Puurs (FC2)	3 Nov 2020	294,239	BioNTech; Rentschler	100% automated inspection at Innoscan	1.34%

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Table 13. Lot Genealogy and Vials Rejected During Visual Inspection for Particles

DP Lot Number (DP Name)	Fill Volume (mL)	Drug Product (DP)		Date of Manufacture	Manufacturing Scale (vials)	Drug Substance Site of Manufacture	Inspection method	% vials rejected during inspection due to particles
		LNP Site (Process)	Fill/Finish Site					
EL1484	0.45	Puurs	Pfizer Puurs (FC2)	4 Nov 2020	277,608	BioNTech; Rentschler	100% automated inspection at Innoscan	0.58%
EL1283	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 18)	11 Nov 2020	245,895	Pfizer Andover	100% automated inspection	0%
EL1284	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 18)	17 Nov 2020	214,305	Pfizer Andover	100% automated inspection	0%
EL3246	0.45	Pfizer Kalamazoo	Pfizer Kalamazoo (Line 8)	19 Nov 2020	204,360	Pfizer Andover	100% automated inspection	0%
EJ6795	0.45	Puurs	Pfizer Puurs (FC2)	12 Nov 2020	282,645	Pfizer Andover	100% automated inspection at Innoscan	0.89%
EJ6796	0.45	Puurs	Pfizer Puurs (FC2)	13 Nov 2020	293,828	Pfizer Andover	100% automated inspection at Innoscan	0.58%
EJ6797	0.45	Puurs	Pfizer Puurs (FC2)	17 Nov 2020	293,526	Pfizer Andover	100% automated inspection at Innoscan	0.48%

COVID-19 Vaccine (BNT162, PF-07302048)

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Response to 20-Nov-2020 FDA Query

Literature References

None

SUPPORTING DOCUMENTATION

None

Previously submitted supporting documentation

[Section P.2 Pharmaceutical Development \(modRNA\)](#), SN0137

QUERY 10

Please identify the source of the lipids used for the impacted DP lots.

RESPONSE 10

Previously submitted Section P.2 Pharmaceutical Development, Table P.2-18. Lipids Used in BNT162b2 Drug Product Manufacture is amended below as [Table 14](#) with the inspection method and the percentage of vials that were rejected due to particles during inspection (same data as in [Table 13](#)). It now lists for each DP lot, the lipid lots used during manufacturing, the related inspection method and percentage of vials rejected due to particles. No correlation is observed between the frequency of vials with particles and the lipid lots used.

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Table 14. Lipids Used in BNT162b2 Drug Product Manufacture^a

Drug Product Lot	ALC-0315		ALC-0159		DSPC		Cholesterol		Inspection method	% vials rejected during inspection due to particles
	Manufacturer	Lot Number	Manufacturer	Lot Number	Manufacturer	Lot Number	Manufacturer	Lot Number		
BCV40720-P /ED3938	Avanti	GALC0315-10 GALC0315-11	Avanti	GALC0159-11	Lipoid	556500-2190388-01	Wilshire ^b	P60349	100% Manual Visual Inspection	0.06%
BCV40820-P /EE3813	Avanti	GALC0315-12	Avanti	GALC0159-11	Lipoid	556500-2190395-01	Wilshire	P60349	100% Manual Visual Inspection	0.02%
BCV4/L05 /EE8492	Avanti	GALC0315-12	Avanti	GALC0159-12	Lipoid	556500-2190395-01	Wilshire	P60349	100% automated inspection at IL7	0.41%
BCV4/L06 /EE8493	Avanti	GALC0315-13	Avanti	GALC0159-12	Lipoid	556500-2190395-01	Wilshire	P90390	100% automated inspection at IL7	0.06%
BCV4/L07 /EJ0553	Avanti	GALC0315-12/ GALC0315-13	Avanti	GALC0159-12	Lipoid	556500-2190395-01	Wilshire	P90390	100% automated inspection at IL7	0.34%
BCV4/L08 /EJ1685	Croda	DTP/465/3	Avanti	GALC0159-12	Lipoid	556500-2180372-01 556500-2200421-01	Wilshire	P90390	100% automated inspection at IL7	0.16%
BCV4/L09 /EJ1686	Croda	DTP/465/3	Avanti	GALC0159-12/ALC0159-104	Lipoid	556500-2200421-01	Wilshire	P90390	100% automated inspection at IL7	0.04%

COVID-19 Vaccine (BNT162, PF-07302048)
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Table 14. Lipids Used in BNT162b2 Drug Product Manufacture^a

Drug	ALC-0315		ALC-0159		DSPC		Cholesterol		Inspection	% vials
BCV4/L10 /EK1768	Croda	1755889	Avanti	ALC0159-104	Lipoid	556500-2200421-01	Wilshire	P90390	100% automated inspection at IL7	0.30%
EG5411	Croda	DTP/465/1	Avanti	GALC0159-12	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at Innoscan	0.29%
EJ0701	Croda	DTP/465/1	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% Manual Visual Inspection	0%
EH9978	Croda	DTP/465/1	Avanti	GALC0159-12	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at Innoscan	1.30%
EJ0724	Avanti	GALC0315-14	Avanti	ALC0159-105	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at IL7	0.01%
EH9899	Croda	DTP/465/3	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection	0.01%
EJ1688	Croda	1755889	Avanti	ALC0159-105	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at IL7	0.06%
EK4176	Croda	1760275	Avanti	ALC0159-104	Lipoid	556500-2200421-01	Wilshire	P90390	100% automated inspection at IL7	0.03%
EK4175	Croda	1760275	Avanti	ALC0159-106	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at IL7	0.09%
EJ1691	Croda	1760275	Avanti	ALC0159-106	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at IL7	1.17%

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Table 14. Lipids Used in BNT162b2 Drug Product Manufacture^a

Drug	ALC-0315		ALC-0159		DSPC		Cholesterol		Inspection	% vials
EK2808	Croda	1760275	Avanti	ALC0159-104	Avanti	DSPCIIS-111	Avanti	SCHOLB-105	100% automated inspection at Innoscan	0.57%
EK5730	Croda	DTP/465/3	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection	0.09%
EL0140	Croda	1755889	Avanti	ALC0159-106	Avanti	DSPCIIS-111	Avanti	SCHOLS-129	100% automated inspection at IL7	0.52%
EL0142	Croda	1755889	Avanti	ALC0159-106	Avanti	DSPCIIS-111	Avanti	SCHOLS-129	100% automated inspection at IL7	0.81%
EL0141	Croda	1755889	Avanti	ALC0159-104	Lipoid	556500-2200421-01	Wilshire	P90390	100% automated inspection at IL7	0.15%
EL0725	Croda	DTP/465/3	Avanti	ALC0159-106	Avanti	DSPCIIS-112	Avanti	SCHOLS-129	100% automated inspection at Innoscan	1.20%
EK9231	Croda	DTP/465/3	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection	0.02%
EK4237	Croda	1755889, 1760275	Avanti	ALC0159-107	Avanti	DSPCIIS-111	Avanti	SCHOLS-129	100% automated inspection at IL7	3.68%
EL0739	Croda	DTP/465/3	Avanti	ALC0159-106	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection at Innoscan	1.34%
EL1484	Croda	DTP/465/3	Avanti	ALC0159-106	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection at Innoscan	0.58%

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Table 14. Lipids Used in BNT162b2 Drug Product Manufacture^a

Drug	ALC-0315		ALC-0159		DSPC		Cholesterol		Inspection	% vials
EL1283	Croda	DTP/465/3	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection	0%
EL1284	Croda	1760275	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection	0%
EL3246	Croda	1760275	Avanti	ALC0159-105	Avanti	DSPCIIS-112	Avanti	SCHOLS-129	100% automated inspection	0%
EJ6795	Croda	1760275	Avanti	ALC0159-104	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection at Innoscan	0.89%
EJ6796	Croda	1760275, DTP/465/3	Avanti	ALC0159-104	Avanti	DSPCIIS-112	Avanti	SCHOLB-105	100% automated inspection at Innoscan	0.58%
EJ6797	Croda	0001781853	Avanti	ALC0159-106	Avanti	DSPCIIS-111	Avanti	SCHOLS-129	100% automated inspection at Innoscan	0.48%

- a. Only lipids used for BNT162b2 manufacture are listed as BNT162b1 is no longer under development.
 b. Wilshire is now Evonik.

COVID-19 Vaccine (BNT162, PF-07302048)

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Response to 20-Nov-2020 FDA Query

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

[Section P.2 Pharmaceutical Development \(modRNA\)](#), SN0137

QUERY 11

For DP lots with visible particles, please provide batch analysis data and stability data to support that there is no impact on DP quality.

RESPONSE 11

As described in the responses to Query 9 and Query 10, visible particles have been observed during 100% inspection in a small number of vials for nearly all DP lots. Therefore, the drug product batch analysis data and stability data previously submitted to the IND are inclusive of lots with visible particles. Future emergency supply DP lots will also be enrolled in formal stability studies and results of all studies will be provided as they become available.

