"Exhibit A"

Exhibit A of the Affidavit of Christopher Mark James

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Provisional Consent to the Distribution of a New Medicine

Pursuant to section 23(1) of the Medicines Act 1981, the Minister of Health hereby provisionally consents to the sale, supply or use in New Zealand of the new medicine set out in the Schedule hereto:

Schedule

Product:	**Comirnaty (COVID-19 mRNA vaccine)**
Active Ingredient:	BNT162b2 [mRNA] 0.5mg/mL
Dosage Form:	Concentrate for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturer:	Pfizer Manufacturing Belgium NV, Puurs, Belgium

Note: This consent is given subject to the following conditions:

Provisional consent is to be granted for nine months to address an urgent clinical need.

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, the dates of which may be altered by mutual agreement with Medsafe:

1. Prepare a “Dear Healthcare Professional” letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of this product. Due date: February 2021.

2. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

3. Provide Certificates of Analysis to Medsafe for the first three batches of vaccine intended to be distributed in New Zealand prior to distribution.

4. Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.

5. Provide data to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5’cap levels and presence of the poly(A) tail. These data should also address the potential for translation into truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterisation data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. Due date: July 2021. Interim report: March 2021.

6. Provide the analysis of the main peak of the RNA integrity test representing the full-length RNA, that addresses 5’cap levels and presence of the poly(A) tail. Due date: July 2021. Interim report: March 2021.

7. Provide the reassessment of the active substance specification for the DNA template purity and impurities. Due date: July 2021.

8. Provide active substance process validation data regarding the finalised indirect filter qualification assessment and the shipping validation between sites. Due date: July 2021.

9. Comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance. Due date: July 2021.

10. Provide a discussion of the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterisation of protein expression for the active substance. Due date: July 2021.

11. Provide additional data for the active substance to confirm the identities of the observed western blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. Due date: July 2021. Interim report: March 2021.

12. Provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in the active substance. Due date: July 2021.

13. Reassess and revise the active substance and finished product specifications acceptance limits as further data becomes available from ongoing clinical trials and in-line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. Due date: July 2021. Interim report: March 2021.

14. Introduce an active substance specification to control poly(A) tail length, which is considered a critical attribute and should be controlled on each batch. A suitable method should be developed and appropriate acceptance criteria should be set. Due date: July 2021. Interim report: March 2021.

15. Provide additional data to support the suitability of the method used for %poly(A) tail, or develop and introduce an alternative suitable assay. The %poly(A) tail should be characterised following any future active substance process changes. Due date: July 2021. Interim report: March 2021.

16. Revise the mRNA integrity and polydispersity finished product specifications as further data becomes available from ongoing clinical trials and in-line with manufacturing process capability. Due date: July 2021. Interim report: March 2021.

17. Provide additional data to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. Due date: July 2021. Interim report: March 2021.

18. Lipid-related impurities should be further evaluated and an appropriate control strategy should be introduced, suitably justified and provided for assessment. Due date: July 2021. Interim report (LMS content in commercial FP batches, investigation results): March 2021.

19. Provide the summary report on the completed commercial scale process validation activities, specifically for the PPQ-batches manufactured at the Pfizer Puurs, Belgium commercial facility. Due date: March 2021.

20. Provide test results of future process validation-batches of finished product tested according to the extended comparability testing protocol. Due date: March 2021.

21. Expand the description of the finished product manufacturing process with the following details:

1. when the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated;
2. the configuration of filters used in finished product manufacture;
3. the surface area of the sterile filter should be adapted to the batch size, unless otherwise justified;
4. that process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes.

Due date: July 2021.

22. Provide data that verifies the in-process test methods used for the finished product. Due date: March 2021.

23. Provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation via a Changed Medicine Notification.

24. Provide a risk assessment with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). The control strategy for elemental impurities should be justified based on the risk assessment. Due date: July 2021.

25. Provide updated finished product stability data as it becomes available, including stability data for the process performance qualification batches.

26. Provide a detailed summary of the ALC-0315 manufacturing process completed at the Avanti and Croda manufacturing sites. The differences in manufacture between the two sites will also be clearly detailed. Due date: July 2021. Interim report: February 2021.

27. Provide a detailed description of the ALC-0315 starting materials (including the general synthetic route), the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: July 2021. Interim report: February 2021.

28. Provide a discussion regarding the control of the raw materials for ALC-0315. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials and solvents used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021. Interim report: February 2021.

29. Provide information and justification on critical steps and intermediates (including specifications) for ALC-0315. Due date: July 2021. Interim report: February 2021.

30. Provide a discussion regarding process development for ALC-0315 with emphasis on the identification and purge of impurities. Due date: July 2021.

31. Notify Medsafe of any changes to the ALC-0315 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine Notifications.

32. Further evaluate specified impurities for ALC-0315 and include appropriate specification limits for individual impurities when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. Due date: July 2021. Interim report: April 2021.

33. Update the control of the solvent residues to those that are used in the manufacture of the ALC-0315 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical

method should be detailed and validated where necessary. Due date: July 2021.

34. Update the ALC-0315 assay and impurities limits when additional supporting data is available. Due date: July 2021.

35. Provide detailed method validation reports for assay, impurities, and residual solvents for ALC-0315. Due date: July 2021.

36. Provide ALC-0315 impurity standard information for any identified impurities reported. Due date: July 2021.

37. Provide a retest period and storage condition for ALC-0315 based on stability data. Due date: July 2021. Interim report: April 2021.

38. Provide updated stability data for ALC-0315 manufactured at the Avanti and Croda sites. Due date: July 2021. Interim report: April 2021.

39. Provide a detailed description of the ALC-0159 excipient manufacturing process and yields. This should include the reagents and solvents used, reaction conditions, and in-process controls. If applicable, reprocessing, reworking, and recovery/reuse operations should also be detailed. Due date: February 2021.

40. Provide information regarding the control of ALC-0159 raw materials. This should include the manufacture, qualified suppliers, and quality controls of the starting materials. The in-house controls applied to the raw materials used should also be detailed, as should the control of any potentially genotoxic contaminants. Due date: July 2021. Interim report: February 2021.

41. Provide information and justification on critical steps and intermediates (including specifications) for ALC-0159. Due date: July 2021. Interim report: February 2021.

42. Provide a discussion regarding process development for ALC-0159 with particular emphasis on identification and purge of impurities. Due date: July 2021.

43. Notify Medsafe of any changes to the ALC-0159 manufacturing process and/or suppliers/manufacturers/testing sites using Changed Medicine Notifications.

44. Provide studies on the impact of the molecular weight and polydispersity of carboxy-MPEG on ALC-0159 and include acceptance criteria for these parameters in the starting material, as applicable. Due date: July 2021. Interim report: April 2021.

45. Update the control of the solvent residues to those that are used in the manufacture of the ALC-0159 excipient. The solvents which are not used should be removed from the specifications. Associated changes to the analytical method should be detailed and validated where necessary. Due date: July 2021. Interim report: February 2021.

46. Update the ALC-0159 assay and impurities limits when additional supporting data is available. Due date: July 2021. Interim report: April 2021.

47. Further evaluate specified impurities for ALC-0159 and include appropriate specification limits for individual impurities when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. Due date: July 2021. Interim report: April 2021.

48. Provide detailed method validation reports for assay, impurities and residual solvents for ALC-0159. Due date: July 2021. Interim report: April 2021.

49. Provide impurity standard information for any identified impurities reported for ALC-0159. Due date: July 2021.

50. Provide a retest period and storage condition for ALC-0159 based on stability data. Due date: July 2021. Interim report: April 2021.

51. Provide updated stability data for ALC-0159. Due date: July 2021. Interim report: April 2021.

52. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.

53. Provide the six months analysis data from Study C4591001. Report due: April 2021.

54. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.

55. Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.

56. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.

57. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.

58. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Dated this 3rd day of February 2021.

CHRIS JAMES, Group Manager, Medsafe, Ministry of Health (pursuant to delegation given by the Minister of Health on 11 September 2013).

2021-go338 03-02-2021 13:55

Renewal of Provisional Consent to the Distribution of a Medicine

Pursuant to section 23(4A) of the Medicines Act 1981, the Minister of Health hereby renews the provisional consent to the sale, supply or use in New Zealand of the medicine set out in the Schedule hereto:

Schedule

Product:	**Comirnaty (COVID-19 mRNA vaccine)**
Active Ingredient:	BNT162b2 [mRNA] 0.5mg/mL
Dosage Form:	Concentrate for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturers:	Pfizer Manufacturing Belgium NV, Puurs, Belgium Polymun Scientific Immunobiologische Forschung GmbH, Klosterneuburg, Austria Mibe GmbH Arzneimittel, Brehna, Germany BioNTech Manufacturing Marburg GmbH, Marburg, Germany Baxter Oncology GmbH, Westfalen, Germany Allergopharma GmbH & Co. KG, Reinbek, Germany Novartis Pharma Stein AG, Stein, Switzerland Delpharm Saint Remy, Saint Remy Sur Avre, France

Provisional consent is granted for two years from 3 November 2021.

This consent is given subject to the following conditions:

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
2. Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
3. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
4. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
5. Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.
6. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
7. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
8. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Dated this 28th day of October 2021.

CHRIS JAMES, Group Manager, Medsafe, Ministry of Health (pursuant to delegation given by the Minister of Health on 11 September 2013).

2021-go4666 28-10-2021 12:30

Regulatory Affairs Department Australia/New Zealand
Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Australia

4 November 2021

The Manager
MEDSAFE
Ministry of Health
133 Molesworth Street
Thorndon Wellington 6011
NEW ZEALAND

TT50-10853

Dear Sir/Madam,

New Medicine Application – Additional Strength Grade 5

COMIRNATY (tozinameran) COVID-19 VACCINE 0.5 mg/mL concentrate for injection

- **Extension of Indication: for children 5 to <12 years of age**
- **New Formulation, Strength and Dosage:**
  Tris/Sucrose formulation (0.1 mg/mL) as 30 µg/0.3 mL and 10 µg/0.2 mL

This application seeks provisional consent to extend the indications for COMIRNATY COVID-19 VACCINE to include children 5 to <12 years of age. The proposed indication is:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals **5 years of age** and older. The use of this vaccine should be in accordance with official recommendations.*

COMIRNATY COVID-19 VACCINE concentrate for injection currently has provisional consent for the indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals **12 years of age** and older. The use of this vaccine should be in accordance with official recommendations.*

Renewal of the Provisional Consent for COMIRNATY was Gazetted on 28 October 2021 for two years from 3 November 2021.

This application to extend the indication to include children 5 to <12 years of age is accompanied by Module 3 updates to register a new drug product formulation in two strengths using a tromethamine (Tris) buffer instead of a phosphate-buffered saline (PBS). This new COMIRNATY drug product formulation is referred to as the Tris/Sucrose formulation. The current registered formulation under TT50-10853 is now referred to as the PBS/Sucrose formulation.

The new Tris/Sucrose formulation will be supplied in two strengths and two fill volumes to support vaccination of different age groups.

- Individuals 12 years of age and older: The 30 µg RNA dose is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume,
- Children age 5 to <12 years: The 10 µg RNA dose is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume.

The Tris/Sucrose formulation provides an improved stability profile and greater ease of use at administration sites, compared to the current PBS/Sucrose formulation.

Clinical Need

Since the initial outbreak of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, SARS-CoV-2 infections and the resulting disease, coronavirus disease 2019 (COVID-19), have spread globally with over 243 million confirmed COVID-19 cases and over 4.9 million deaths being reported to the World Health Organization as of 25 October 2021. [https://covid19.who.int/]

COVID-19 is highly contagious, serious, and potentially fatal or life-threatening disease, and can lead to hospitalisation and serious illness in children, including Multisystem Inflammatory Syndrome in Children (MIS-C). The emergence of COVID-19 variants such as Delta, that have been shown to be more contagious than the original Alpha variant (https://www.unicef.org/coronavirus/what-you-need-know-about-delta-variant), has heightened the need for protection of a broader spectrum of the community using efficacious COVID-19 vaccines. Therefore, due to the nature of the disease and the absence of any vaccine to protect children younger than 12, there is an urgency to obtain approval for use of COMIRNATY in individuals 5 to <12 years of age, as supported by the available clinical data.

The existing PBS/Sucrose formulation would require only 0.1 mL to administer the 10 µg dose in individuals aged 5 to <12 years which is difficult to measure accurately with standard syringes. Vaccination of this patient population is better supported by the 1.3 mL presentation of the new Tris/sucrose formulation which provides an easier-to-measure 0.2 mL dose.

Current Therapies

Currently available therapies have different benefit-risk profiles depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet need for a licensed prophylactic vaccine during the ongoing pandemic, that has been demonstrated to be safe and efficacious in the paediatric population.

In New Zealand there are three vaccines currently registered for the prevention of COVID-19 including COMIRNATY. The other two vaccines are indicated for adults aged 18 years and older) only. This application for COMIRNATY presents the only COVID-19 vaccine with data supporting use in children as young as 5 years of age.