Literature References

None

SUPPORTING DOCUMENTATION

None

COVID-19 Vaccine (BNT162, PF-07302048)

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REGARDING THE DS MANUFACTURING PROCESS:

QUERY 12

At BNT, there will be a hold/transportation step at 2-8°C (from Mainz to Rentschler). However, the duration of this step (“≥ 96”) is not accurate. Please specify the duration of this step.

RESPONSE 12

We acknowledge this inconsistency in the previous submission. The hold/transportation time of the Proteinase K Pool is ≤ 96 h. The corresponding Table S.2.2.-4 in Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls (modRNA) [BNT Mainz and Rentschler] has been corrected.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

[3.2.S.2.2 Description of Manufacturing Process and Process Controls \(modRNA\) \[BNT Mainz and Rentschler\]](#), Replaced

Previously submitted supporting documentation

None

QUERY 13

Regarding the DS manufacture at Pfizer, Andover, please specify the conditions and length of hold time for the filtered DS before being dispensed into EVA containers, if applicable.

RESPONSE 13

The UFDF pool undergoes a bulk final 0.45/0.2 µm filtration into a flexible container. The filtered DS is then mixed, sampled and dispensed into EVA containers. The whole process from bulk filtration to end of dispense into EVA containers takes less than 24 hours as described in Section 3.2.S.2.5 Process Validation and/or Evaluation - Hold Times [Andover]. This is considered continuous processing and not evaluated as hold time.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

[Section S.2.5 Process Validation and/or Evaluation - Hold Times \(modRNA\) \[Andover\]](#), SN0137

QUERY 14

Please describe the target concentrations (both in terms of U/mL and mg/mL) for the active proteins (DNase I, proteinase K, pyrophosphatase, RNase inhibitor, and T7 polymerase) used in the In Vitro Transcription, DNase I Digestion, and Proteinase K Digestion steps.

RESPONSE 14

In Table 15 below, the vendor specifications are provided, as well as the target concentration in the reaction for the active proteins used in the In Vitro Transcription, DNase I Digestion and Proteinase K digestion steps. The vendor formulates the active proteins in units (U) per volume. The concentration in mg/mL is provided by the vendor as report results in CoA for a subset of these enzymes and has not been used to set target concentration for the active proteins. Volumes for the active proteins that are defined in the filing were determined using the target concentration and the target value in the vendor specification.

Below, the vendor specifications are provided, as well as the target concentration in the reaction for the active proteins used in the In Vitro Transcription, DNase I Digestion and Proteinase K digestion steps. The vendor formulates the active proteins in units (U) per volume. The concentration in mg/mL is provided by the vendor as report results in CoA for a subset of these enzymes and has not been used to set target concentration for the active proteins. Target concentrations for the active proteins are defined based on the vendor specifications for activity.

Table 15. Active Proteins Vendor Specification and Target Concentration During In Vitro Transcription, DNase I Digestion and Proteinase K Steps

Raw material	Vendor Specification (U/ μ L solution)	Target Concentration (U/ L starting IVT volume)
RNase inhibitor	40 ± 6	50,000
Pyrophosphatase	0.10 ± 0.02	100
T7 polymerase	200 ± 21	16,000,000
DNase I	50 ± 9	400,000
Proteinase K	≥ 0.600	676

Literature References

None

SUPPORTING DOCUMENTATION

None

QUERY 15

Please provide a description of the process controls implemented during the sanitization, equilibration, and reuse procedure for the ultrafiltration/diafiltration (UFDF) membrane.

RESPONSE 15

The Pfizer, Andover and Rentschler, Laupheim membrane sanitization, equilibration, and reuse procedures are provided below. Process controls described in this section are included in a membrane lifetime protocol that will be provided for the BLA submission.

Pfizer, Andover

Sanitization

For sanitization, an initial WFI flush is performed followed by a 0.5 M NaOH solution flush and recirculation for 60 min through the membrane. Following this sanitization, a subsequent WFI flush is performed prior to determining the normalized water permeability (NWP). The membranes are then stored in 0.1 N NaOH.

Equilibration

Prior to UFDF execution, a WFI flush is performed to remove the 0.1 N NaOH storage solution. Following the WFI flush, the membranes are equilibrated with equilibration buffer. As shown in [Table 16](#), bioburden and endotoxin samples are pulled from the retentate line after equilibration is completed to demonstrate effective microbial control during membrane storage. Furthermore, pH and conductivity are tested for retentate and permeate after equilibration.

Reuse

Membranes intended for re-use are flushed with DS formulation buffer after use and sanitized as described above.

[Table 16](#) below tabulates the process controls implemented for membrane reuse at commercial scale.

Table 16. Routine Process Controls Implemented During the Sanitization, Equilibration, and Reuse procedure (Pfizer, Andover)

Membrane Performance Test
Normalized membrane permeability post commissioning or cleaning (% recovery)
Equilibration retentate: bioburden (CFU/10mL) ^a
Equilibration retentate: endotoxin (EU/mL) ^a
Post diafiltration 2 permeate conductivity (mS/cm)
Post diafiltration 2 permeate pH
UFDF retentate pre-recovery product pool: bioburden (CFU/10mL)
UFDF retentate pre-recovery product pool: endotoxin (EU/mL)
Drug substance residual DNA template (ng DNA/mg RNA)
Step yield (%)

Abbreviations: CFU = colony forming units; EU = endotoxin units; UFDF = ultrafiltration/diafiltration; WFI = water for injection

a. Testing is performed as part of membrane lifetime validation and the testing frequency may be changed after validation is complete

Rentschler, Laupheim

Sanitization

The TFF system and membrane are sanitized pre- and post-use. If the membrane was used before, samples for bioburden and endotoxins are pulled between end of storage and pre-use sanitization.

For sanitization, an initial WFI flush is performed followed by a 1.0 M NaOH solution flush and recirculation for 60 – 65 min through the membrane. Subsequently, the normalized membrane permeability (NMP) is measured. For NMP 0.1 M NaOH is used. The membranes are then stored in 0.1 N NaOH.

Equilibration

Prior to UFDF batch execution, the membranes are equilibrated with equilibration buffer. As shown in [Table 17](#), bioburden and endotoxin samples are pulled from the retentate and permeate line after equilibration is completed to demonstrate effective microbial control during membrane storage. Furthermore, pH and conductivity are tested for retentate and permeate after equilibration.

Reuse

Membranes intended for re-use are flushed with DS formulation buffer after use and sanitized as described above.

[Table 17](#) below tabulates the process controls implemented for membrane reuse at commercial scale.

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Table 17. Routine Process Controls Implemented During the Sanitization, Equilibration, and Reuse Procedure

Step	Process controls
Sanitization	Post storage retentate and permeate: bioburden (CFU/10mL)
	Post storage retentate and permeate: endotoxins (EU/mL)
	Normalized membrane permeability post commissioning (%)
	Pre-use: membrane integrity test
Equilibration	Post equilibration retentate and permeate: bioburden (CFU/10mL)
	Post equilibration retentate and permeate: endotoxins (EU/mL)
	Post equilibration retentate and permeate: pH
	Post equilibration retentate and permeate: conductivity (mS/cm)
Reuse	Normalized membrane permeability post use (%)
	Pre storage: bioburden (CFU/10mL)
	Pre storage: endotoxins (EU/mL)
	Pre storage retentate and permeate: conductivity (mS/cm)

Abbreviations: CFU = colony forming units; EU = endotoxin units;

Literature References

None

SUPPORTING DOCUMENTATION

None

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QUERY 16

Please note that all drug substance process steps must be performed under cGMP conditions. Data to support complete process validation under cGMP conditions must be available at the time of BLA submission.

RESPONSE 16

The sponsor confirms that all drug substance process steps are performed under cGMP conditions. Complete data process validation details will be provided in the BLA.

Literature References

None

SUPPORTING DOCUMENTATION

None

REGARDING THE DP MANUFACTURING PROCESS:

QUERY 17

Please provide a description of the process controls implemented during the sanitization, equilibration, and reuse procedure for the tangential flow filtration (TFF) membrane.

RESPONSE 17

Sanitization/Equilibration

Polymun, Austria and DermaPharm, Germany

Sanitization/Equilibration

The TFF membranes used in the drug product (DP) manufacturing process are currently used once and then discarded. For Polymun, these filters are not supplied gamma irradiated/pre-sterilized. However, for DermaPharm, these filters arrive gamma irradiated/pre-sterilized. In both cases, the filters are sanitized by a flush and recirculation through the TFF membranes with 0.1 N sodium hydroxide (NaOH). The filters are then equilibrated for at least 24 hours with the same NaOH buffer. If the TFF membranes are not used after 24 hours of the initial NaOH sanitization step, the TFF membranes can be stored in 0.1 N NaOH at 2-8 °C.

After this sanitization step, the filters are rinsed with WFI until conductivity of the permeate stream reaches the conductivity of the WFI. For equilibration and pre-conditioning prior to use in DP processing, a citrate buffer flush and recirculation are then performed until a permeate pH of 3.9-4.1 is achieved.

Reuse

A regeneration/reuse process for the TFF membranes in the DP manufacturing process is not currently planned.

Pfizer Puurs, Belgium and Pfizer Kalamazoo, MI, US

Sanitization/Equilibration

The TFF membranes used in the DP manufacturing process are currently used once and then discarded. These filters arrive gamma irradiated/pre-sterilized. As such, a sanitization is not required prior to use. However, a flush/recirculation through the TFF membrane is performed with WFI or citrate buffer, after which a pre-use integrity test is performed with WFI or citrate buffer. If citrate buffer was not used in the prior step, an additional citrate buffer flush and recirculation is performed for equilibration. The TFF membranes are then used for DP processing.

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Reuse

A regeneration/reuse process for the TFF membranes is targeted for implementation in GMP manufacturing of drug product in December 2020. The implementation of a regeneration/reuse procedure will include additional controls including TFF membrane cleaning with $\geq 20\%$ isopropyl alcohol (IPA), WFI and NaOH and a subsequent pre-use sanitization with NaOH as well as additional sampling and testing through a concurrent validation protocol to ensure appropriate membrane performance and microbial and residual carryover control. Performance tests for the concurrent validation protocol for membrane reuse will include but not be limited to those shown in Table 18.

Table 18. Performance Tests Implemented for Concurrent Validation for Membrane Regeneration and Reuse

Membrane Performance Test
Normalized water permeability post commissioning or cleaning (% recovery)
Membrane integrity test
Post-CIP: bioburden
Post-CIP: endotoxin
Post TFF: bioburden (pre-bioburden reduction filtration) ^a
Post TFF: endotoxin (pre-bioburden reduction filtration) ^a
Yield (%)

a. Routine in-process test

Abbreviations: CFU = colony forming units; CIP = clean in place; EU = endotoxin units; TFF = tangential flow filtration

Literature References

None

SUPPORTING DOCUMENTATION

None

REGARDING THE VALIDATION OF ANALYTICAL PROCEDURES:

QUERY 18

In 2.3.1 Introduction p. 4 (Amendment 138; submitted on November 16, 2020), you stated that “the same method and validation information apply to each testing location”. However, the summaries of qualification/validation study results provided thus far (3.2.S.4.3 and 3.2.P.5.3) do not appear to contain site-specific information. Please explicitly specify that the same critical reagents are used for each testing site. If so, please provide data to demonstrate comparable assay performance between testing sites. If different SOPs/critical reagents are used, please provide additional assay validation data.

RESPONSE 18

Additional method validation data are being provided for the BioNTech/Rentschler sites. The test method standard operating procedure numbers for drug substance and drug product testing are listed in [Table 19](#) and [Table 20](#) below. The Pfizer Andover and Chesterfield laboratories perform all drug product testing and drug substance testing for DS manufactured at Pfizer, Andover. The Pfizer laboratories use the same standard operating procedures. Both laboratories were included in the co-validation of the test methods, and the intermediate precision determined through the reproducibility studies were suitable to demonstrate consistent performance. The compendial method verifications were performed at the Chesterfield or Andover site. The Pfizer validation data were provided in Section S.4.3 Validation of Analytical Procedures (modRNA) of SN0137 (submitted 16 November 2020). The BioNTech and Rentschler laboratories perform release and stability testing for drug substance manufactured at BioNTech/Rentschler sites. The site and method of validation are provided in [Table 19](#). The BioNTech/Rentschler validation data are presented in [Table 21](#) to [Table 26](#) (excluding the BioNTech immunoblot validation for dsRNA, which was provided in a previous amendment). For methods which use critical reagents, the same lot or an alternate qualified lot is used across testing sites. The intermediate precision determined in the method validation studies are used to demonstrate consistent assay performance between sites. As indicated in [Table 19](#), all drug substance 5'-Cap and Poly(A) tail testing are performed by Pfizer; all dsRNA testing is performed by BioNTech.

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Table 19. Drug Substance Testing

Quality Attribute	Analytical Procedure	Pfizer			BioNTech/Rentschler		
		Test Method Procedure Number	Verification or Validation Report #	Site Participating in Validation	Test Method Procedure Number	Verification or Validation Report #	Site Participating in Validation
Clarity, Coloration	Appearance	TM100010539	VAL100131145	Verification of compendia	RL-SOP-00984/ RL-SOP-00994	RL-Statement-00084	Rentschler
pH	Potentiometry	TM100010538	VAL100131145	Verification of compendia	RL-SOP-00995	RL-Statement-00084	Rentschler
Content (RNA Concentration)*	Platform UV Spectroscopy	TM100010308	VAL100188111 VAL100121467	Chesterfield, MO	RL-SOP-02645	RL-Report -09484	Rentschler
Identity of Encoded RNA Sequence	RT-PCR	TM100010407	VAL100121706	Co-validation performed at Andover, MA and Chesterfield, MO	TM-072-038	MVR-20-0017	BioNTech, Mainz
RNA Integrity	Capillary Gel Electrophoresis	TM100010392	VAL100122020	Co-validation performed at Andover, MA and Chesterfield, MO	TM-072-039	MVR-20-0018	BioNTech, Mainz
5' - Cap	RP-HPLC	TM100010578	VAL100123137	Co-validation performed at Andover, MA and Chesterfield, MO	NA	NA	NA
Poly(A) Tail	ddPCR	TM100010379	VAL100123048	Co-validation performed at Andover, MA and Chesterfield, MO	NA	NA	NA
Residual Template DNA	qPCR	TM100010388	VAL100121343	Co-validation performed at Andover, MA and Chesterfield, MO	TM-072-028	MVR-20-0007	BioNTech, Mainz
dsRNA	Immunoblot	NA	NA	NA	PAN-0720-K	VAL-2083-VB	BioNTech, IMFS
Bacterial Endotoxin*	Endotoxin (LAL)	TM100010753	VAL100121189	Andover, MA	RL-SOP-00860	RL-Report-09494	Rentschler
Bioburden*	Bioburden	TM100010714	VAL100121185	Andover, MA	RL-SOP-00858	RL-Report-09493	Rentschler

*Performed at Andover, MA and Rentschler as an IPC during DS manufacturing

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Table 20. Drug Product Testing

Quality Attribute	Analytical Procedure	Test Method Procedure Number	Verification or Validation Report #	Site Participating in Validation
Appearance (Visual, Particles)	Appearance	TM100010539	VAL100131145	Verification of compendia
Subvisible Particles	Subvisible particulate matter	TM100010541	VAL100131145 VAL100126212	Verification of compendia
pH	Potentiometry	TM100010538	VAL100131145	Verification of compendia
Osmolality	Osmometry	TM100010540	VAL100131145	Verification of compendia
LNP Size and Polydispersity	Dynamic Light Scattering (DLS)	TM100010649	VAL100123376	Co-validation performed at Andover, MA and Chesterfield, MO
RNA Encapsulation and Content*	Fluorescence assay	TM100010402	VAL100123417	Co-validation performed at Andover, MA and Chesterfield, MO
RNA Integrity	Capillary Gel Electrophoresis	TM100010392	VAL100122020	Co-validation performed at Andover, MA and Chesterfield, MO
Lipid Content and Identity	HPLC-CAD	TM100010322	VAL100123165	Co-validation performed at Andover, MA and Chesterfield, MO
Container Content for injections	Volume of Injections in containers	TM100010614	VAL100131145	Verification of compendia
Identity of encoded RNA sequence	RT-PCR	TM100010407	VAL100121706	Co-validation performed at Andover, MA and Chesterfield, MO
In Vitro Expression	Cell-based flow cytometry	TM100010380	VAL100122803	Co-validation performed at Andover, MA and Chesterfield, MO
Bacterial Endotoxin	Endotoxin	Performed at DP manufacturing site	NA***	Kalamazoo, MI Puurs, Belgium NA
Sterility	Sterility	Performed at DP manufacturing site	NA***	Kalamazoo, MI Puurs, Belgium NA
CCI**	Dye Incursion	TM100010635	RPT-49795, INX100330679	Verification

*Also run as an IPC during DP manufacturing (INX100426408). Supplemental verification performed (VAL100121467)

**Run at T0 for stability batches only

***Verification results pending

(Note: Drug Product In-Process Controls, Sterility, and Endotoxin testing is performed at Pfizer Global Supply (PGS) Drug Product manufacturing sites)

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Table 21. Validation Summary for the UV Spectroscopy Analytical Procedure (BioNTech)

Validation Parameter	Results
Precision – Repeatability (System)	RSD = $\leq 0.36\%$
Precision – Repeatability (Method)	RSD = $\leq 1.21\%$
Precision – Intermediate	RSD = $\leq 2.9\%$
Accuracy	99.0 – 101.1%
Specificity	Clear determination of the analyte in the presence of other substances.
Linearity	Linearity plot is linear by visual inspection Coefficient of determination (R^2) = 0.999
Range	Range (A260) = 0.2 – 1.0
Robustness (prepared sample stability, other)	The method is robust against different lots of cuvettes

Table 22. Validation Summary for the RT-PCR Analytical Procedure for Drug Substance (BioNTech)

Validation Parameter	Results
Specificity	The RT-PCR assay was able to detect RNA from BNT162b2 DS only and there was no cross reactivity with other non-specific RNA products. The positive signal was observed only in the positive control and the BNT162b2 DS samples. No positive signal was found in the non-target samples and negative control.
Robustness: Amplification extension time	The assay was able to detect RNA from DS using amplification extension times of 31, 33, and 35 seconds in the thermocycle profile.