Clinical Data

This submission is supported by a one pivotal clinical trial, Study C4591007. Commencing with a Phase 1 dose-finding study, Phase 2/3 of Study C4591007 evaluated both the safety and immunogenicity of COMIRNATY as a vaccine against COVID-19.

Whilst the study included 4 different age groups, only the 5 to <12 years age group is analysed in the submitted application. The doses examined in Phase 1 were 10 μg, 20 μg and 30 μg, and the 10 μg dose was selected for the Phase 2/3 part of the study.

Efficacy

The effectiveness of COMIRNATY in children is based on immunobridging; demonstrating the immune response to COMIRNATY 10 μg at 1 month after Dose 2 in children 5 to <12 years of age is within the prespecified margin of that observed at 1 month after Dose 2 of COMIRNATY 30 μg in young adults 16 to 25 years of age.

Efficacy analyses for the 5 to <12 years of age group were prespecified to be conducted when at least 22 confirmed COVID-19 cases had accrued in participants without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days post-Dose 2, and only if immunobridging success criteria had first been met. The event-driven efficacy analysis was not conducted as an insufficient number of confirmed COVID-19 cases accrued by the submission cut-off date of 06 September 2021.

Based on SARS-CoV-2 50% neutralising titres at 1 month after Dose 2, children aged 5 to <12 years had a similar immune response to the two-dose primary series of COMIRNATY 10 μg compared to young adults 16 to 25 years of age who received two doses of COMIRNATY 30 μg.

The study demonstrated strong immune responses and high vaccine efficacy in the proposed patient population.

Safety

Data from approximately 2,250 children 5 to <12 years of age with a follow-up time of at least 2 months after Dose 2 showed COMIRNATY at 10 μg was safe and well-tolerated in the proposed patient population.

In this patient population the safety and tolerability profile of COMIRNATY 10 μg when administered as a two-dose primary series 3 weeks apart, reflects age-appropriate events that are consistent with a paediatric general population and the known reactogenicity profile of COMIRNATY. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

Pharmacovigilance

The EU Risk Management Plan Version 3.0 dated 13 October 2021 (Data lock point 06 September 2021) is provided in Module 1.13.

Quality aspects of the Tris/Sucrose new drug product formulation

The Tris/Sucrose drug product formulation is a preservative-free, sterile dispersion of lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration. It is based on the current PBS/Sucrose formulation, with the same pH (7.4) but with a lower RNA concentration (0.1 mg/mL) in 10 mM Tris buffer, 300 mM sucrose.

The key differences in the formulations are summarised in the table below.

	Original PBS/Sucrose (current indication)	**Tris/Sucrose** (for current indication)	**Tris/Sucrose** (for new indication)
Vial cap colour	Purple	Grey	Orange
Age range	Over 12 Years	Over 12 Years	5 to <12 Years
Pharmaceutical form	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
Fill Volume	0.45 mL	2.25 mL	1.3 mL
Volume/dose	0.3 mL	0.3 mL	0.2 mL
µg RNA/dose	30 µg	30 µg	10 µg
Dilution required	Yes (1.8 mL saline)	No	Yes (1.3 mL saline)
Doses/vial	6	6	10
Strength (RNA) in vial	500 µg/mL	100 µg/mL	100 µg/mL
Pack size	195	10, 195	10, 195

Single-dose and multi-dose vial formats are planned, with the only difference being the fill volume. This submission is for the multi-dose vial only.

Specifications

[redacted]

Vial container

Two new vial types were chosen for the Tris/Sucrose drug product. A 2 mL borosilicate glass with 1.2 mm wall thickness compared to the 2 mL borosilicate glass vials with 0.85 mm glass thickness used for PBS/Sucrose drug product, and 2 mL aluminosilicate glass vials.

Both vial types met all safety considerations and demonstrated robustness to aggressive freezing parameters with challenging formulations and improved resistance to glass breakage, which is at increased risk due to the greater fill volume for Tris/Sucrose drug product compared to PBS/Sucrose drug product (1.3 mL and 2.25 mL versus 0.45 mL).

Analytical Procedures

[redacted]

Shelf-life and Stability

The initial commercial shelf life proposed for the Tris/Sucrose formulated drug product is 6 months when stored at the long-term storage condition of -90°C to -60°C. This shelf life is based on the currently available stability data for the PBS/Sucrose drug product, the 24 weeks development stability data, and the 3 months stability data from the three Tris/Sucrose primary drug product lots manufactured at Puurs.

The Tris/Sucrose formulation is also stable for 10 weeks storage at 2°C to 8°C at the point of use, within the 6 months shelf-life, based on the stability studies at 2°C to 8°C storage and thermal cycling studies performed.

Dose form nomenclature
The Tris/Sucrose drug product formulation is manufactured in two dosage forms that correspond to the two strengths. Both use the physical characteristic descriptor of '*dispersion*'.

- 2.25 mL fill volume 30 µg RNA dose is a *'dispersion for injection'*, administered without dilution, providing 6 doses of 30 µg RNA dose in 0.3 mL injection volume.

- 1.3 mL fill volume 10 µg RNA dose is a *'concentrate for dispersion for injection'*, requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses of 10 µg RNA dose in 0.2 mL injection volume.

The EU artwork mock-ups submitted herein refer to the 30 µg and 10 µg dosage forms as *dispersion for injection* and *concentrate for dispersion for injection*, respectively. This is the EU approved dosage form descriptor and best describes the properties of this formulation. For New Zealand registered product *dispersion* has been changed to *suspension* as appropriate throughout the cover letter, Datasheet (DS), CMI, application forms and other Module 1 documents.

International Non-Proprietary Name (INN)

Pfizer received approval from the TGA for the Australian Biological Name (ABN) *tozinameran* based on the INN, for the active ingredient previously referred to as BNT162b2 [mRNA]. From an evaluation perspective, reference to tozinameran and BNT162b2[mRNA] in this application are interchangeable. BNT162b2[mRNA] will be updated to tozinameran as appropriate in due course. The ABN will also be applicable to the PBS/Sucrose formulated product.

Datasheet

The DS submitted with this application is a new and separate version specifically for the Tris/Sucrose COMIRNATY drug product formulation in support of the expanded proposed indication for individuals *5 years of age and older*. The new 1.3 mL vial for Tris/Sucrose is required to administer COMIRNATY to children aged 5 to <12 years. Pfizer considers a separate DS for the Tris/Sucrose presentations will facilitate a smooth transition for the introduction of supply of the new Tris/Sucrose formulation and eventual depletion of stock of the PBS/Sucrose formulation that supports the existing 12 years of age and older indication.

The tracked changes are prepared based on the clean copy COMIRNATY DS that was submitted by e-mail to Medsafe on 28 October 2021, incorporating the amendments requested by Medsafe for the 6-month post Dose 2 Booster application.

Labelling

The label mock-ups provided in Module 1.3.3 do not comply with the Medsafe requirements for container and packaging labelling because manufacturing sites are not yet able to implement market-specific labels. Pfizer therefore requests exemption to supply the multi-market labels proposed with this application. The following artwork mock-ups are provided in Module 1.3:

- 30 µg vial label
- 30 µg carton x 10 vials
- 30 µg tray x 195 vials
- 10 µg vial label
- 10 µg carton x 10 vials

Artwork mock-ups for the 195 pack will be the same as the 10 pack for the 10 µg and 30 µg with minor changes consistent with the different pack size.

New Zealand Medicines Terminology (NZMT) Listing Certificate

The NZMT listing certificates for the new presentations 30 µg/0.3 mL dose and the 10 µg/0.2 mL dose are provided in Module 1.2.1.1.

Declarations

An assurance is provided that:

- There have been no other changes made to the Datasheet other than those specified in this application
- There have been no other changes made to Module 3 other than those specified in this application
- The dossier components provided to by EFT to Medsafe on 23 October 2021, ahead of the official submission of this application, are the same as those contained in the enclosed NeeS submission.

CTD Dossier and Content

In support of this application, a dossier is provided in NeeS format via Medsafe's electronic file transfer (EFT) system. Payment of the evaluation fee for this application will be made via electronic funds transfer upon receipt of the invoice from Medsafe.

Pfizer looks forward to the review of the enclosed application by Medsafe. Should you have any questions regarding the above please feel free to contact me directly on [redacted] or via email at [redacted] with a copy to [redacted]

Yours sincerely,

[redacted]

[redacted]

Senior Regulatory Affairs Associate

Ref: PfLEET 2021-0072943; PCF 2021-004346, 2021-005905

NEW MEDICINE APPLICATION FORM
PRESCRIPTION MEDICINE

One copy of this form must be completed for each separate prescription medicine (name + dose form + drug substance(s) + strength + classification + flavour, as applicable). If there is an over-the-counter (OTC) classification of the same medicine, then the New Medicine Application form – OTC Medicine must be used.

The Guide to completing a New Medicine Application – Prescription Medicine form (Application Guide) referred to in this form is available on the Medsafe website as a separate document. Please do not submit the Application Guide document to Medsafe.

The macro enabled form is no longer available for use.

1. Proposed product details, required for all applications

Type of application: **Additional Strength – Grade 5**

Type of high risk medicine (if applicable):

- Biological or biotechnological ☐
- Vaccine ☒
- Blood product ☐

Proposed trade name: **COMIRNATY**

Identifier (if the proposed trade name is the drug substance name):

Drug substance: **tozinameran**

Dose form (refer to Application Guide): **Injection, concentrate**

Strength (include units): **10 micrograms/0.2 mL dose**

New Zealand Classification (refer to Application Guide): **Prescription**

Route of administration (refer to Application Guide): **Intramuscular**

ATC classification (refer to Application Guide): **J07BX03**

Proposed indications:

The proposed extension of indication is supported by the new 10 microgram/0.2 mL dose dosage form:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and over."

The current provisionally approved indication is:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and over."

New Zealand Medicines Terminology:

A New Zealand Medicines Terminology Listing Certificate should be provided as part of the Medsafe application process.

The New Zealand Medicines Terminology Listing Certification has been attached ☒ (Refer to http://www.nzulm.org.nz or email listings@nzmt.org.nz for further details on NZMT listings)

2. Additional information, where applicable:

- **All products**

The product is currently approved in the following countries: **See Module 1 for detailed information on the Foreign Regulatory Status).**

The product is currently pending approval in the following countries: **N/A**

- **Clinical data including bioequivalence studies (if applicable)**

If bioequivalence studies were performed, indicate the following, where applicable:

New Zealand reference product and strength with which the biostudy was conducted: **N/A**

Australian reference product and strength with which the biostudy was conducted: **N/A**

Other reference product and strength with which the biostudy was conducted: **N/A**

- **Application based on a parent product**

If this application is a line extension for another product, provide the parent product details:

Parent product name: **N/A**

Parent product dose form: **N/A**

Parent product strength: **N/A**

Parent product classification: **N/A**

Additional application, submitted concurrently with the parent product: ☐ **N/A**

Indicate the difference between the parent product and the new product (refer to Application Guide): **N/A**

Parent product file number(s), if known: TT50- **N/A**

Details of 'parent product' sponsor(s): **N/A**

Full access to the rights to the product(s) has been provided by the sponsor(s) of the 'parent product': **N/A**

Comments: **N/A**

- **Application based on an overseas approval (abbreviated process)**

If this application is for consent to distribute a new product that was approved by one of the recognised regulatory authorities since 2001, and the reports from that process have been provided, indicate the following:

Regulatory authority name: **N/A**

Regulatory authority country: **N/A**

If EU, specify the procedure used: **N/A**

3. Applicant and Sponsor details

New Zealand Sponsor

Name and street address:

Pfizer New Zealand Limited
Level 10, 11 Britomart Place
Auckland CBD
Auckland 1010

Postal address (eg. PO Box):

Pfizer New Zealand Limited
PO Box 3998
Shortland Street
Auckland 1140

Contact phone number: [redacted]

Applicant

All correspondence relating to the application (including the invoice) will be sent to this person.

Name and designation of the person submitting this application:

[redacted]
Senior Regulatory Affairs Associate

Postal address:

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney
NSW 2000

Email address: [redacted] and [redacted]

Contact phone number: [redacted]

4. Fees and Invoice details

Comments:

All fees are GST inclusive.

Enter customer reference required on the invoice here (max 20 characters):

PFZ COV19 NMA 05Nov21

NB: All acknowledgement letters and invoices will be emailed but not sent in hard copy.