Table 23. Validation Summary for the Capillary Gel Electrophoresis Analytical Procedure for Drug Substance (BioNTech)

Validation Parameter	Results
Precision – Repeatability (System)	RSD = 1.68 %
Precision – Repeatability (Method)	RSD = 0.64 %
Precision – Intermediate	RSD = 1.75 %
Accuracy	Recovery: 100 -102 %
Specificity	Specificity shown. No interference in the area of the RNA peak
Linearity (Concentration)	Linearity plot is linear by visual inspection in the range of 30 – 250 % Coefficient of determination (R^2) = 0.9832
Linearity (Integrity)	Linearity plot is linear by visual inspection in the range of 23.1 – 71.6 % Coefficient of determination (R^2) = 0.999

Table 24. Validation Summary for the qPCR Analytical Procedure (BioNTech)

Validation Parameter	Results
Precision – Repeatability (System)	RSD (level: Ct values) = $\leq 0.7\%$ RSD (level: copies/mL) = $\leq 12.6\%$
Precision – Repeatability (Method)	RSD = 3.5%
Precision – Intermediate	RSD = $\leq 6.4\%$
Accuracy	98-101%
Specificity	Specificity is proven. Specific signal using RNA drug substance in comparison to a negative control sample.
Linearity	Linearity plot is linear by visual inspection Coefficient of determination (R^2) = 0.9974
Detection Limit (DL)	DL = 0.001 pg/mL
Quantitation Limit (QL)	QL = 0.1 pg/mL

Validation for the Bioburden Analytical Procedure (Rentschler)

The validation of the bioburden analytical procedure was performed following the principles described in USP <61>, Ph. Eur. 2.6.12, and JP 4.05 for BNT162b2 drug substance (DS). The method validation (challenge recovery test) challenges the test method to ensure that the test articles are non-inhibitory to the recovery of inoculated microorganisms.

The samples tested for the presence of bioburden are generally expected to be non-bacteriostatic/non-fungistatic, or to be readily neutralized by membrane filtration. To demonstrate this, the bioburden assay was performed with the addition of a microbial inoculum composed of specified organisms (USP recommended). The challenge recovery testing was performed for each test article with each microorganism along with the appropriate inoculum control.

The acceptance criterion for this validation was as follows:

In the presence of the test article, the mean count of each test organism may not differ by a factor greater than 2 from the value of the inoculum control.

Three batches of BNT162b2 DS (target concentration of 2.25 mg/mL), 10 mL in at least duplicates per organism, were tested for the validation of the method.

Table 25. Challenge Recovery Testing Results for Drug Substance (Rentschler)

Batch	Organism	Recovery factor
20E162001 (Rentschler 1071539)	<i>A. brasiliensis</i>	0.8
	<i>B. subtilis</i>	1.0
	<i>C. albicans</i>	0.8
	<i>P. aeruginosa</i>	1.0
	<i>S. aureus</i>	0.8
20E162002 (Rentschler 1071542)	<i>A. brasiliensis</i>	0.9
	<i>B. subtilis</i>	1.2
	<i>C. albicans</i>	0.9
	<i>P. aeruginosa</i>	1.3
	<i>S. aureus</i>	1.0
20E162003 (Rentschler 1071544)	<i>A. brasiliensis</i>	1.3
	<i>B. subtilis</i>	0.9
	<i>C. albicans</i>	1.6
	<i>P. aeruginosa</i>	1.3
	<i>S. aureus</i>	1.4

a. Challenge recovery testing was performed for each test article with each microorganism, as well as corresponding inoculum control in triplicate.

Validation for the Bacterial Endotoxin Analytical Procedure (Rentschler)

The validation of the bacterial endotoxins test, using the kinetic turbidimetric limulus amebocyte lysate (LAL) analytical procedure, for BNT162b2 drug substance (DS) was performed in alignment with the USP <85>, Ph. Eur. 2.6.14 and JP 4.01. The validation focused on the following parameters:

- The criteria for the standard curve must be valid.
- The sample solution must not interfere with the test (e.g. inhibition/enhancement)
- The sample must have a maximum valid dilution (MVD) established.

The MVD is the maximum allowable dilution of the test article at which the endotoxin limit can be determined. The general equation to determine MVD is:

- $MVD = (\text{endotoxin limit}) / (\lambda)$
Where,
 $\lambda = 0.01 \text{ EU/mL}$ (label sensitivity of the lysate)

Three batches of BNT162b2 DS (target concentration, 2.25 mg/mL) were diluted and tested. The inhibition/enhancement acceptance criterion for the spike recovery is 50-200%.

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Table 26. Inhibition/Enhancement Results for BNT162b2 Drug Substance (Rentschler)

Batch Number	Sample Dilution	Spike Recovery (%)	Results (EU/mL)
20E162001 (Rentschler 1071539)	1:100	101	0.5049
		100	0.4985
		110	0.5487
20E162002 (Rentschler 1071542)	1:100	121	0.6079
		113	0.5636
		130	0.6506
20E162003 (Rentschler 1071544)	1:100	115	0.5775
		108	0.5387
		100	0.4979

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

[Section S.4.3 Validation of Analytical Procedures \(modRNA\)](#), SN0137

QUERY 19

Please provide the SOP and validation report for the in vitro expression assay for DP. With continued manufacturing experience, please update the stringency of the specification according to manufacturing process and assay capabilities.

RESPONSE 19

The SOP and validation report for the in vitro expression assay for the drug product are provided with this response. The sponsor acknowledges CBER's request to re-evaluate and update, if necessary, the stringency of the specification according to manufacturing process and assay capabilities.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

Test Method: [TM1000010380](#), new

Validation Report: [VAL100122803](#), new

Previously submitted supporting documentation

None

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QUERY 20

Please note, all analytical assays must be validated prior to BLA submission. Complete validation reports should be submitted to the IND when they are available.

RESPONSE 20

Current validation data have been provided in the IND. The sponsor acknowledges that additional validation data should be provided following transfers of the release and stability methods to the additional commercial testing labs. After these transfers are completed, updated validation reports will be provided.

Literature References

None

SUPPORTING DOCUMENTATION

None

33 Confirmed Lots of Pfizer/BioNTech COVID 19 Vaccine

28 million doses knowingly manufactured without GMP or quality compliance

40,000+ Adverse Events and 1,025+ deaths must be investigated

In My Previous Video

- Do all lots contain “the same” product?
- Found up to 12 times higher lot-to-lot variability in covid vaccines vs seasonal flu vaccines
- Found 1% of lots associated with 80% of adverse event reports for covid vaccines
- Excessive lot-to-lot variability is highly unusual, points to non-compliant manufacturing, and must be investigated.

FDA Good Manufacturing Practices (GMP):

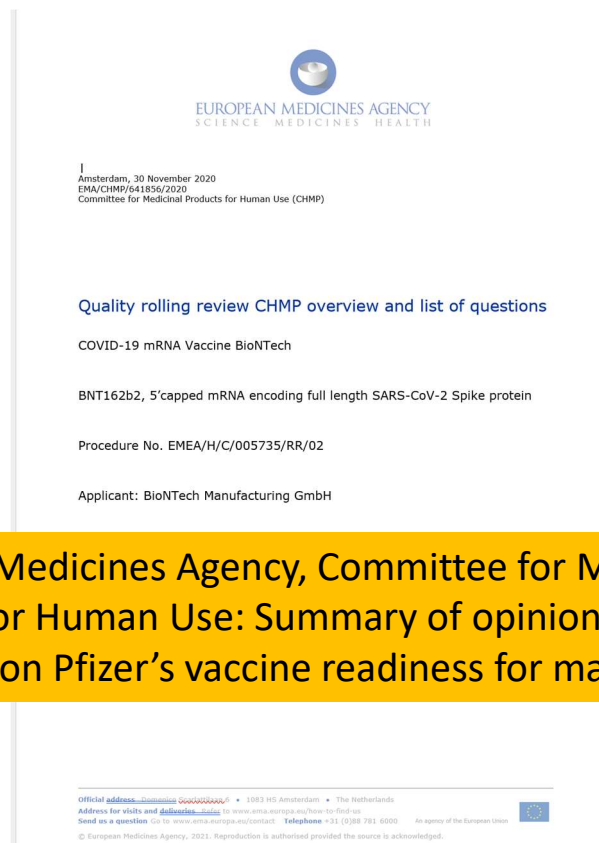
21CFR210.1

- High quality, consistency and purity standards for drugs/vaccines:
 - Expectation that every new lot/batch is “almost the same” as all previous lots
 - Expectation that vaccines from different manufacturers for a disease indication are “the same” or interchangeable product
- Current FDA GMP regulations were developed after several adulterated or poorly tested products poisoned and killed 100s of people (early 1900's to 1960's)
- “The failure to comply ...shall render such drug to be adulterated ...shall be subject to regulatory action”.