5. Product formulation:

Name of ingredient (For drug substance, identify amount equivalent to free base, if applicable)	**Type of ingredient**	**Quantity** (specify units)	**Quality standard**
Component name (if applicable)			
Tozinameran	**Active ingredient**	**130 mcg**	**In-house**
ALC-0315	**Excipient**	[redacted]	
ALC-0159	**Excipient**	[redacted]	
DSPC	**Excipient**	[redacted]	
Cholesterol	**Excipient**	[redacted]	
Sucrose	**Excipient**	[redacted]	
Tromethamine (Tris base)	**Excipient**	[redacted]	
Tris (hydroxymethyl) aminomethane hydrochloride	**Excipient**	[redacted]	
Water for injections	**Excipient**	[redacted]	

Proprietary ingredients

- If the quantitative formulation of any proprietary ingredients has been previously provided to Medsafe, list the proprietary ingredient name and the associated reference number(s): **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, this information is presented in Module 3 on page: **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, but this information will be sent directly from the supplier, list the ingredient name, identifier, and supplier: **N/A**

6. Product packaging, patient information, and storage conditions:

Container closure system and administration device:	Primary container: **Vial** Materials and description: **Clear Type I glass** Closure: **Rubber stopper, aluminium overseal and grey flip off cap** Materials and description: **Stopper is composed of Datwyler FM457 gray bromobutyl rubber that is not manufactured from dry natural rubber (latex).**
	Secondary container: **Carton** Materials and description: **Cardboard**
	Administration device: **N/A** Materials and description:
Pack size(s) to be registered:	**10 vials, 195 vials**
A package insert is to be supplied with the product:	**Yes**

Proposed shelf life and storage conditions:	Protect from light	Protect from moisture	Do not refrigerate	Do not freeze
6 months from date of manufacture stored in the freezer at -90°C to -60°C.	☒	☐	☐	☐
Single period of up to 10 weeks for unopened thawed vial stored at 2° to 8°C (Refrigerate, do not freeze) within the 6-month shelf life. Do not refreeze thawed vials.	☐	☐	☐	☒
Between 8°C and 30°C for up to 24 hours.	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

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7. Production

Manufacturing of the drug substance

Name of drug substance	Refer to current TPDR TT50-10853
Name of manufacturer	
Manufacturing site address	
Regulatory authority which issued the GMP evidence	
GMP evidence date of expiry	
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Manufacturing of the drug product

Name of manufacturer	Pfizer Manufacturing Belgium
Manufacturing site address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Manufacturing steps carried out at this site	LNP production and bulk drug product formulation Fill and finish Release for Supply

Name of manufacturer	BioNTech Manufacturing GmbH
Manufacturing site address	Kupferbergterrasse 17 – 19 55116 Mainz Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-11828-1 exp 11 Mar 2023
Manufacturing steps carried out at this site	Release for Supply

Packing of the drug product

Name of packer	Pfizer Manufacturing Belgium
Site address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA

GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Packing steps carried out at this site	Primary packaging Secondary packaging

Testing of the drug product

Name of testing site	Pfizer Manufacturing Belgium
Address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Testing steps carried out at this site	Release and stability testing

Name of manufacturer	Pfizer Ireland Pharmaceuticals
Manufacturing site address	Grange Castle Grange Castle Business Park Clondalkin, Dublin 22 Ireland
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-11828-1 exp 11 Mar 2023
Manufacturing steps carried out at this site	Release and stability testing

Biostudy/clinical site (if applicable)

Name of testing site	**N/A**
Address	

Bioanalytical testing site (if applicable)

Name of testing site	N/A
Address	

New Zealand site of batch release

Name of release site	Pfizer New Zealand Limited
Street address of batch release site	Level 1, Suite 1-4, Building B 8 Nugent Street Grafton Auckland 1023

8. Provided information

Documentation (Please ensure ALL relevant sections in this table are completed)	**Section**	**Volumes(s)**
If available, electronic dossier (two copies, hyperlinked, and copy-enabled) should be provided.		
Module 1		NeeS
• Detailed table of contents for the dossier	1.1	
• Labels	1.3.3	
• Data sheet	1.3.1	
• Package Insert	N/A	
• GMP documentation	1.7.2	
• CEP with declaration of access	N/A	
Abbreviated process documentation		N/A
• Detailed table of the overseas regulatory history	1.10.1	
• Evaluation reports from overseas regulatory authorities	Annex II	
• Company responses to issues raised and evaluation of the responses by overseas regulatory authorities	N/A	
• Overseas approval details (approval letter, specifications)	Annex II	
CTD Module 2 Overviews and Summaries		NeeS
CTD Module 3, or, for lower risk medicines, EU Part II Chemical, pharmaceutical, and/or biological documentation		NeeS
• Drug product formulation/Batch formula	3.2.P.1.1 3.2.P.3.2	
• Drug product release and expiry specifications	3.2.P.5	
• Proprietary ingredients formulation	N/A	
CTD Module 4 Toxicological and pharmacological (pre-clinical) documentation		N/A
CTD Module 5 Clinical Documentation		NeeS
• Bioequivalence study results	N/A	
• Bridging study between the reference product used in the biostudy and the New Zealand reference product	N/A	
• Bioanalytical method validation	3.2.R	
Drug Master File(s) or Plasma Master File(s)		N/A
Letter(s) of access to the Drug Master File(s) or Plasma Master File(s)	N/A	
Total number of volumes submitted:		N/A

Regulatory Affairs Department Australia/New Zealand
Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Australia

12 November 2021[i]

The Manager
MEDSAFE
Ministry of Health
133 Molesworth Street
Thorndon Wellington 6011
NEW ZEALAND

TT50-10853

Dear Sir/Madam,

New Medicine Application – New dosage form – Grade 2

COMIRNATY (tozinameran) COVID-19 VACCINE 0.5 mg/mL concentrate for injection

- **Extension of Indication: for children 5 to <12 years of age**
- **New Formulation, Strength and Dosage:**
  Tris/Sucrose formulation (0.1 mg/mL) as 30 µg/0.3 mL and 10 µg/0.2 mL

This application seeks provisional consent to extend the indications for COMIRNATY COVID-19 VACCINE to include children 5 to <12 years of age. The proposed indication is:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals **5 years of age** and older. The use of this vaccine should be in accordance with official recommendations.*

COMIRNATY COVID-19 VACCINE concentrate for injection currently has provisional consent for the indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals **12 years of age** and older. The use of this vaccine should be in accordance with official recommendations.*

Renewal of the Provisional Consent for COMIRNATY was gazetted on 28 October 2021 for two years from 3 November 2021.

This application to extend the indication to include children 5 to <12 years of age is accompanied by Module 3 updates to register a new drug product formulation in two strengths using a tromethamine (Tris) buffer instead of a phosphate-buffered saline (PBS). This new COMIRNATY drug product formulation is referred to as the Tris/Sucrose formulation. The current registered formulation under TT50-10853 is now referred to as the PBS/Sucrose formulation.

The new Tris/Sucrose formulation will be supplied in two strengths and two fill volumes to support vaccination of different age groups.

- Individuals 12 years of age and older: The 30 µg RNA dose is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses, each a 30 µg RNA dose in 0.3 mL injection volume,
- Children age 5 to <12 years: The 10 µg RNA dose is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses, each a 10 µg RNA dose in 0.2 mL injection volume.

The Tris/Sucrose formulation provides an improved stability profile and greater ease of use at administration sites, compared to the current PBS/Sucrose formulation.

Clinical Need

Since the initial outbreak of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, SARS-CoV-2 infections and the resulting disease, coronavirus disease 2019 (COVID-19), have spread globally with over 243 million confirmed COVID-19 cases and over 4.9 million deaths being reported to the World Health Organization as of 25 October 2021. [https://covid19.who.int/]

COVID-19 is highly contagious, serious, and potentially fatal or life-threatening disease, and can lead to hospitalisation and serious illness in children, including Multisystem Inflammatory Syndrome in Children (MIS-C). The emergence of COVID-19 variants such as Delta, that have been shown to be more contagious than the original Alpha variant (https://www.unicef.org/coronavirus/what-you-need-know-about-delta-variant), has heightened the need for protection of a broader spectrum of the community using efficacious COVID-19 vaccines. Therefore, due to the nature of the disease and the absence of any vaccine to protect children younger than 12, there is an urgency to obtain approval for use of COMIRNATY in individuals 5 to <12 years of age, as supported by the available clinical data.

The existing PBS/Sucrose formulation would require only 0.1 mL to administer the 10 µg dose in individuals aged 5 to <12 years which is difficult to measure accurately with standard syringes. Vaccination of this patient population is better supported by the 1.3 mL presentation of the new Tris/sucrose formulation which provides an easier-to-measure 0.2 mL dose.

Current Therapies

Currently available therapies have different benefit-risk profiles depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet need for a licensed prophylactic vaccine during the ongoing pandemic, that has been demonstrated to be safe and efficacious in the paediatric population.

In New Zealand there are three vaccines currently registered for the prevention of COVID-19 including COMIRNATY. The other two vaccines are indicated for adults aged 18 years and older) only. This application for COMIRNATY presents the only COVID-19 vaccine with data supporting use in children as young as 5 years of age.

Clinical Data

This submission is supported by a one pivotal clinical trial, Study C4591007. Commencing with a Phase 1 dose-finding study, Phase 2/3 of Study C4591007 evaluated both the safety and immunogenicity of COMIRNATY as a vaccine against COVID-19.

Whilst the study included 4 different age groups, only the 5 to <12 years age group is analysed in the submitted application. The doses examined in Phase 1 were 10 μg, 20 μg and 30 μg, and the 10 μg dose was selected for the Phase 2/3 part of the study.

Efficacy
The effectiveness of COMIRNATY in children is based on immunobridging; demonstrating the immune response to COMIRNATY 10 μg at 1 month after Dose 2 in children 5 to <12 years of age is within the prespecified margin of that observed at 1 month after Dose 2 of COMIRNATY 30 μg in young adults 16 to 25 years of age.

Efficacy analyses for the 5 to <12 years of age group were prespecified to be conducted when at least 22 confirmed COVID-19 cases had accrued in participants without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days post-Dose 2, and only if immunobridging success criteria had first been met. The event-driven efficacy analysis was not conducted as an insufficient number of confirmed COVID-19 cases accrued by the submission cut-off date of 06 September 2021.

Based on SARS-CoV-2 50% neutralising titres at 1 month after Dose 2, children aged 5 to <12 years had a similar immune response to the two-dose primary series of COMIRNATY 10 μg compared to young adults 16 to 25 years of age who received two doses of COMIRNATY 30 μg.

The study demonstrated strong immune responses and high vaccine efficacy in the proposed patient population.

Safety

Data from approximately 2,250 children 5 to <12 years of age with a follow-up time of at least 2 months after Dose 2 showed COMIRNATY at 10 μg was safe and well-tolerated in the proposed patient population.

In this patient population the safety and tolerability profile of COMIRNATY 10 μg when administered as a two-dose primary series 3 weeks apart, reflects age-appropriate events that are consistent with a paediatric general population and the known reactogenicity profile of COMIRNATY. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

Pharmacovigilance

The EU Risk Management Plan Version 3.0 dated 13 October 2021 (Data lock point 06 September 2021) is provided in Module 1.13.

Quality aspects of the Tris/Sucrose new drug product formulation

The Tris/Sucrose drug product formulation is a preservative-free, sterile dispersion of lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration. It is based on the current PBS/Sucrose formulation, with the same pH (7.4) but with a lower RNA concentration (0.1 mg/mL) in 10 mM Tris buffer, 300 mM sucrose.

The key differences in the formulations are summarised in the table below.

	Original PBS/Sucrose (current indication)	**Tris/Sucrose** (for current indication)	**Tris/Sucrose** (for new indication)
Vial cap colour	Purple	Grey	Orange
Age range	Over 12 Years	Over 12 Years	5 to <12 Years
Pharmaceutical form	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
Fill Volume	0.45 mL	2.25 mL	1.3 mL
Volume/dose	0.3 mL	0.3 mL	0.2 mL
µg RNA/dose	30 µg	30 µg	10 µg
Dilution required	Yes (1.8 mL saline)	No	Yes (1.3 mL saline)
Doses/vial	6	6	10
Strength (RNA) in vial	500 µg/mL	100 µg/mL	100 µg/mL
Pack size	195	10, 195	10, 195

Single-dose and multi-dose vial formats are planned, with the only difference being the fill volume. This submission is for the multi-dose vial only.

Specifications

[redacted]

Vial container

Two new vial types were chosen for the Tris/Sucrose drug product. A 2 mL borosilicate glass with 1.2 mm wall thickness compared to the 2 mL borosilicate glass vials with 0.85 mm glass thickness used for PBS/Sucrose drug product, and 2 mL aluminosilicate glass vials.

Both vial types met all safety considerations and demonstrated robustness to aggressive freezing parameters with challenging formulations and improved resistance to glass breakage, which is at increased risk due to the greater fill volume for Tris/Sucrose drug product compared to PBS/Sucrose drug product (1.3 mL and 2.25 mL versus 0.45 mL).

Analytical Procedures

[redacted]

Shelf-life and Stability

The initial commercial shelf life proposed for the Tris/Sucrose formulated drug product is 6 months when stored at the long-term storage condition of -90°C to -60°C. This shelf life is based on the currently available stability data for the PBS/Sucrose drug product, the 24 weeks development stability data, and the 3 months stability data from the three Tris/Sucrose primary drug product lots manufactured at Puurs.

The Tris/Sucrose formulation is also stable for 10 weeks storage at 2°C to 8°C at the point of use, within the 6 months shelf-life, based on the stability studies at 2°C to 8°C storage and thermal cycling studies performed.

Dose form nomenclature

The Tris/Sucrose drug product formulation is manufactured in two dosage forms that correspond to the two strengths. Both use the physical characteristic descriptor of '*dispersion*'.