2008 Chinese Heparin Adulteration

- Pharmaceutical company [Baxter International](#) subcontracted the creation of precursor chemicals of Heparin to [Scientific Protein Laboratories](#), an American company with production facilities located in China.
- Scientific Protein Laboratories then used counterfeit precursor (OSCS) to create the chemicals ordered. OSCS can be 100 times less expensive to produce than heparin.
- Baxter then sold this adulterated heparin in the US, which killed 81 people, and left 785 severely injured.
- This caught the attention of the media and the [USA Food and Drug Administration](#) leading to numerous ongoing lawsuits.
- The FDA has stated that it does not have the funds nor bear the responsibility to inspect on a regular basis overseas upstream processors of finished active pharmaceutical ingredients such as heparin. However, according to the internationally harmonized guideline, ICH Q7, API manufacturers are fully responsible for qualifying their suppliers through on-site audits, testing, and regular communications.

Pfizer, FDA, and EMA Documents from End of November 2020



European Medicines Agency, Committee for Medicinal Products for Human Use: Summary of opinion from the regulators on Pfizer's vaccine readiness for market use

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Response to CBER Comments Received on 20 November 2020
Regarding Overall CMC Information

25 November 2020

Pfizer's responses to the FDA questions regarding manufacturing quality and compliance with current regulatory requirements

Opinion of the European Regulators:

- Pfizer/BioNTech manufacturing processes (at all sites) were **NOT GMP compliant**:
 - Not able to produce consistent product
 - No plan/deadline as to when they were going be in compliance
- 117 Major Objections and Concerns listed by the regulators on 30+ pages:
 - For any normal product, all would need to be resolved before authorization would happen

If non-GMP compliant production is allowed, ANY ingredient, process, quality control or packaging step of the vaccine can be manipulated, changed, and interfered with accidentally or on purpose!

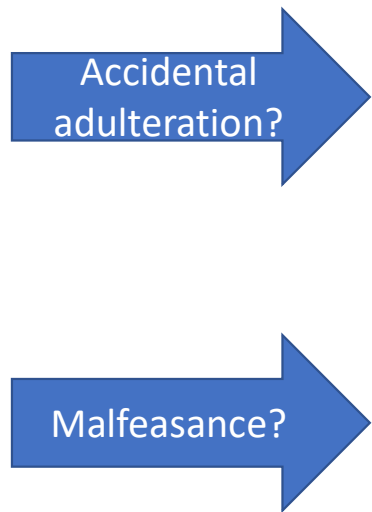
33 Pfizer C19 Vaccine Lots for 28 million doses had been produced before EMA Opinion. They were shipped anyway.

Data From VAERS as of 12/2021

Lot (batch)	# Vials	Date manuf	All AE	Perm Disabil	Life Threat	Deaths
ED3938	19,010	16-Jul-20	-	-	-	-
EE3813	30,193	29-Jul-20	-	-	-	-
EE8492	67,665	5-Aug-20	656	123	9	2
EE8493	68,445	5-Aug-20	597	118	14	2
EG5411	201,258	3-Sep-20	-	-	-	-
EH9899	179,400	7-Oct-20	3,630	45	34	23
EH9978	304,869	23-Sep-20	-	-	-	-
EJ0553	164,580	25-Sep-20	476	74	19	20
EJ0701	200,265	26-Sep-20	-	-	-	-
EJ0724						8
EJ1685						4
EJ1686						8
EJ1688						2
EJ1691						-
EJ6795						17
EJ6796						5
EJ6797						3
EK1768						4
EK2808						-
EK4175						7
EK4176	131,625	16-Oct-20	1,339	39	26	34
EK4237	140,985	5-Nov-20	122	18	1	2
EK5730	191,295	22-Oct-20	4,102	37	40	24
EK9231	230,685	4-Nov-20	3,860	63	46	49
EL0140	155,610	29-Oct-20	1,856	24	28	61
EL0141	156,195	29-Oct-20	499	68	12	14
EL0142	138,060	29-Oct-20	1,802	28	36	42
EL0725	272,073	30-Oct-20	919	68	20	50
EL0739	294,239	3-Nov-20	1,023	131	33	19
EL1283	245,895	11-Nov-20	2,492	48	51	60
EL1284	214,305	17-Nov-20	2,790	40	34	45
EL1484	277,608	4-Nov-20	1,478	152	32	37
EL3246	204,360	19-Nov-20	2,417	54	24	43
Total	5,724,844		40,097	1,614	747	1,025

- 40,000+ Injuries
- 1,600+ Permanent Disabilities
- 747 Life Threatening Events (we don't know if later survived)
- 1,025 Deaths
- Includes 1 death of a child (5yo)

Are Covid-19 Vaccines Adulterated Products?



Without GMP-compliance, we cannot tell what
is in the vials!

Find out more at [HOWBAD.INFO](https://howbad.info)

- Check specific lot numbers for VAERS adverse event reports for US and some EU lot numbers
- View latest videos
- Follow research updates

Toksiske Pfizer vaccinebatches

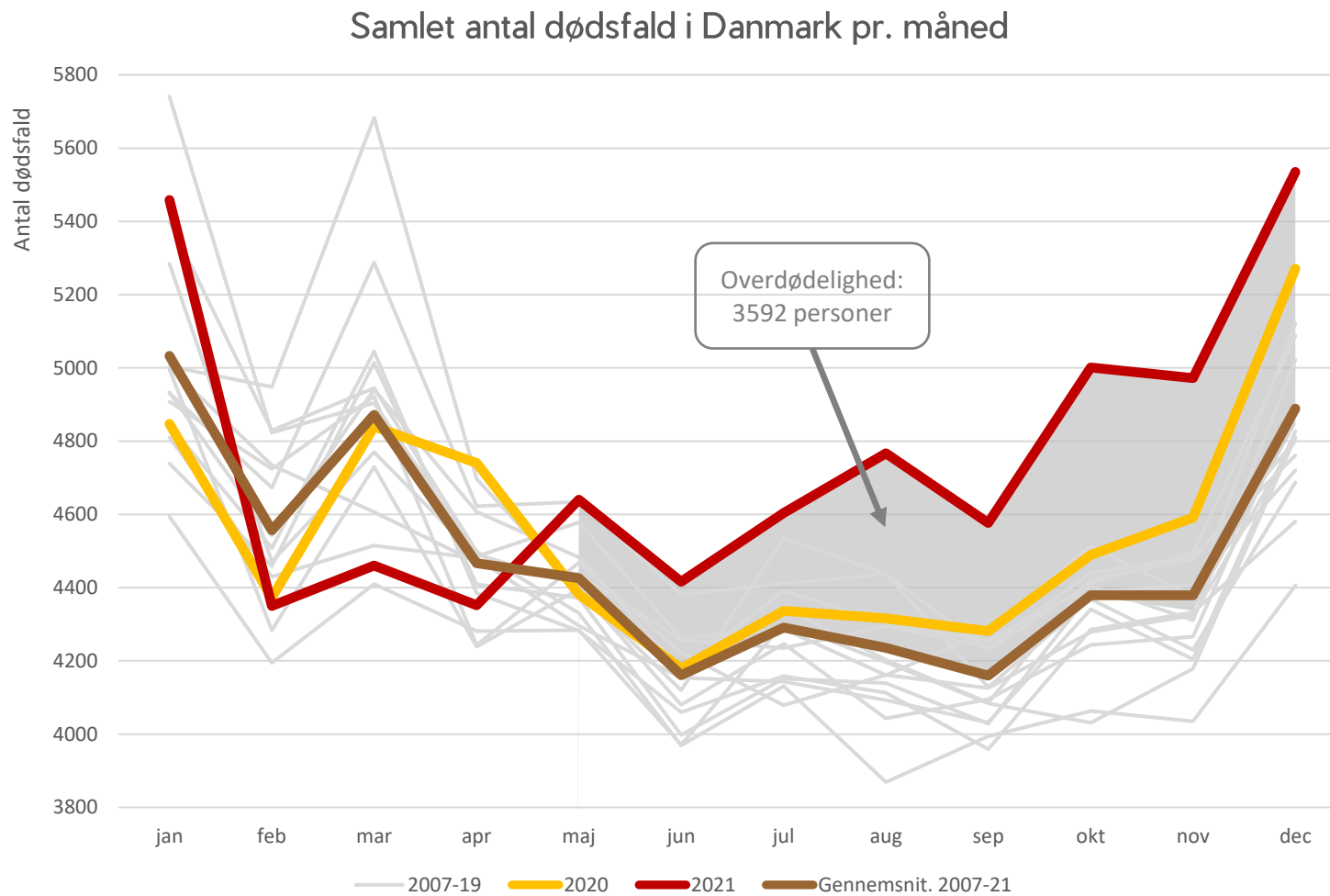
af Max Schmeling, Statistiker / Økonom, Cand.merc.(log)

Liste over Toksiske Pfizer Covid-19 vaccinebatches (opdateret: 12-12-2021)

Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch
EK9788	2410	EE8493	589	FE6975	279	FK0596	126
ER1741	2088	EX8679	582	FC8289	278	EJ0724	126
EM0477	1888	EW8904	575	FE2090	278	EW0203	125
EW4109	1864	EK4243	570	FA2453	276	FF3620	124
EJ6797	1829	EK4244	566	FF0900	273	EN1194	121
ER1749	1719	el8723	564	FF2752	249	EW6327	119
EP9605	1501	EM6950	560	EX2405	249	EK4237	119
ET8885	1481	FC0681	558	FA7338	247	EY7065	117
EW3143	1463	EX3599	531	FE3065	244	FD0350	116
EL1484	1419	FE1573	524	FE8405	243	FE8206	116
FA1027	1212	FD5996	521	FE4728	240	FE4721	114
Ff3319	1162	FC3098	519	FD9309	237	FG4509	113
EJ6134	1162	FE1510	515	FG7387	236	FD0927	113
EM4965	1161	El8713	507	FE7053	236	FE8162	111
EJ6136	1157	FC5089	493	ER9449	230	FF2382	110
EP2163	1106	FC1526	491	FC3661	229	EY0572	105
EJ6788	1099	FA5833	489	FC1131	228	FG3716	104
EW4811	1089	EJ1688	489	FE7051	227	EW0193	104
EW2239	1087	EL0141	473	EK4176	221	EW0221	101
EJ6790	1081	EW2245	472	EY5423	218	EY0583	99
EP9598	1064	FF3318	471	FA5843	214	EW0199	93
ER2659	1056	EX3617	466	FC5295	207	FG0978	91
EJ6789	1024	EX3510	461	FC8736	203	FH0161	90
ET3620	996	FC5435	456	FA5715	203	FC9880	90
FD6840	992	EY3014	450	EW6326	200	FH0151	87
EW6126	992	EY4834	445	FG4686	199	FF9944	86
EJ6795	990	Fe8087	435	FC1440	199	FC5436	86
EP2166	989	ET3045	429	Fh3220	198	FF9942	83
EL0739	988	EY5420	428	FJ5782	198	FE6029	83
ET1831	985	FA4597	428	FG4442	197	FE3064	83
EJ6796	968	FE8244	427	Fg3712	196	FG6270	82
FE6208	963	FC8889	426	EY3860	195	FJ5790	81

Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch	Batchkode	Antal bivirkninger pr. batch
EW2246	963	FF8222	424	EP6775	186	Ek4241	79
FE3380	945	FF8288	424	FG6431	184	fg9019	78
ER9480	941	FE2625	424	FC1439	184	EK4245	75
ET3674	928	FF0688	422	FF2834	183	FD0348	74
FD0168	894	FD0785	419	FD8274	183	FD1945	73
FD4555	889	EJ0553	419	FC1433	179	EY0578	72
EK1768	845	FD9234	410	FC5029	178	FF2018	70
ER7449	837	FE7010	404	Fg3739	177	FA7842	70
EL0725	828	FC3095	403	EY5422	172	FJ7489	67
EW4815	825	FD7958	400	FD0932	169	ET6924	67
ET6956	824	FC2473	387	ER0641	167	EL1406	65
ER9470	821	FA4632	386	EW0201	166	EN1198	64
EX0893	812	EY2172	379	FE7011	162	FC2495	63
ET7205	806	EY0779	378	FF7481	161	FA7478	63
FD8813	793	FF4213	376	FA8142	156	FD7204	62
FD1921	776	FD7959	373	FC5947	151	FA9091	62
EX6537	750	FE2707	372	EY0573	151	FF5357	61
EL1491	727	FA7082	371	FC6984	147	FH3023	59
EY2173	722	FE2296	358	FF3622	145	FG7911	58
EN1185	712	EJ3002	357	FC6997	142	FC9909	58
ER7934	711	FC3558	354	FF2832	141	Ew0206	58
EN3924	704	FA7812	350	fh8469	140	EW0195	58
FA4598	698	ET9096	342	EW0207	139	FF8871	57
FC9001	684	EY7015	340	FC2229	135	Fd7206	56
FA8016	682	FE2083	330	FD0889	133	EW3344	56
EE8492	651	EL7834	330	FA7083	133	FA8721	54
FA5831	649	FE1248	327	FC1435	133	EY0579	53
EX7389	641	EY5456	322	FF0843	131	EP6017	52
EX8680	632	FE9174	312	ER1742	131	Fg7898	51
ER7812	628	FG4493	309	FF2782	130	FA9090	48
FF0680	622	FA5829	309	EX6564	130	FK0108	43
FC2336	612	FF2153	306	FH0114	127	EL0203	43
fd5613	604	EW2243	302	FF4204	127	EX0438	42
Fc3143	596	FE8235	290	Fk0112	127		
EW9127	594	FG6273	288	FC1436	127		
EX7823	594	FA5765	288	EW5279	127		

Overdødelighed 2021 - Samlet antal dødsfald i Danmark pr. måned



Kilde: Danmarks Statistik DODC1¹.

¹<https://www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp?MainTable=DODC1&PLanguage=0&PXSid=0&wsid=cftree>

Guide til reproduktion af resultaterne.

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- Anvend menuen Insert->PivotTable->From DataModel
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- Ved at sortere på Values fås de to første grafer, der viser fordeling. Ved at sortere på Row Labels vises systematikken.

Datafilerne kan også sammenkøres i de fleste statistikpakker, ved at matche på variabelen VAERS_ID i datafilerne.

Åbent brev til:

Folketinget, Epidemiudvalget, Epidemikommissionen,
Sundhedsministeren, Statsministeren, Sundhedsstyrelsen og
Statens Serum Institut

Systematiske forskelle i antal bivirkninger mellem Covid-19 vaccinebatches på op til 5021 gange.

af Max Schmeling, Statistiker / Økonom, Cand.merc.(log)

Jeg henvender mig til dem angående et yderst foruroligende fund af forskelle i antallet af bivirkninger mellem Covid-19 vaccinebatches. Fundene viser at der er op til en faktor 3648 i forskelle mellem antallet af bivirkninger i de enkelte Covid-19 vaccinebatches fra Pfizer. For Moderna er der tale om op til en faktor 5021. Selv om at dette fund i sin alvorlighed skulle synes slemt nok, er situationen langt værre, da der i denne forskellighed i bivirkninger ses en systematik relateret til selve batchnumrene.

Indledning

Jeg arbejder som selvstændig uafhængig økonom og statistisk rådgiver, typisk for analysevirksomheder og mediebureauer og større virksomheder. Disse resultater er kommet til mit kendskab gennem Craig Kooper som er en engelsk, researcher ved Kingston University, London. Fordi implikationerne af resultaterne netop er så alvorlige som er tilfældet, har jeg selv reproduceret og verificeret resultaterne og er kommet til samme konklusion. Vigtigheden at disse resultater kan næppe underdrives, hvilket er grunden til min henvendelse. Resultater i det følgende er udarbejdet af undertegnede.

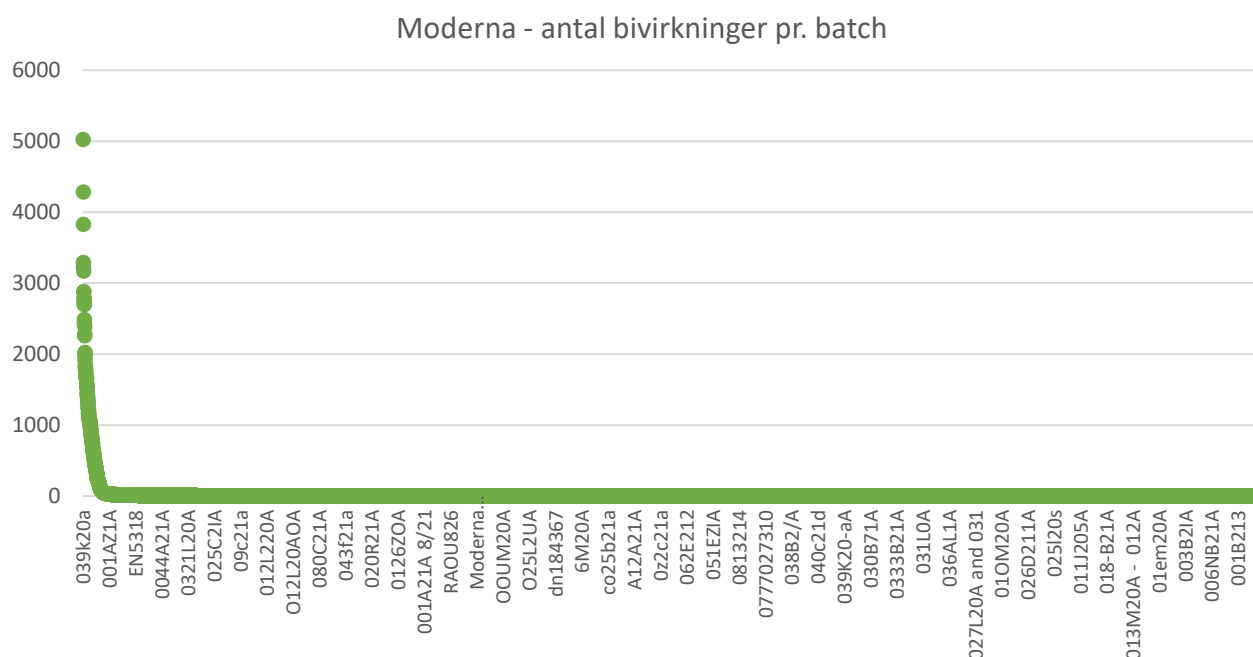
Dataene, der analyseres, er fra den Amerikanske bivirkningsdatabase VAERS¹. Dette fordi at den europæiske bivirkningsdatabase EudraVigilance ikke umiddelbart rapporterer vaccinebatch numre. VAERS databasen er ligesom det danske og europæiske bivirkningsrapporteringssystem begrænset på flere måder. De væsentligste begrænsninger er at systemet er passivt, således at bivirkninger ikke automatisk indsamles, men kræver at en sundhedsfaglig person foretager indberetningen, hvilket leder til andet problem, som er en stor grad af underrapportering. Ingen af disse begrænsninger kan dog antages at påvirke denne analyses resultater nævneværdigt da den bias, begrænsningerne giver må antages at være ens for alle vaccinebatches. Det største problem ved analysen synes faktisk at være at datakvaliteten for vaccinebatchnummeret er påvirket af at indrapporteringen af nummeret sker som fritext og ikke prædefineret. Dette giver noget støj grundet tastefejl. Alligevel er resultaterne tydelige nok til understøtte de viste resultater. Analysens metode er beskrevet i bilag 1, således at denne let kan reproducere.