- 2.25 mL fill volume 30 µg RNA dose is a *'dispersion for injection'*, administered without dilution, providing 6 doses of 30 µg RNA dose in 0.3 mL injection volume.

- 1.3 mL fill volume 10 µg RNA dose is a *'concentrate for dispersion for injection'*, requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses of 10 µg RNA dose in 0.2 mL injection volume.

The EU artwork mock-ups submitted herein refer to the 30 µg and 10 µg dosage forms as *dispersion for injection* and *concentrate for dispersion for injection*, respectively. This is the EU approved dosage form descriptor and best describes the properties of this formulation. For New Zealand registered product *dispersion* has been changed to *suspension* as appropriate throughout the cover letter, Datasheet (DS), CMI, application forms and other Module 1 documents.

International Non-Proprietary Name (INN)

Pfizer received approval from the TGA for the Australian Biological Name (ABN) *tozinameran* based on the INN, for the active ingredient previously referred to as BNT162b2 [mRNA]. From an evaluation perspective, reference to tozinameran and BNT162b2[mRNA] in this application are interchangeable. BNT162b2[mRNA] will be updated to tozinameran as appropriate in due course. The ABN will also be applicable to the PBS/Sucrose formulated product.

Datasheet

The DS submitted with this application is a new and separate version specifically for the Tris/Sucrose COMIRNATY drug product formulation in support of the expanded proposed indication for individuals *5 years of age and older*. The new 1.3 mL vial for Tris/Sucrose is required to administer COMIRNATY to children aged 5 to <12 years. Pfizer considers a separate DS for the Tris/Sucrose presentations will facilitate a smooth transition for the introduction of supply of the new Tris/Sucrose formulation and eventual depletion of stock of the PBS/Sucrose formulation that supports the existing 12 years of age and older indication.

The tracked changes are prepared based on the clean copy COMIRNATY DS that was submitted by e-mail to Medsafe on 28 October 2021, incorporating the amendments requested by Medsafe for the 6-month post Dose 2 Booster application.

Labelling

The label mock-ups provided in Module 1.3.3 do not comply with the Medsafe requirements for container and packaging labelling because manufacturing sites are not yet able to implement market-specific labels. Pfizer therefore requests exemption to supply the multi-market labels proposed with this application. The following artwork mock-ups are provided in Module 1.3:

- 30 µg vial label
- 30 µg carton x 10 vials
- 30 µg tray x 195 vials
- 10 µg vial label
- 10 µg carton x 10 vials

Artwork mock-ups for the 195 pack will be the same as the 10 pack for the 10 µg and 30 µg with minor changes consistent with the different pack size.

New Zealand Medicines Terminology (NZMT) Listing Certificate

The NZMT listing certificates for the new presentations 30 µg/0.3 mL dose and the 10 µg/0.2 mL dose are provided in Module 1.2.1.1.

Declarations

An assurance is provided that:

- There have been no other changes made to the Datasheet other than those specified in this application
- There have been no other changes made to Module 3 other than those specified in this application
- The dossier components provided to by EFT to Medsafe on 23 October 2021, ahead of the official submission of this application, are the same as those contained in the enclosed NeeS submission.

CTD Dossier and Content

In support of this application, a dossier is provided in NeeS format via Medsafe's electronic file transfer (EFT) system. Payment of the evaluation fee for this application will be made via electronic funds transfer upon receipt of the invoice from Medsafe.

Pfizer looks forward to the review of the enclosed application by Medsafe. Should you have any questions regarding the above please feel free to contact me directly on [redacted] or via email at [redacted] with a copy to [redacted]

Yours sincerely,

[redacted]

[redacted]
Senior Regulatory Affairs Associate

Ref: PfLEET 2021-0072943; PCF 2021-004346, 2021-005905

[i] This letter replaces the original cover letter dated 4 November 2021.

NEW MEDICINE APPLICATION FORM
PRESCRIPTION MEDICINE

One copy of this form must be completed for each separate prescription medicine (name + dose form + drug substance(s) + strength + classification + flavour, as applicable). If there is an over-the-counter (OTC) classification of the same medicine, then the New Medicine Application form – OTC Medicine must be used.

The Guide to completing a New Medicine Application – Prescription Medicine form (Application Guide) referred to in this form is available on the Medsafe website as a separate document. Please do not submit the Application Guide document to Medsafe.

The macro enabled form is no longer available for use.

1. Proposed product details, required for all applications

Type of application: **New dosage form – Grade 2**

Type of high risk medicine (if applicable):

- Biological or biotechnological ☐
- Vaccine ☒
- Blood product ☐

Proposed trade name: **COMIRNATY**

Identifier (if the proposed trade name is the drug substance name):

Drug substance: **tozinameran**

Dose form (refer to Application Guide): **Injection, concentrate**

Strength (include units): **10 micrograms/0.2 mL dose**

New Zealand Classification (refer to Application Guide): **Prescription**

Route of administration (refer to Application Guide): **Intramuscular**

ATC classification (refer to Application Guide): **J07BX03**

Proposed indications:

The proposed extension of indication is supported by the new 10 microgram/0.2 mL dose dosage form:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and over."

The current provisionally approved indication is:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and over."

New Zealand Medicines Terminology:

A New Zealand Medicines Terminology Listing Certificate should be provided as part of the Medsafe application process.

The New Zealand Medicines Terminology Listing Certification has been attached ☒ (Refer to http://www.nzulm.org.nz or email listings@nzmt.org.nz for further details on NZMT listings)

2. Additional information, where applicable:

- **All products**

The product is currently approved in the following countries: **See Module 1 for detailed information on the Foreign Regulatory Status).**

The product is currently pending approval in the following countries: **N/A**

- **Clinical data including bioequivalence studies (if applicable)**

If bioequivalence studies were performed, indicate the following, where applicable:

New Zealand reference product and strength with which the biostudy was conducted: **N/A**

Australian reference product and strength with which the biostudy was conducted: **N/A**

Other reference product and strength with which the biostudy was conducted: **N/A**

- **Application based on a parent product**

If this application is a line extension for another product, provide the parent product details:

Parent product name: **N/A**

Parent product dose form: **N/A**

Parent product strength: **N/A**

Parent product classification: **N/A**

Additional application, submitted concurrently with the parent product: ☐ **N/A**

Indicate the difference between the parent product and the new product (refer to Application Guide): **N/A**

Parent product file number(s), if known: TT50- **N/A**

Details of 'parent product' sponsor(s): **N/A**

Full access to the rights to the product(s) has been provided by the sponsor(s) of the 'parent product': **N/A**

Comments: **N/A**

- **Application based on an overseas approval (abbreviated process)**

If this application is for consent to distribute a new product that was approved by one of the recognised regulatory authorities since 2001, and the reports from that process have been provided, indicate the following:

Regulatory authority name: **N/A**

Regulatory authority country: **N/A**

If EU, specify the procedure used: **N/A**

3. Applicant and Sponsor details

New Zealand Sponsor

Name and street address:

Pfizer New Zealand Limited
Level 10, 11 Britomart Place
Auckland CBD
Auckland 1010

Postal address (eg. PO Box):

Pfizer New Zealand Limited
PO Box 3998
Shortland Street
Auckland 1140

Contact phone number: [redacted]

Applicant

All correspondence relating to the application (including the invoice) will be sent to this person.

Name and designation of the person submitting this application:

[redacted]
Senior Regulatory Affairs Associate

Postal address:

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney
NSW 2000

Email address: [redacted] and [redacted]

Contact phone number: [redacted]

4. Fees and Invoice details

Comments:

All fees are GST inclusive.

Enter customer reference required on the invoice here (max 20 characters):

PFZ COV19 NMA 05Nov21

NB: All acknowledgement letters and invoices will be emailed but not sent in hard copy.

5. Product formulation:

Name of ingredient (For drug substance, identify amount equivalent to free base, if applicable)	**Type of ingredient**	**Quantity** (specify units)	**Quality standard**
Component name (if applicable)			
Tozinameran	**Active ingredient**	**130 mcg**	**In-house**
ALC-0315	**Excipient**	[redacted]	
ALC-0159	**Excipient**	[redacted]	
DSPC	**Excipient**	[redacted]	
Cholesterol	**Excipient**	[redacted]	
Sucrose	**Excipient**	[redacted]	
Tromethamine (Tris base)	**Excipient**	[redacted]	
Tris (hydroxymethyl) aminomethane hydrochloride	**Excipient**	[redacted]	
Water for injections	**Excipient**	[redacted]	

Proprietary ingredients

- If the quantitative formulation of any proprietary ingredients has been previously provided to Medsafe, list the proprietary ingredient name and the associated reference number(s): **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, this information is presented in Module 3 on page: **N/A**
- If the quantitative formulation of any proprietary ingredients has not been previously provided to Medsafe, but this information will be sent directly from the supplier, list the ingredient name, identifier, and supplier: **N/A**

6. Product packaging, patient information, and storage conditions:

Container closure system and administration device:	Primary container: **Vial** Materials and description: **Clear Type I glass** Closure: **Rubber stopper, aluminium overseal and grey flip off cap** Materials and description: **Stopper is composed of Datwyler FM457 gray bromobutyl rubber that is not manufactured from dry natural rubber (latex).**
	Secondary container: **Carton** Materials and description: **Cardboard**
	Administration device: **N/A** Materials and description:
Pack size(s) to be registered:	**10 vials, 195 vials**
A package insert is to be supplied with the product:	**Yes**

Proposed shelf life and storage conditions:	Protect from light	Protect from moisture	Do not refrigerate	Do not freeze
6 months from date of manufacture stored in the freezer at -90°C to -60°C.	☒	☐	☐	☐
Single period of up to 10 weeks for unopened thawed vial stored at 2° to 8°C (Refrigerate, do not freeze) within the 6-month shelf life. Do not refreeze thawed vials.	☐	☐	☐	☒
Between 8°C and 30°C for up to 24 hours.	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

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7. Production

Manufacturing of the drug substance

Name of drug substance	Refer to current TPDR TT50-10853
Name of manufacturer	
Manufacturing site address	
Regulatory authority which issued the GMP evidence	
GMP evidence date of expiry	
DMF number, if known Or Certificate of Suitability number	TT60- R -CEP - -Rev
Letter of access provided	☐

Manufacturing of the drug product

Name of manufacturer	Pfizer Manufacturing Belgium
Manufacturing site address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Manufacturing steps carried out at this site	LNP production and bulk drug product formulation Fill and finish Release for Supply

Name of manufacturer	BioNTech Manufacturing GmbH
Manufacturing site address	Kupferbergterrasse 17 – 19 55116 Mainz Germany
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-11828-1 exp 11 Mar 2023
Manufacturing steps carried out at this site	Release for Supply

Packing of the drug product

Name of packer	Pfizer Manufacturing Belgium
Site address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA

GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Packing steps carried out at this site	Primary packaging Secondary packaging

Testing of the drug product

Name of testing site	Pfizer Manufacturing Belgium
Address	Rijksweg 12 Puurs, 2870 Belgium
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-04395-1 exp 31 Dec 2021
Testing steps carried out at this site	Release and stability testing

Name of manufacturer	Pfizer Ireland Pharmaceuticals
Manufacturing site address	Grange Castle Grange Castle Business Park Clondalkin, Dublin 22 Ireland
Regulatory authority which issued the GMP evidence	TGA
GMP evidence date of expiry	MI-2020-CL-11828-1 exp 11 Mar 2023
Manufacturing steps carried out at this site	Release and stability testing

Biostudy/clinical site (if applicable)

Name of testing site	**N/A**
Address	

Bioanalytical testing site (if applicable)

Name of testing site	N/A
Address	

New Zealand site of batch release

Name of release site	Pfizer New Zealand Limited
Street address of batch release site	Level 1, Suite 1-4, Building B 8 Nugent Street Grafton Auckland 1023

8. Provided information

Documentation (Please ensure ALL relevant sections in this table are completed)	**Section**	**Volumes(s)**
If available, electronic dossier (two copies, hyperlinked, and copy-enabled) should be provided.		
Module 1		NeeS
• Detailed table of contents for the dossier	1.1	
• Labels	1.3.3	
• Data sheet	1.3.1	
• Package Insert	N/A	
• GMP documentation	1.7.2	
• CEP with declaration of access	N/A	
Abbreviated process documentation		N/A
• Detailed table of the overseas regulatory history	1.10.1	
• Evaluation reports from overseas regulatory authorities	Annex II	
• Company responses to issues raised and evaluation of the responses by overseas regulatory authorities	N/A	
• Overseas approval details (approval letter, specifications)	Annex II	
CTD Module 2 Overviews and Summaries		NeeS
CTD Module 3, or, for lower risk medicines, EU Part II Chemical, pharmaceutical, and/or biological documentation		NeeS
• Drug product formulation/Batch formula	3.2.P.1.1 3.2.P.3.2	
• Drug product release and expiry specifications	3.2.P.5	
• Proprietary ingredients formulation	N/A	
CTD Module 4 Toxicological and pharmacological (pre-clinical) documentation		N/A
CTD Module 5 Clinical Documentation		NeeS
• Bioequivalence study results	N/A	
• Bridging study between the reference product used in the biostudy and the New Zealand reference product	N/A	
• Bioanalytical method validation	3.2.R	
Drug Master File(s) or Plasma Master File(s)		N/A
Letter(s) of access to the Drug Master File(s) or Plasma Master File(s)	N/A	
Total number of volumes submitted:		N/A

Joint report on expected impacts to Maaori children and their whaanau from the planned shift to the COVID-19 Protection Framework

Monday 29nd November 2021

Introduction

1. This is a Statement of Evidence co-authored by

   1.1. Dr Danny de Lore,

   1.2. Dr Erik Andersen,

   1.3. Dr Teuila Percival,

   1.4. Dr Jin Russell,

   1.5. Dr Owen Sinclair, and

   1.6. Associate Professor Siouxsie Wiles.

2. We have been provided with a copy of the Amended Statement of Claim filed by the New Zealand Maaori Council before the Waitangi Tribunal on 1 November 2021. We have been asked by the New Zealand Maaori Council to complete this report in relation to the issues raised in that claim. Specifically, we have been asked to provide expert evidence on the expected impacts to Maaori children and their whaanau from the Government's planned decision to shift to the COVID-19 Protection Framework on the 3rd of December 2021, and our expert opinions on the need for an equitable paediatric COVID-19 vaccine rollout.

3. This evidence constitutes the personal expert opinions of its authors and is not the evidence of their employers who are not involved in this matter.

Code of conduct for expert witnesses

4. It is intended that this report will be annexed to an affidavit for filing in the Waitangi Tribunal and for possible use in other fora.

5. The authors have been provided with Schedule 4 to the High Court Rules - Code of conduct for expert witnesses. We have read that code. While it is

intended that this affidavit is to be relied on initially in the Waitangi Tribunal and not the High Court, we nevertheless agree to comply with that code in the completion of this report and with respect to any related evidence we are later asked to give. The matters addressed in this report are within the authors' area of expertise.

Qualifications

6. Relevant to the matters to be addressed in this Statement of Evidence, our qualifications are as follows:

Dr Danny de Lore

6.1. Ko Ngaati Tuwharetoa te iwi. Dr de Lore has a Bachelor of Medicine and Bachelor of Surgery and a Diploma in Child Health. He is a Fellow of the Royal Australasian College of Physicians, qualifying in 2013. Dr de Lore is a Consultant General Paediatrician at Lakes DHB. He is a member of the Royal Australasian College of Physicians Maaori Health Committee and Chair of the RACP Indigenous Child Working Group. He is an Honorary Lecturer at the University of Auckland Medical School.

Dr Erik Andersen

6.2. He uri ahau noo Ngaati Raukawa ki te Tonga. Dr Andersen is a Consultant Paediatric Neurologist at Capital and Coast DHB, providing care for the lower North Island. He completed a Bachelor of Medicine and Bachelor of Surgery in 2005, a Diploma of Child Health in 2010 from the University of Otago. He is a Fellow of the Royal Australasian College of Physicians, having qualified in 2015 as a Specialist Paediatric Neurologist. He also works as a Senior Clinical Lecture in Paediatrics at the University of Otago and as part of Te Roopuu Whakakaupapa Urutaa in the Hospital Care team.

Dr Teuila Percival

6.3. Dr Percival is a Consultant Paediatrician at KidzFirst Childrens Hospital, Counties Manukau Health. She has a Bachelor of Medicine and Bachelor of Surgery from the University of Auckland 1983. She is a

Fellow of the Royal Australasian College of Physicians, qualifying in 1993. She is an Honorary Senior Lecturer in the Department of Paediatrics at the University of Auckland.

Dr Jin Russell

6.4. Dr Russell is a Consultant Developmental Paediatrician at Starship Children's Health. She has a Bachelor of Medicine and Bachelor of Surgery in 2007 and a Diploma of Paediatrics in 2009 from the University of Auckland. She is a Fellow of the Royal Australasian College of Physicians, having qualified in 2020 as a Specialist Paediatrician in Community Child Health. She is currently completing her Doctorate of Philosophy (Paediatrics) in the field of paediatric and life-course epidemiology at the Centre for Longitudinal Research at the University of Auckland.

Dr Owen Sinclair

6.5. Ko Te Rarawa Te Iwi. Dr Sinclair has been a General Paediatrician with the Whanganui District Health Board since 2012. He has been working in acute lead paediatrics since 2018. He is an honorary lecturer at The University of Auckland Medical school. He gained a Bachelor of Medicine and Bachelor of Surgery in 1999. He became a Fellow of the Royal Australasian College of Physicians in 2012 in both General Paediatrics and Paediatric emergency medicine. He gained a Masters of Public Health in 2017. He is currently a member of the COVID Vaccine Independent monitoring board, The NRA working group into immunisation in Tamariki and Mokopuna Pae ora: Oranga Peepi & Oranga Tamariki (Early Years) for the Transition Unit assisting in the establishing of Health New Zealand, Transition Unit - Maaori Health Authority.

Associate Professor Siouxsie Wiles

6.6. Dr Wiles is an Associate Professor at the Faculty of Medical and Health Sciences at the University of Auckland. She graduated with a First Class Bachelor of Science Honours degree in medical microbiology from the

University of Edinburgh, Scotland in 1997 and with a PhD in microbiology from Edinburgh Napier University, Scotland in 2002. She worked as a postdoctoral researcher in the field of infectious diseases at Imperial College London, England from 2000-2007. In 2007, she was appointed as a lecturer in the Department of Infectious Diseases at Imperial College London. In 2009, she was awarded a Sir Charles Hercus fellowship from the Health Research Council of New Zealand and relocated to the University of Auckland. She was appointed as a Senior Lecturer at the University of Auckland in 2014. In 2019, she was appointed a Member of the New Zealand Order of Merit for services to microbiology and science communication. She is currently a member of the Chief Science Advisor to the Prime Minister, Dame Prof Juliet Gerrard's infectious diseases expert panel.

Materials relied on

7. Where we have relied on any source material for any of the data or opinions set out below, we have included these sources in numbered footnotes.

Background

8. The Crown has failed to achieve equitable health outcomes for Maaori. Maaori continue to experience higher infant mortality rates,[1] higher rates of paediatric diseases,[2] higher rates of suicide,[3] and lower life expectancy.[4] The authors are

[1] Rutter, C., Walker, S. Infant mortality inequities for Maaori in New Zealand: a tale of three policies. Int J Equity Health 20, 10 (2021). https://doi.org/10.1186/s12939-020-01340-y.

[2] The Royal Australasian College of Physicians. Indigenous child health in Australia and Aotearoa New Zealand [Internet]. 2020. Cited 24 November 2021. Sydney. Available from https://www.racp.edu.au/docs/default-source/advocacy-library/indigenous-ch-statement-on-ich.pdf.

[3] Ministry of Health. Suicide and intentional self-harm dad [Internet]. Cited 24 November 2021. Available from https://www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/suicide-and-intentional-self-harm.

[4] Stats NZ. National and subnational period life tables: 2017-2019. [Internet]. 2021. Cited 24 November 2021. Available from https://www.stats.govt.nz/information-releases/national-and-subnational-period-life-tables-2017-2019.

concerned that the Crown's response to the COVID-19 pandemic does not further exacerbate these already stark inequities.

9. COVID-19 is an illness caused by the highly infectious SARS-CoV-2 virus.[5] COVID-19 poses a significant danger to life and can cause chronic debilitating illness.[6, 7, 8, 9, 10]

10. The elderly and people with a variety of other pre-existing health conditions are more at risk of more serious outcomes from a COVID-19 infection.[11, 12]

11. The Pfizer vaccine, which is available in New Zealand, has been proven to be safe and highly effective at reducing both the likelihood of infection and the severity of illness.

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[5] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 5, 536–544 (2020).

[6] Wu, Z. & McGoogan, J. M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 323, 1239–1242 (2020).

[7] Chen, T. et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368, m1091 (2020).

[8] Yang, X. et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 8, 475–481 (2020).

[9] Twohig, K. A., et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis. Aug 27:S1473-3099(21)00475-8 (2021). doi: 10.1016/S1473-3099(21)00475-8.

[10] Higgins, V., et al. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Crit Rev Clin Lab Sci. 58(5):297-310 (2021). doi: 10.1080/10408363.2020.1860895.

[11] Tian, J. et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 21, 893–903 (2020).

[12] Liu, Y. et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur. Respir. J. 55, 2001112 (2020).

12. By reducing the likelihood of infection amongst those who are vaccinated, the Pfizer vaccine can also reduce the overall level of community transmission.[13]

13. Receiving one dose of the Pfizer vaccine provides measurable benefits.[14, 15] However, far greater benefits come from being "fully vaccinated". This requires two doses of the Pfizer vaccine given at least 3 weeks apart and an additional two-week period after the second dose for the recipient to develop full protective immunity.[16,17]

14. The Pfizer vaccine has so far been approved by Medsafe for use only by people aged 12 and above.[18] Pfizer says that it has concluded stage 2/3 trials establishing a safe and effective protocol for the use of its vaccine with 5- to 11-year-olds.[19] The FDA and Health Canada have examined that data and

[13] Polcak, P.F., et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N. Engl. J. Med. 383:2603-2615 (2020). doi: 10.1056/NEJMoa2034577.

[14] Barda, N., et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet (2021). doi: 10.1016/S0140-6736(21)02249-2.

[15] Steyn, N., Plank, M., Hendy, S. Modelling to support a future COVID-19 strategy for Aotearoa New Zealand. (2021). Available online: https://www.tepunahamatatini.ac.nz/2021/09/23/modelling-to-support-a-future-covid-19-strategy/.

[16] Nasreen, s., et al. Effectiveness of mRNA and ChAdOx1 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. medRxiv (2021). doi: https://doi.org/10.1101/2021.06.28.21259420.

[17] Lopez Bernal, J., et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. medRxiv (2021). doi: https://doi.org/10.1101/2021.05.22.21257658.

[18] Medsafe COMIRNATYTM COVID-19 vaccine New Zealand Data Sheet. Available at: https://www.medsafe.govt.nz/profs/Datasheet/c/comirnatyinj.pdf.

[19] Walter, E.B., et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. (2021). N. Engl. J. Med. doi: 10.1056/NEJMoa2116298.

approved the Pfizer vaccine for use in the United States and Canada, respectively.[20, 21] Medsafe is presently examining that data in New Zealand.[22]

Expected impacts to Maaori children and their whaanau from the planned shift to the COVID-19 Protection Framework

15. A shift to the COVID-19 Protection Framework, the movement of individuals outside of Taamaki, and any loosening of international borders before Maaori achieve equivalent proportions of vaccination coverage to the broader population will negatively and disproportionately affect the health of Maaori children and their whaanau. Maaori currently have the lowest proportions of vaccination coverage of all major ethnic groups in Aotearoa. According to the Ministry of Health at the time of writing (as of Tuesday 23rd November 2021), 64.3% of eligible Maaori have been administered two vaccine doses, compared to 78.9% of Pacific Peoples, >95% of Asian, and 84.1% of European/Other ethnicity.[23] Comparing the second doses administered figures given by the Ministry of Health with the 2018 census data gives a proportion of the total population double vaccinated as 74.9%, and the proportion of the Maaori population double vaccinated as 47.6%.

16. In addition to national vaccination rates, the proportion of eligible Maaori vaccinated at a local community level must also be considered. If SARS-CoV-2 were to be present in a particular local area, it is the vaccination rates within

[20] FDA approval announcement. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age.

[21] Health Canada. [Internet] Cited 29 November 2021.Available at: https://www.canada.ca/en/public-health/services/vaccination-children/covid-19.html.

[22] Radio New Zealand. Medsafe intends analysing paediatric vaccine data over Christmas break. [Internet] Cited 29 November 2021. Available at: https://www.rnz.co.nz/news/national/456595/medsafe-intends-analysing-paediatric-vaccine-data-over-christmas-break.

[23] Ministry of Health. Covid-19 vaccine data. [Internet]. 2021. Cited 22 November 2021. Available from https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-vaccine-data#ethnicity.

that community and not the regional or national vaccination rate that is important for protecting the community from COVID-19.

17. While differences remain between the proportion of eligible Maaori who are vaccinated compared with the wider population, Maaori children will be disproportionately at risk of exposure to the SARS-CoV-2 virus and subsequent COVID-19 infection.

18. The SARS-CoV-2 delta variant of concern is highly transmissible and is the dominant strain worldwide. Transmission risk varies widely by setting,[24, 25, 26] and is reduced by vaccination.[27, 28] Transmission of SARS-CoV-2 within households is the dominant form of transmission in the current outbreak.[29] The secondary attack rate is 45.6% which means nearly half of household members

[24] Singanayagam, A., Hakki, S., Dunning, J., et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis. 2021; Oct 29;S1473-3099(21)00648-4. doi: 10.1016/S1473-3099(21)00648-4. Available from https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00648-4/fulltext.

[25] Ng, O.T., Koh, V., Chiew, C.J., et al. Impact of Delta Variant and Vaccination on SARS-CoV-2 Secondary Attack Rate Among Household Close Contacts. Lancet Reg Health West Pac. 2021 Dec;17:100299. doi: 10.1016/j.lanwpc.2021.100299. Available from https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(21)00208-X/fulltext.