¹ <https://vaers.hhs.gov/data/datasets.html?>

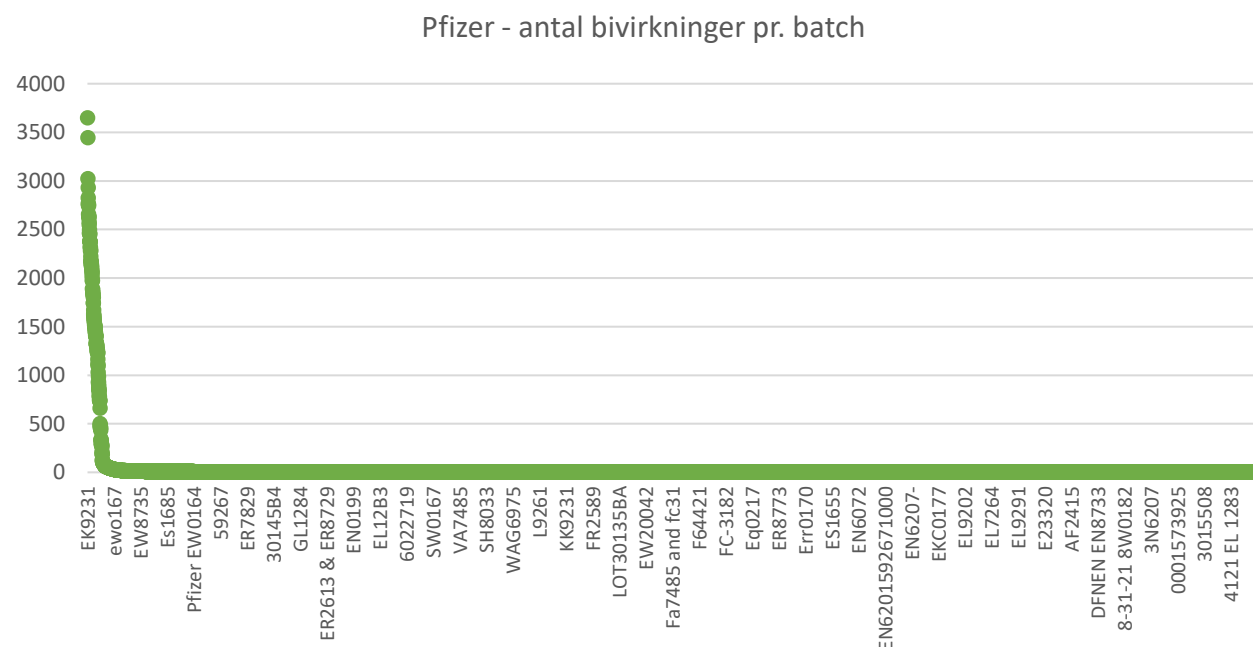
Bivirkninger pr. vaccinebatch

Nedenfor ses antallet af bivirkninger pr. vaccinebatch og sorteret efter antal

Moderna



Pfizer



Som det ses af graferne, er resultaterne ekstremt skævt fordelt. For langt de fleste batches, Pfizer: 95,9% Moderna: 95,6% ses kun op til 10 bivirkninger, men for et mindretal af batchene Pfizer: 4,1% Moderna: 4,4% ses op til Pfizer: 3648, Moderna: 5021 bivirkninger. Det kan altså konstateres, at et mindretal af vaccinebatchene producerer op til 5021 gange flere bivirkninger end hvad man kan kalde baseline. Konsekvenserne af dette resultat er helt åbenbar. **Det er umuligt at give informeret samtykke ifm. vaccination mod COVID-19, da risikoen ganske enkelt ikke kan kendes.** Dermed bliver vaccination mod COVID-19 jfr.

sundhedsloven kapitel 5, §15 formentlig ulovlig. Samtidig vil vaccination under disse forhold stride imod Nürnberg kodekset, specielt punkt 1.

Systematik i forhold til Vaccinebatchnumre

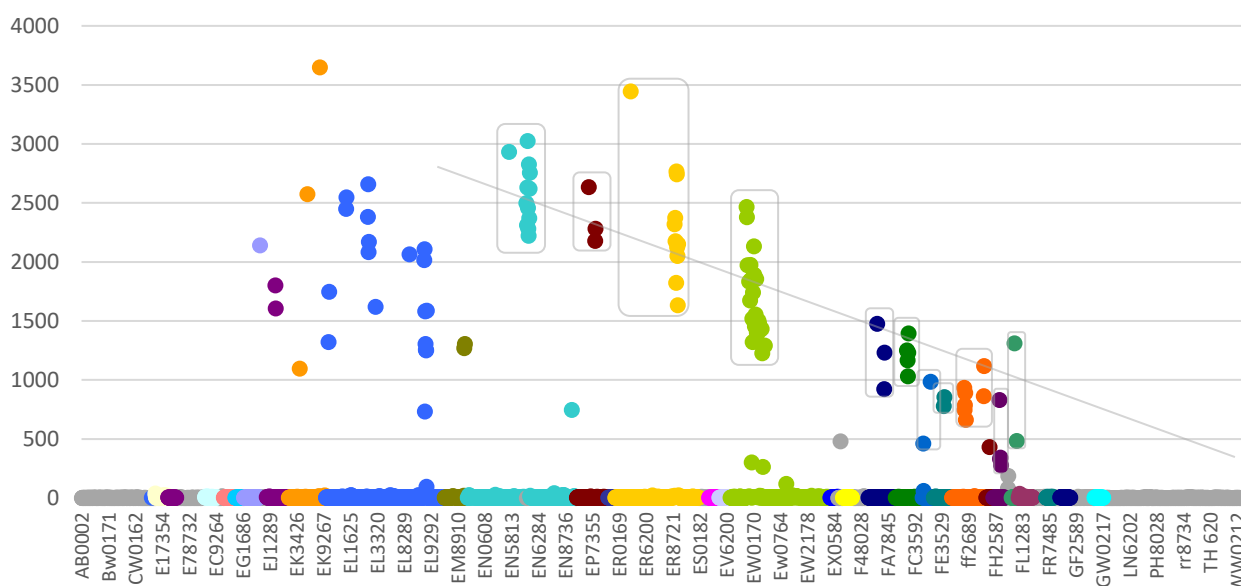
Det antages i det følgende, at vaccinebatchnumre er genereret i en fortløbende nummereret sekvens, indeholdende både bogstaver og tal. Den for Pfizer mest forekommende syntaks er formen AB1234, som består af to bogstaver efterfulgt af 4 tal cifre. Dette er ikke fuldstændigt entydigt i data, bl.a. grundet ovennævnte begrænsninger, men det er tydeligt at denne syntaks er den normale form for batchnummer for Pfizer vaccinen.

I figuren nedenfor, er antallet af bivirkninger pr. batchnummer sorteret alphanumerisk ift., batchnummer meget varierende. Dataene er de samme som ovenfor, med den forskel, at alle batches, som ikke overholder syntaksen ovenfor er fjernet. Dette bevirker, at næsten alle fejl indtastninger fjernes, selv om noget reel data også forsvinder. Billedet er helt identisk uanset om man renser data eller ej, men bliver lidt mere overskueligt ift. farverne i nedenstående graf.

Da dataene er identiske ift. tidligere grafer er det alene relevant at se på systematikken. Farvelægningen er lavet for at adskille de største batchserier ift. bogstavskode. Datapunkterne for de enkelte batches er eks. orange for alle EK##### batches, blå for alle EL##### batches, cyan for alle EN##### batches, osv. Som eksempel kan EN serien (cyan) anvendes. Denne serie består af 320 batches startende med EN0101 og sluttende med EN9899. I EN serien ses 12 batches, der hver har over 2000 bivirkninger pr. batch og for 11 af disse er batchnumrene fortløbende nummereret fra EN6198 – EN6208. Det er helt tydeligt, at vaccinebatches med meget høje antal bivirkninger forekommer som isolerede klynger af batches, der er en del af en større batchserie.

Pfizer – Antal bivirkninger

Antal bivirkninger pr. vaccine batch sorteret efter batchnummer



Dette skaber et tidsrum mellem hver af disse klynger hvor der kun ses vaccinebatches med meget få bivirkninger. Samtidigt ses der, startende med batchserien EN (cyan), klynger af batches med mange bivirkninger, men som klynge for klynge er faldende i niveau. Dette mønster er tydeligt relateret til batchnumrene og dermed kan det konstateres at der er en systematik i fordelingen af batches med

overnormalt antal bivirkninger set i forhold til batchnummeret. Der ses en lignende systematik for Moderna vaccinerne, men denne er ikke bragt her, da Pfizer vaccinen er langt den dominerende vaccine i Danmark.

Alvorligheden af dette resultat kan ikke understreges nok, da det skaber et plausibelt argument for at mønstret repræsenterer et forsøg. Den faldende tendens kan ikke forklares ved at man måske skulle forsøge at justere på visse indholdsstoffer for at mindske bivirkninger, da baseline jo viser at det er det, der produceres i 96% af tilfældene. Ej heller kan tendensen forklares som fejlagtige batches grundet mønstret. Tendensen kunne indikere et dosseringsforsøg, selv om at dette selvfølgelig ikke er muligt at bevise ud fra data. Skulle dette være tilfældet foregår der altså en form for forsøg bag ved vaccineprogrammerne. Så utænkeligt som dette forekommer ser jeg ikke umiddelbart andre forklaringer.

Hvorfor skulle bestemte tætte klynger af vaccinebatches producere op til 3648 gange flere bivirkninger end hovedparten af batches i samme batchserie, samt være organiseret i et blokmønster med faldende antal bivirkninger mellem klyngerne? Tilstedeværelsen af mønstret udelukker tilfældighed som forklaring og hvis det ikke er tilfældigt, så er der en årsag.

Den umiddelbare indvending mod resultatet vil utvivlsomt og naturligt være, at resultaterne ikke er repræsentative for Danmark, da VAERS registrerer bivirkninger i USA, men denne kritik kan uden videre tilsidesættes af flere årsager. For det første er Pfizer vaccinen af samme formulering i både USA og EU, så resultaterne må alene ud fra denne observation være overførbare til Danmark.

Hertil skal tilføjes, at det fremgår af tabel DODC1 fra Danmarks Statistik, at der siden 1. maj 2021 har været en uforklarlig, statistisk signifikant og i forhold til de sidste 15 år, rekordsættende overdødelighed på 2928 personer opgjort måned for måned. Sandsynligheden for denne overdødelighed skulle være et tilfældigt udsving er 0,0000000001%. Der findes dermed et bestyrket mistankegrundlag for at resultaterne fra VAERS også vil kunne findes i de danske bivirkningsdata og man bliver derfor, hvis ikke andet lægges til grund, nødt til at antage at dette er rent faktisk et tilfælde.

Jeg skal derfor indtrængende anmode dem om straks af verificere disse resultater, samt undersøge om tilsvarende resultater findes for det Danske COVID-19 vaccinationsprogram.

Jeg er naturligvis klar over hvilke implikationer dette vil kunne tænkes at få, samt hvor absurd det må forekomme, at forestille sig at skulle stoppe COVID-19 vaccineprogrammet på nuværende tidspunkt. Men forestil dem alternativet. Stil dem selv spørgsmålet om de ville føle dem tryk ved at lade deres eget barn vaccinere? Hvad skal forældre hvis børn ender med svære skader tænke? Hvad ville de selv tænke?

Vi ser samtidig både i Danmark og på verdensplan et hastigt stigende pres på den gruppe af borgere, som ikke har ladet sig vaccinere. I Danmark har statsministeren endda sat sig selv i spidsen for dette pres, mens den danske stat har indgået kontrakter med Pfizer og Moderna der fratager disse for ethvert ansvar. Hvem vil tage ansvaret? Vil de selv tage ansvaret? Hvad vil borgere, der er blevet presset til vaccination med skade til følge gøre?

Personligt finder jeg resultaterne yderst forfærdende, idet at de kan underbygge en opfattelse om at vaccinerne ikke bliver produceret eller givet med et beneficialt formål.

Jeg håber at have leveret tilstrækkelig information til at understrege alvorligheden af denne henvendelse og jeg håber at de vil tage de rigtige valg og iværksætte de relevante initiativer i denne situation idet jeg henviser til de konventioner, der i mange år har sikret vores rettigheder i forhold medicinske behandlinger.

Aarhus d.14.12.2021

Max Schmeling

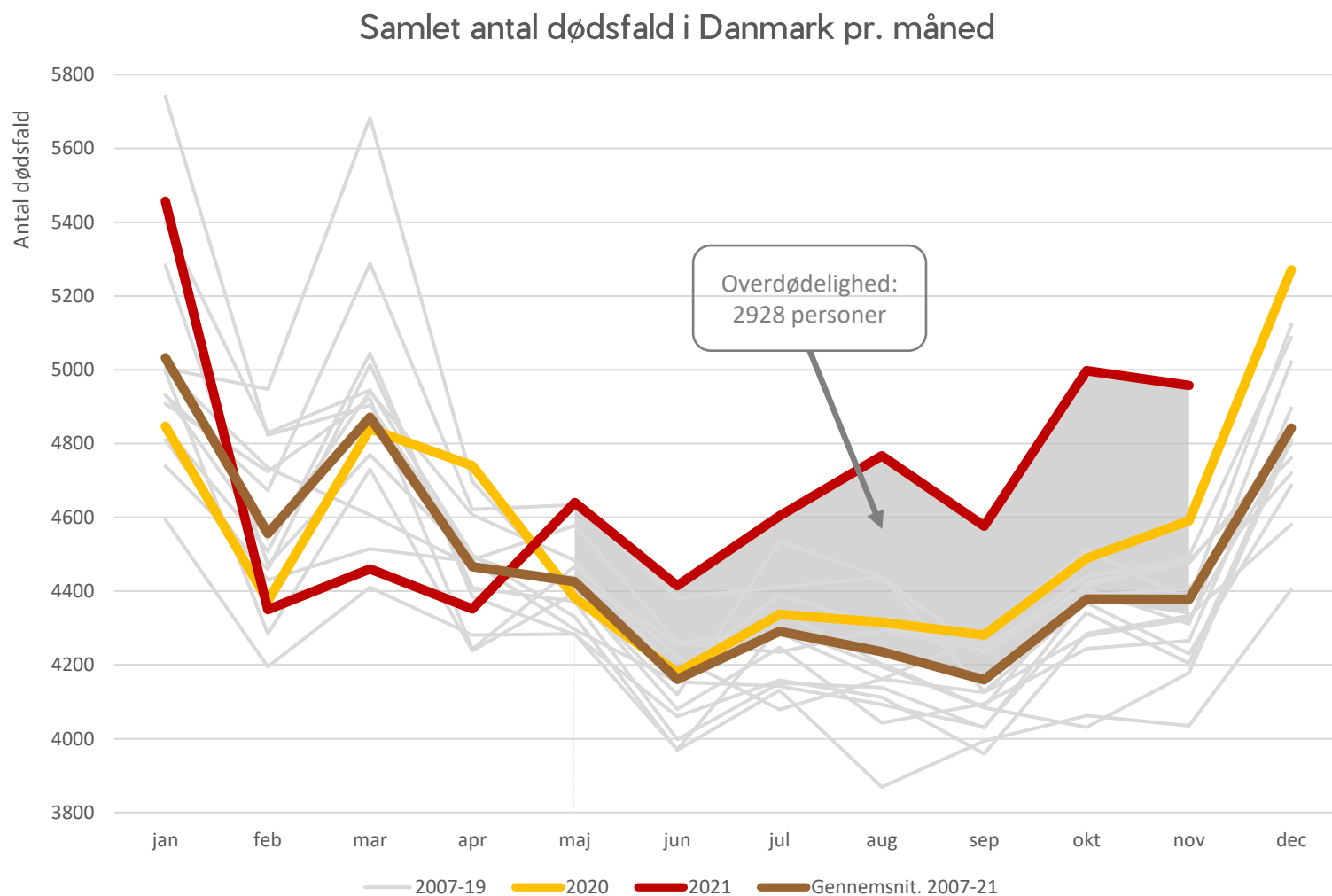
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Bilag 2 – Samlet antal dødsfald i Danmark pr. måned



Kilde: Danmarks Statistik DODC1².

²<https://www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp?MainTable=DODC1&PLanguage=0&PXSID=0&wsid=cftree>