[26] Lee, B., U. A high attack rate of 90% of SARS-CoV-2 Delta variant infections in crew personnel on a single navy ship. J Travel Med. 2021 Oct 20;taab168. doi: 10.1093/jtm/taab168. Available from https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taab168/6404468.

[27] Ng, O.T., Koh, V., Chiew, C.J., et al. Impact of Delta Variant and Vaccination on SARS-CoV-2 Secondary Attack Rate Among Household Close Contacts. Lancet Reg Health West Pac. 2021 Dec;17:100299. doi: 10.1016/j.lanwpc.2021.100299. Available from https://www.thelancet.com/journals/lanwpc/article/PIIS2666-6065(21)00208-X/fulltext.

[28] Lee, B., U. A high attack rate of 90% of SARS-CoV-2 Delta variant infections in crew personnel on a single navy ship. J Travel Med. 2021 Oct 20;taab168. doi: 10.1093/jtm/taab168. Available from https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taab168/6404468.

[29] New Zealand Ministry of Health. COVID-19 Variants Update. 22/11/2021. Available from https://www.health.govt.nz/system/files/documents/pages/22-november-2021-variants-update-summary.pdf.

are becoming infected.[30] While there is evidence that infected children are less likely to transmit the virus than adults in educational settings,[31] infected children can and do transmit to other household members.[32] 20% of Maaori households are classified as crowded, versus 4% of European households.[33] Furthermore, for children and young people aged 0 - 19 years there is a higher percentage of crowding across all ethnicities.[34]

19. The SARS-CoV-2 delta variant evolved to become 97% more infectious.[35] The virus will continue to evolve while transmission continues globally. In the future, new variants of concern may emerge that are more transmissible or cause more severe illness. For example, on 25 November 2021 South African Minister of Health Dr Joe Phaahia and the director of the Centre for Epidemic Response & Innovation (CERI) Professor Tulio de Oliveira announced that they had recently identified a new variant of SARS-CoV-2 in the lineage B.1.1.529 with a large

[30] Ibid.

[31] National Centre for Immunisation Research and Surveillance (NCIRS). COVID-19 in schools and early childhood education and care services – the experience in NSW: 16 June to 31 July 2021. National Centre for Immunisation Research and Surveillance, NSW Health. [Internet]. 2021. Cited 22 November 2021. Available from https://www.ncirs.org.au/sites/default/files/2021-09/NCIRS%20NSW%20Schools%20COVID_Summary_8%20September%2021_Final.pdf.

[32] Paul, L.A., Daneman, N., Schwartz, K.L., et al. Association of age and pediatric household transmission of SARS-CoV-2 infection. *JAMA Pediatr*. 2021;175(11):1151-1158. doi:10.1001/jamapediatrics.2021.2770. Available from https://jamanetwork.com/journals/jamapediatrics/fullarticle/2783022.

[33] Ministry of Health. Analysis of Household Crowding based on Census 2013 data. Wellington: Ministry of Health. 2014. ISBN 978-0-478-42850-6 (online). Available from https://www.health.govt.nz/system/files/documents/publications/analysis-of-household-crowding-based-on-census-13-data-dec14-v2.docx.

[34] Ibid.

[35] New Zealand Ministry of Health. COVID-19 Variants Update. 22/11/2021. Available from https://www.health.govt.nz/system/files/documents/pages/22-november-2021-variants-update-summary.pdf.

number of both known and unknown mutations.[36] This variant was named Omicron and classified as a Variant of Concern (VOC) by the World Health Organisation on 26 November.[37] The emergence of new variants constitutes an ongoing risk to the health of Maaori communities if Maaori have inequitable vaccination coverage.

20. The younger age structure of the Maaori population means that a relatively larger proportion of Maaori compared to the wider population are children who are unable to be vaccinated at present and remain susceptible to infection, with risk of onward spread to their households and communities. According to the 2018 Census, 32% of Maaori are under 15-years of age, versus 19.6% of the total population being under 15-years of age.[38] At the time of writing (as of Tuesday 23rd November 2021), in the current August delta outbreak, Maaori represent 43% of COVID-19 cases, 32% of hospitalised cases, and 43% of

[36] South Africa News 24. Urgent briefing on latest developments around the Covid-19 vaccination programme. [Internet] Cited 29 November 2021. Available from https://www.youtube.com/watch?v=Vh4XMueP1zQ.

[37] World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. [Internet] Cited 29 November 2021. Available from https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern.

[38] 2018 Census, NZ Stat Table Viewer. Statistics New Zealand. [Internet]. 2021. Cited 23 November 2021. Available from http://nzdotstat.stats.govt.nz/wbos/Index.aspx?_ga=2.145049588.1928536397.1637656731-896706472.1637656731#.

deaths,[39, 40] despite Maaori comprising approximately 16.5% of the total population.[41]

21. Maaori children experience worse health outcomes compared to non-Maaori for many other health conditions.[42] Compared to children of European ethnicity, Maaori children experience a higher burden of risk factors for severe illness and/or negative outcomes from COVID-19 infection,[43] including but not limited

[39] Covid-19: Case demographics. Ministry of Health. [Internet]. 2021. Cited 23 November 2021. Available from https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-case-demographics#aug-2021.

[40] Taonui, R. Another Maaori death and highest cases since Covid-19 began. Waatea News. [Internet]. 23 November 2021. Cited 28 November 2021. Available from https://waateanews.com/2021/11/23/dr-rawiri-taonui-another-maori-death-and-highest-cases-since-covid-19-began/

[41] 2018 Census, NZ Stat Table Viewer. Statistics New Zealand. [Internet]. 2021. Cited 23 November 2021. Available from http://nzdotstat.stats.govt.nz/wbos/Index.aspx?_ga=2.145049588.1928536397.1637656731-896706472.1637656731#.

[42] The Royal Australasian College of Physicians. Indigenous child health in Australia and Aotearoa New Zealand [Internet]. 2020. Cited 23 November 2021. Sydney. Available from https://www.racp.edu.au/docs/default-source/advocacy-library/indigenous-ch-statement-on-ich.pdf; and Duncanson, M; Oben, G; Adams, J; Richardson, G; Wicken, A; Pierson M. Health and wellbeing of under-15 year olds in Aotearoa 2018 [Internet]. Dunedin; 2019. Available from: https://www.otago.ac.nz/nzcyes

[43] Graff, K., Smith, C., Silveira, L., et al. Risk factors for severe Covid-19 in Children. The Pediatric Infectious Disease Journal: April 2021 - Volume 40 - Issue 4 - p e137-e145. doi: 10.1097/INF.0000000000000304. Available from https://journals.lww.com/pidj/Fulltext/2021/04000/Risk_Factors_for_Severe_COVID_19_in_Children.2.aspx?context=FeaturedArticles&collectionId=3.

to asthma and chronic respiratory conditions,[44] obesity,[45] and diabetes.[46] In a large systematic meta-analysis of laboratory-confirmed COVID-19 cases in children, 1 in 20 children with comorbidities experienced severe illness due to COVID-19 infection, compared to 1 in 500 children with no pre-existing conditions.[47] In the same study, the risk of mortality from COVID-19 infection was almost three times more likely in children with comorbidities compared to children with no comorbidities.[48] Because Maaori children have a higher burden of pre-existing conditions, it is expected that Maaori children will experience a greater burden of hospitalisation and severe illness as COVID-19 spreads.[49]

22. Maaori children are at significantly more risk of immunisation preventable disease including pertussis[50] and measles[51]. Despite or because of this the health system has long failed to achieve equitable outcomes in childhood immunisations in Maaori. Although there was some improvement between

[44] The Royal Australasian College of Physicians. Indigenous child health in Australia and Aotearoa New Zealand [Internet]. 2020. Cited 23 November 2021. Sydney. Available from https://www.racp.edu.au/docs/default-source/advocacy-library/indigenous-ch-statement-on-ich.pdf.

[45] Ibid.

[46] Sjardin, N., Reed, P., Albert, A., et al. Increasing incidence of type 2 diabetes in New Zealand children <15 years of age in a regional-based diabetes service, Auckland, New Zealand. Journal of Paediatrics and Child Health. 2018;54(9):1005-1010. https://doi.org/10.1111/jpc.13924.

[47] Tsankov, B.K., Allaire, J.M., Irvine, M.A, et al. Severe Covid-19 infection and paediatric comorbidities: A systematic review and meta-analysis. International Journal of Infectious Diseases. 2021;103:246-256. https://doi.org/10.1016/j.ijid.2020.11.163.

[48] Ibid.

[49] Steyn, N., Binny, R.N., Hannah, K., et al. Maaori and Pacific people in New Zealand have a higher risk of hospitalisation for COVID-19. New Zealand Medical Journal. 2021;134(1538):28-43. Available from https://journal.nzma.org.nz/journal-articles/maori-and-pacific-people-in-new-zealand-have-a-higher-risk-of-hospitalisation-for-covid-19-open-access.

[50] Sinclair O. Ethnic inequalities in health: have we made progress? Pertussis mortality and morbidity in New Zealand for Maaori and non-Maaori over the past century: University of Auckland; 2015.

[51] Turner N. A measles epidemic in New Zealand: Why did this occur and how can we prevent it occurring again? N Z Med J. 2019;132(1504):8-12.

2009 and 2017, all of those gains have been lost and the current levels of completed immunisations are dire. The 2-year immunisation levels are 70.2% for Maaori compared to 86% for New Zealand European.[52] This leaves Maaori children vulnerable to a predictable resurgence of these diseases when restrictions are lifted.

23. Overseas evidence shows disproportionate COVID-19 infection rates in indigenous and ethnic minority children (Black, Hispanic and American Indian and Native Alaskan).[53, 54] Children of Racial minority groups are also more likely to be hospitalized with more severe COVID-19 illness.[55]

24. There is emerging evidence regarding persisting symptoms such as headache, fatigue, concentration difficulties, abdominal pain, cough, and chest pain, following COVID-19 infection in a proportion of children, sometimes referred to as 'Long Covid'.[56] A recent systematic review concluded that the small number of published studies of persisting symptoms in children after COVID-19 infection all contained major limitations, such as the lack of a clear case definition, inclusion of children without confirmation of infection, selection bias

[52] Ministry of Health. National and DHB immunisation data. [Internet]. Updated 12 November 2021. Cited 26 November 2021. Available from https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data.

[53] Kim, L., Whitaker, M., O'Halloran, A., et al. Hospitalisation rates and characteristics of children aged <18 years hospitalised with laboratory confirmed COVID-19 - COVID-NET,14 States, March 1-July 25, 2020. MMWR Morb Mortal Wkly Rep 2020 Aug 14;69(32):1081-1088. doi: 10.15585/mmwr.mm6932e3. Available from https://pubmed.ncbi.nlm.nih.gov/32790664/.

[54] Goyal M, Simpson J, Boyle M, Badolato G, Delaney M, McCarter R, Cra-Bramble D. (2020) Racial and/or ethnic and Socioeconomic Disparities of SARS-CoV-2 Infection Among Children. Pediatrics. 2020 Oct;146(4):e2020009951. Available from https://doi.org/10.1542/peds.2020-009951.

[55] US Centers for Disease Control and Prevention. Covid-19 disparities in hospitalizations: Racial and ethnic health disparities. US Centers for Disease Control and Prevention. [Internet]. Updated 22 November 2021. Cited 25 November 2021. Available from https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/racial-ethnic-disparities/disparities-hospitalization.html.

[56] Zimmermann, P., Pittet, L.F.,Curtis,N. How common is Long Covid in children and adolescents? The Pediatric Infectious Disease Journal. 2021;40(12):e482-e487. doi: 10.1097/INF.0000000000003328.

with low response rates, the absence of control groups, and recommended that further research is needed.[57] In the majority of studies reviewed, symptoms did not persist longer than 12 weeks.[58]

25. It is not clear what proportion of infected children experience persisting symptoms after COVID-19 infection.[59] However even if only a small proportion of infected children experience persistent symptoms after COVID-19 infection this would be concerning since large numbers of children are being/will be infected.[60] A recent preprint study with robust methodology which included healthcare data from almost 12,000 children and adolescents in Germany has found that fatigue, cough, and throat/chest pain were more common in children and adolescents at least 3 months post COVID-19 infection compared to the control group who had not tested positive for COVID-19 infection.[61] In the same study, the incidence of persisting symptoms was lower among children and adolescents compared to among adults.[62]

26. Multisystem Inflammatory Syndrome (MIS-C), a rare, severe complication of COVID-19 infection in children, causes fever and inflammation in multiple organ systems.[63] MIS-C occurs more frequently among marginalised Black, non-Black Hispanic, Pacific and indigenous children compared with white children

[57] Ibid.

[58] Ibid.

[59] Ibid.

[60] Ibid.

[61] Roessler, M., Tesch, F., Batram, M. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19. Medrxiv. Preprint. 2021 October 22. Cited 2021 November 24. https://doi.org/10.1101/2021.10.21.21265133.

[62] Ibid.

[63] CDC Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019. Cited 24 November 2021. Available from: https://emergency.cdc.gov/han/2020/han00432.asp.

according to overseas studies,[64, 65] raising concerns that similar inequities may occur for Maaori children.

27. Certain socio-politico-environmental factors also place Maaori children at greater risk of negative health outcomes, such as inequities in access to healthcare,[66] access to well-resourced schooling,[67] poor quality housing and/or housing security,[68] and overcrowding and multi-generational homes.[69] According to the 2013 New Zealand Census, 50% of all Maaori children live in the lowest three deciles on the New Zealand Deprivation Index.[70]

[64] Godfred-Cato S, Bryant B, Leung J, et al. COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074–1080. http://dx.doi.org/10.15585/mmwr.mm6932e2.

[65] Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. JAMA Netw Open. 2021;4(6):e2116420. Published 2021 June 1. https://doi.org/10.1001/jamanetworkopen.2021.16420.

[66] Talamaivao, N., Harris, R., Cormack, D., et al. Racism and health in Aotearoa New Zealand: A systematic review of quantitative studies. NZMJ. 2020;133(1521):55-68. Available from https://journal.nzma.org.nz/journal-articles/racism-and-health-in-aotearoa-new-zealand-a-systematic-review-of-quantitative-studies.

[67] New Zealand Government. Child poverty indicators report. May 2021: New Zealand Government. Available from https://childyouthwellbeing.govt.nz/sites/default/files/2021-05/cpri-report-20210512.pdf.

[68] Ibid.

[69] Ministry of Health. Analysis of Household Crowding based on Census 2013 data. Wellington: Ministry of Health. 2014. ISBN 978-0-478-42850-6 (online). Available from Analysis of Household Crowding based on Census 2013 data https://www.health.govt.nz › files › publications.

[70] Atkinson, J., Salmond, C., Crampton, P. 2014. NZDep2013 Index of Deprivation. Dunedin: University of Otago. Available from: https://www.otago.ac.nz/wellington/otago069936.pdf.

28. However, socio-economic factors are not the only contributors to inequitable health outcomes. Maaori receive lower quality care from the health system compared to non-Maaori.[71, 72]

29. Maaori children are also at greater risk of indirect harm if COVID-19 spreads through Maaori communities, including illness, disability, hospitalisation, and/or loss of a parent, caregiver, or other member of the child's whaanau. These outcomes would result in psychological and socioemotional harms, as well as socioeconomic harms to Maaori children and their whaanau. More than 1.1 million children worldwide are estimated to have experienced the death of a primary parent or caregiver grandparent during the period from March 1, 2020 to April 30, 2021.[73] Indigenous and ethnic minority children are up to 4.5 times more likely to lose a parent or caregiver due to COVID-19 compared to white children.[74] A study published in Pediatrics found that 140,000 children in the United States are estimated to have lost a parent or grandparent caregiver between April 1, 2020 and June 30, 2021.[75] In the same study, an estimated 1 of every 753 white children lost a parent or grandparent caregiver, compared to 1 in 412 Hispanic children, 1 in 310 Black children, and 1 in 168 indigenous children (American Indian/Alaskan native).[76]

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[71] Rumball-Smith J. Not in my hospital? Ethnic disparities in quality of hospital care in New Zealand: a narrative review of the evidence. NZ Med J 2009. 122:1297; 68-83.

[72] Talamaivao, N., Harris, R., Cormack, D., et al. Racism and health in Aotearoa New Zealand: A systematic review of quantitative studies. NZMJ. 2020;133(1521):55-68. Available from https://journal.nzma.org.nz/journal-articles/racism-and-health-in-aotearoa-new-zealand-a-systematic-review-of-quantitative-studies.

[73] Hillis, S.D., Unwin, H.J.T., Chen, Y., et al. Global minimum estimates of children affected by Covid-19-associated orphanhood and deaths of caregivers: a modelling study. Lancet. 2021;398(10298):391-402. https://doi.org/10.1016/S0140-6736(21)01253-8.

[74] Hillis, S.D., Blenkinsop, A., Villaveces, A., et al. Covid-19-associated orphanhood and caregiver death in the United States. Pediatrics. 2021;e2021053760. https://doi-org.ezproxy.auckland.ac.nz/10.1542/peds.2021-053760.

[75] Ibid.

[76] Ibid.

The urgent need for an equitable paediatric COVID-19 vaccine rollout

30. Maaori children have a right to protect themselves and participate in the protection of their whaanau, hapuu and iwi. The principle of tino rangatiratanga derived from Te Tiriti o Waitangi supports the right of Maaori to express their mana motuhake and make autonomous decisions regarding health systems for Maaori. Decisions based on the needs of the general population exacerbate risk for Maaori and do not comply with the principles of equity and active protection afforded to Maaori by Te Tiriti.

31. It is crucial that a COVID-19 vaccination for 5 – 11-year-old children is made widely available as soon as possible after Medsafe approval.

32. Equity for Maaori and upholding Te Tiriti o Waitangi should be central to decisions regarding vaccine approval for children under the age of 12-years. Decisions regarding vaccine approval should go beyond an individual risk/benefit approach, to include wider benefits of vaccination for children, whaanau and their communities. The benefits of vaccination of all children include protection from COVID-19 infection, severe illness, hospitalisation, death, and complications of COVID-19, as well as increasing protection for household members, reducing overall community transmission, and avoiding isolation, quarantine, school closures, and other indirect harms of the pandemic.[77]

33. Planning for an equitable paediatric vaccine rollout for all New Zealand children is a priority. Children with pre-existing conditions, Maaori children, and children with medically vulnerable household members should be prioritised in a vaccine rollout given their increased risk of hospitalisation and severe illness.

34. To reduce barriers to access, a paediatric vaccine rollout should include a school-based vaccination programme and primary health care vaccine sites in

[77] Zimmermann, P., Pittet, L.F., Finn, A., et al. Should children be vaccinated against Covid-19? Archives of Disease in Childhood. 2021;**0**:1–8. doi:10.1136/archdischild-2021-323040. Available from https://adc.bmj.com/content/archdischild/early/2021/11/01/archdischild-2021-323040.full.pdf.

partnership with Maaori leaders and health providers.[78] A substantial further increase/redistribution in funding and resources should be urgently allocated to Maaori health providers and providers in low decile communities to enable planning for the paediatric vaccine rollout.

Protecting Maaori children in educational settings

35. There is strong evidence that the risk of transmission of COVID-19 within educational settings can be substantially reduced using a multi-layered strategy which includes, but is not limited to, the following mitigations: high levels of vaccination among teachers and eligible students; universal wearing of masks for teachers and students above the age of five (depending on the level of community transmission and other factors); improving ventilation to meet indoor air quality standards; provision of devices to measure CO_2 levels within school rooms as part of ventilation audits; provision of air purifiers with HEPA filters for high-risk rooms or rooms which cannot be adequately ventilated; the use of rapid antigen testing for policies to maximise in-person school days and reduce the risk of infected students attending; improving hygiene and cleaning of surfaces; cohorting of students and limiting mixing between cohorts; and, physical distancing where possible.[79, 80]

[78] Whitehead, J., Scott, N., Atatoa-Carr, P., Lawrenson, R. Will access to COVID-19 vaccine in Aotearoa be equitable for priority populations? New Zealand Medical Journal. 2021;134(1535):25-34. Available from https://journal.nzma.org.nz/journal-articles/will-access-to-covid-19-vaccine-in-aotearoa-be-equitable-for-priority-populations-open-access.

[79] European Centre for Disease Prevention and Control. COVID-19 in children and the role of school settings in transmission - Second update. [Internet]. 8 July 2021. Stockholm: ECDC;2021. Available from https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-in-children-and-the-role-of-school-settings-in-transmission-second-update.pdf.

[80] US Centres for Disease Control and Prevention. Covid-19: Guidance for Covid-19 prevention in K-12 schools. [Internet]. Updated 5 November 2021. Cited 29 November 2021. Available from https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/k-12-guidance.html.

Additional recommendations

36. In addition to our recommendations regarding the rollout of a paediatric vaccine for 5-11-year olds, we make the following recommendations that can be implemented immediately and which may mitigate the harm detailed above.

37. Given the disproportionate risks posed to Maaori children and their whaanau from any transmission of COVID-19 within educational settings, we recommend that schools and early childhood education centres (ECEs) in low-decile areas, in areas with lower vaccination coverage, and those schools and ECEs with a high proportion of Maaori students, receive a greater level of funding and resourcing to implement the above mitigations, and that these mitigations are implemented as a matter of urgency.

38. While we note that ventilation can be improved through the opening of doors and windows, this is not a practical solution in winter. Given that the rollout of a paediatric vaccine for 5-11-year olds will not apply to students of ECEs and will not completely mitigate the risk of spread of COVID-19 within schools,[81] we recommend that the Ministry of Education continue to work closely with air quality experts. The provision of devices for CO_2 monitoring and portable air purifiers with HEPA filters to schools and ECEs, with operational guidance provided for schools to support their use, is a matter of urgency before winter arrives.[82]

39. Including ECEs in the provision of devices to monitor CO_2 levels and portable air purifiers with HEPA filters is strongly recommended since children aged 0 - 3 years of age more readily transmit SARS-CoV-2 to household members than

[81] Steyn, N., Plank, M., Hendy, S. Modelling to support a future Covid-19 strategy for Aotearoa New Zealand. Auckland: Te Puunaha Matatini, The University of Auckland. 2021. Available from https://www.tepunahamatatini.ac.nz/2021/09/23/modelling-to-support-a-future-covid-19-strategy/.

[82] US Centres for Disease Control and Prevention. Covid-19: Ventilation in Buildings. [Internet]. Updated 2 June 2021. Cited 29 November 2021. Available from https://www.cdc.gov/coronavirus/2019-ncov/community/ventilation.html#refphf.

school-aged children,[83] and Pfizer vaccine trial data for children <5 years are still awaited.

40. We support the ongoing mandatory use of masks in schools for students in Year 4 and older at the Red and Orange tiers of the COVID-19 Protection Framework, which balances the developmental needs of young children with the need to mitigate risk of COVID-19 transmission. Schools should be resourced to provide masks for students and their whaanau who arrive at school unmasked, to reduce any inequities in ability to access masks.

41. We recommend that urgent preparatory work is undertaken to enable the use of rapid antigen testing to maximise in-person school days while at the same time reducing the risk of infected students attending. Modelling by the Doherty Institute has found that allowing ongoing school attendance for class contacts of a case through a 'test to stay' rapid antigen testing strategy achieves equivalent outbreak containment to home quarantine and maximises face-to-face learning.[84]

[83] Paul, L.A., Daneman, N., Schwartz, K.L., et al. Association of age and pediatric household transmission of SARS-CoV-2 infection. *JAMA Pediatr*. 2021;175(11):1151-1158. doi:10.1001/jamapediatrics.2021.2770. Available from https://jamanetwork.com/journals/jamapediatrics/fullarticle/2783022.

[84] Doherty Institute. Doherty Modelling – Final Report To National Cabinet. [Internet]. Melbourne: Doherty Institute. 5 November 2021. Cited 29 November 2021. Available from https://www.doherty.edu.au/uploads/content_doc/Synthesis_DohertyModelling_FinalReport__NatCab05Nov.pdf.

MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Myo(peri)carditis overview

[redacted]

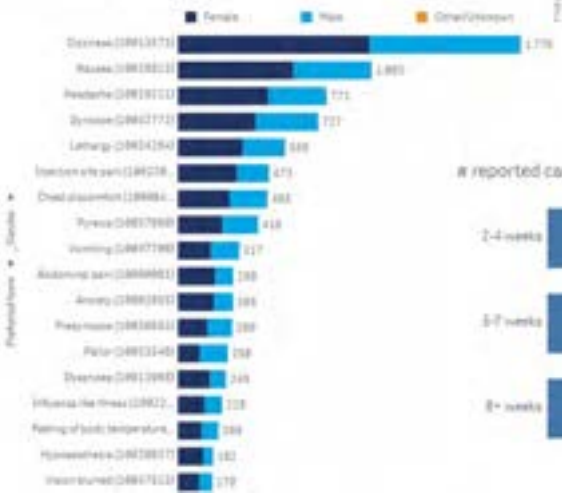
2021

General info on use in children

Vaccination status

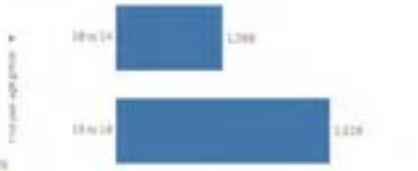
	12 to 14	15 to 19
not vaccinated	14765	20717
booked	665	831
partially vaccinated	23131	27016
fully vaccinated	161611	255573

people who experienced AEFI



Age group at vaccination date

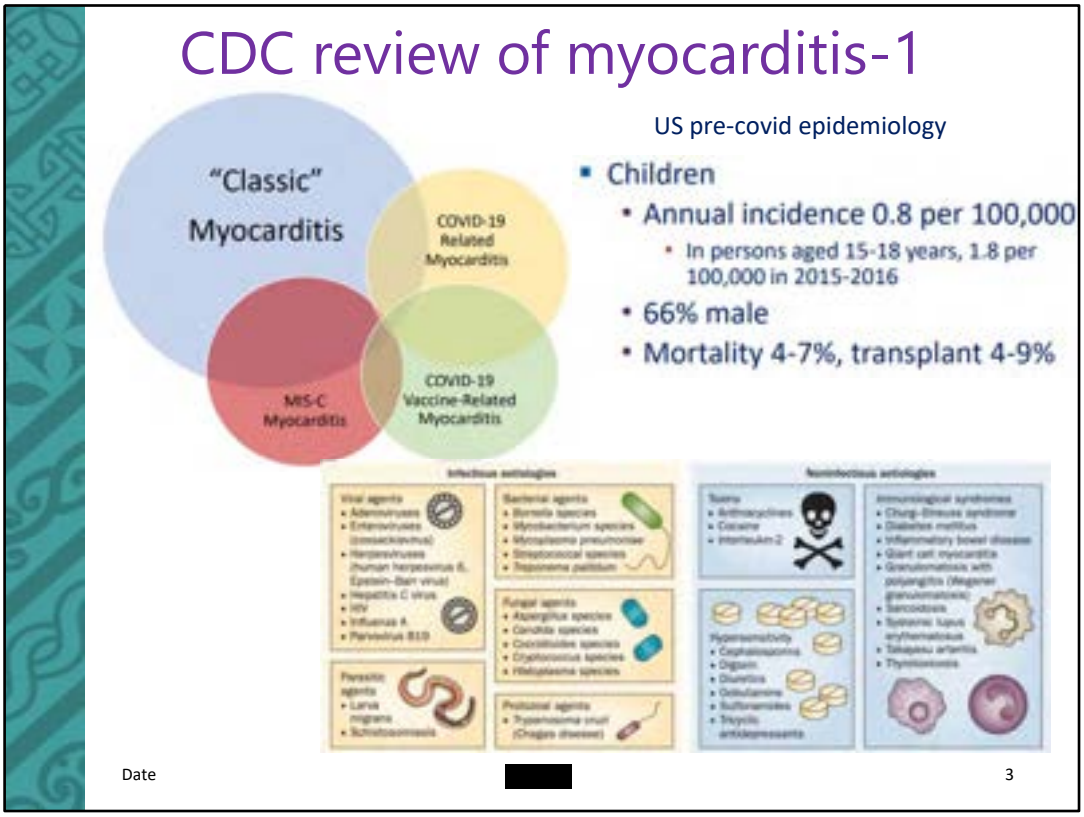
people who experienced AEFI



Dose interval in reported cases – brings back interval for dose1 reports as well as dose 2

reported cases

2

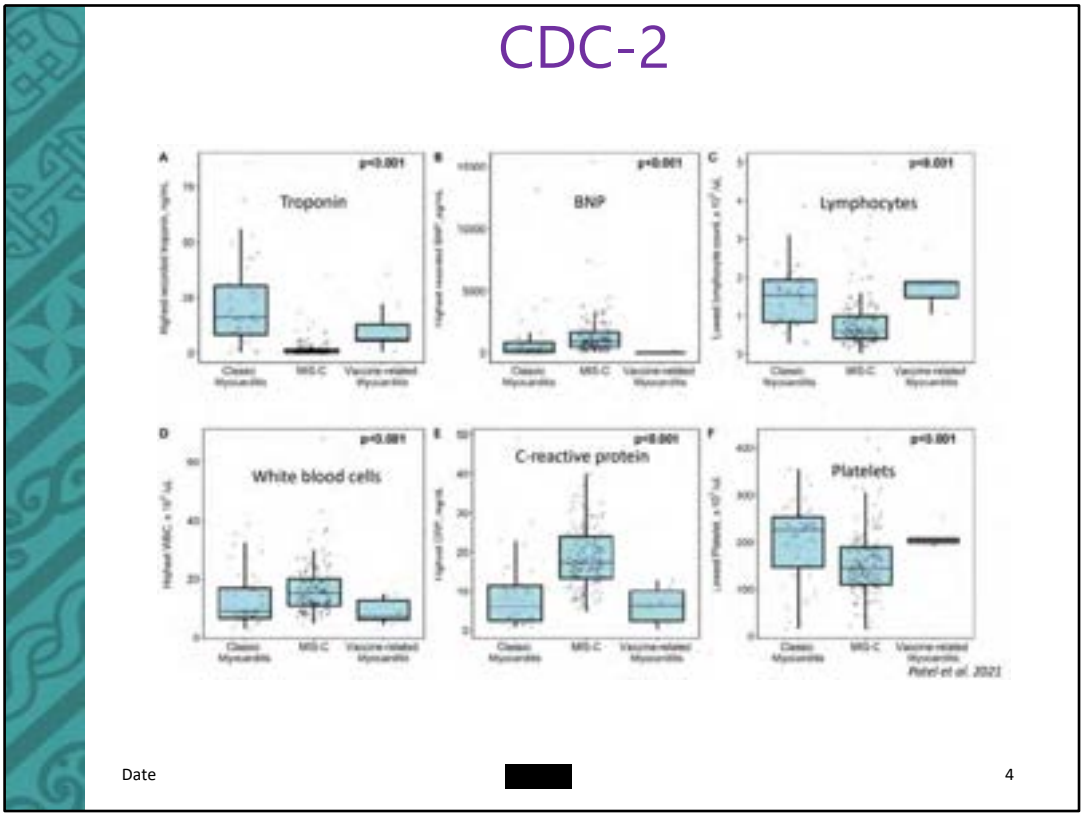


2 November 2021, a CDC review was presented in the US, one of the topics was mRNA Associated Myocarditis.

There they talked about comparing types of myocarditis.

Covid 19 related myocarditis can occur, for example in children **with or without** MIS-C (multisystem inflammatory syndrome in children) (finns oxå MIS-A).

Myocarditis can have many causes. Viral infection is the most common.



Comparison of MIS-C related myocarditis, classic viral myocarditis and Covid-19 vaccine related myocarditis in children (Patel et al 2021).

BNP (brain natriuretic peptide)

Retrospective cohort study.

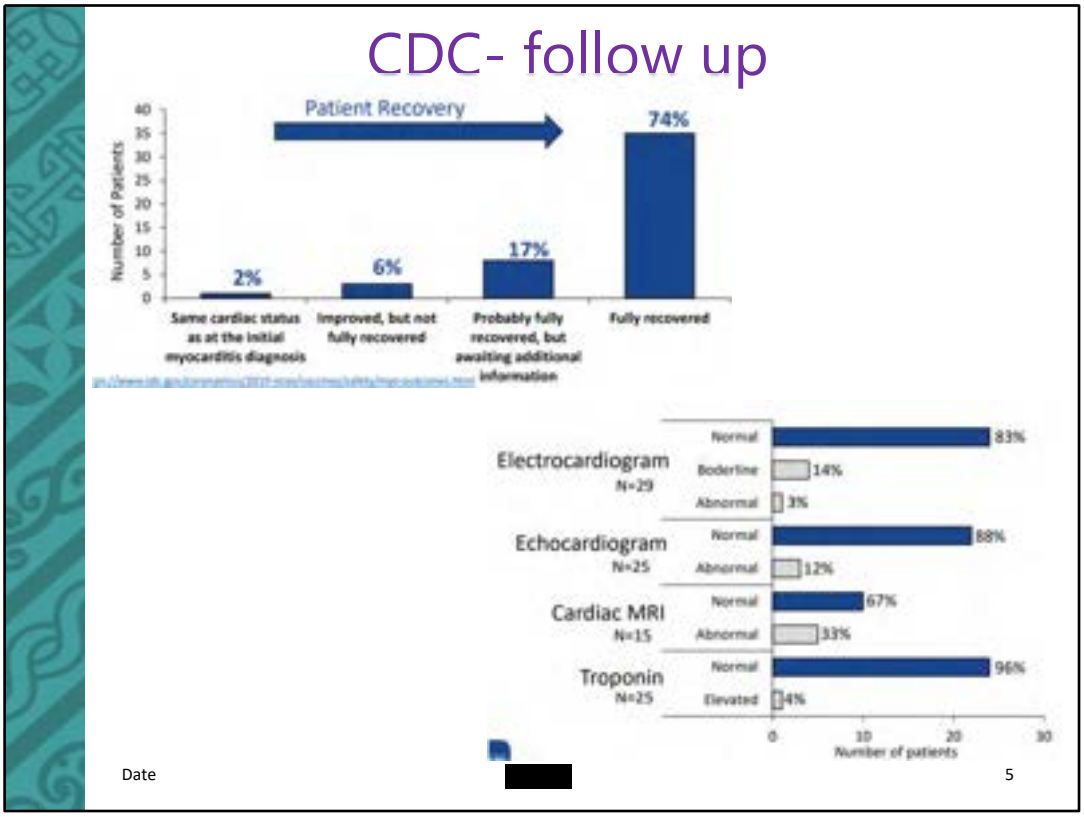
43 patients had classic myocarditis, **149** had MIS-C myocarditis, and **9** had COVID-19 vaccine-related myocarditis. Total **201** patients.

Peak troponin was highest in the classic myocarditis group, whereas the MIS-C myocarditis group had the highest recorded brain
natriuretic peptide (BNP). Lymphopenia, leukocytosis, thrombocytopenia and anemia in the MIS-C group.

Those with MIS-C were younger than those with classic myocarditis (median 7.5 years vs. 14.7 years) and vaccine-related myocarditis (median 15.5 years). All three groups had predominantly male sex.

Three months post discharge,
18 of 40 children (45%) in the classic myocarditis group still required heart failure treatment, whereas only one of the MIS-C myocarditis patients and none of the COVID-19
vaccine-associated myocarditis patients did.

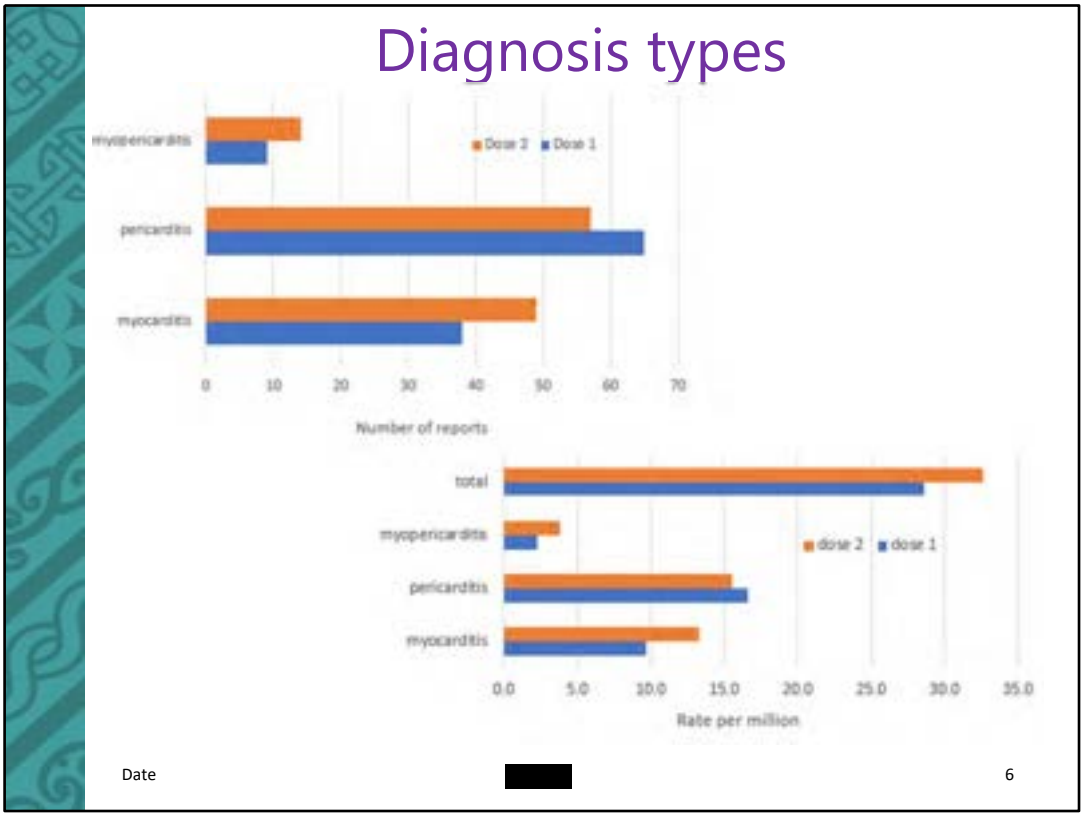
Conclusions: Compared to those with classic myocarditis, those with MIS-C myocarditis had **more significant hematologic derangements and worse inflammation** at presentation, but had **better clinical outcomes**, including rapid recovery of cardiac function. Patients with **COVID-19 vaccine-related myocarditis** had similar clinical presentation to patients with **classic myocarditis**, but their **pattern of recovery was similar to those with MIS-C**, with prompt resolution of symptoms and improvement of cardiac function.



CDC is following up outcome of myocarditis. Some little results starting to come.

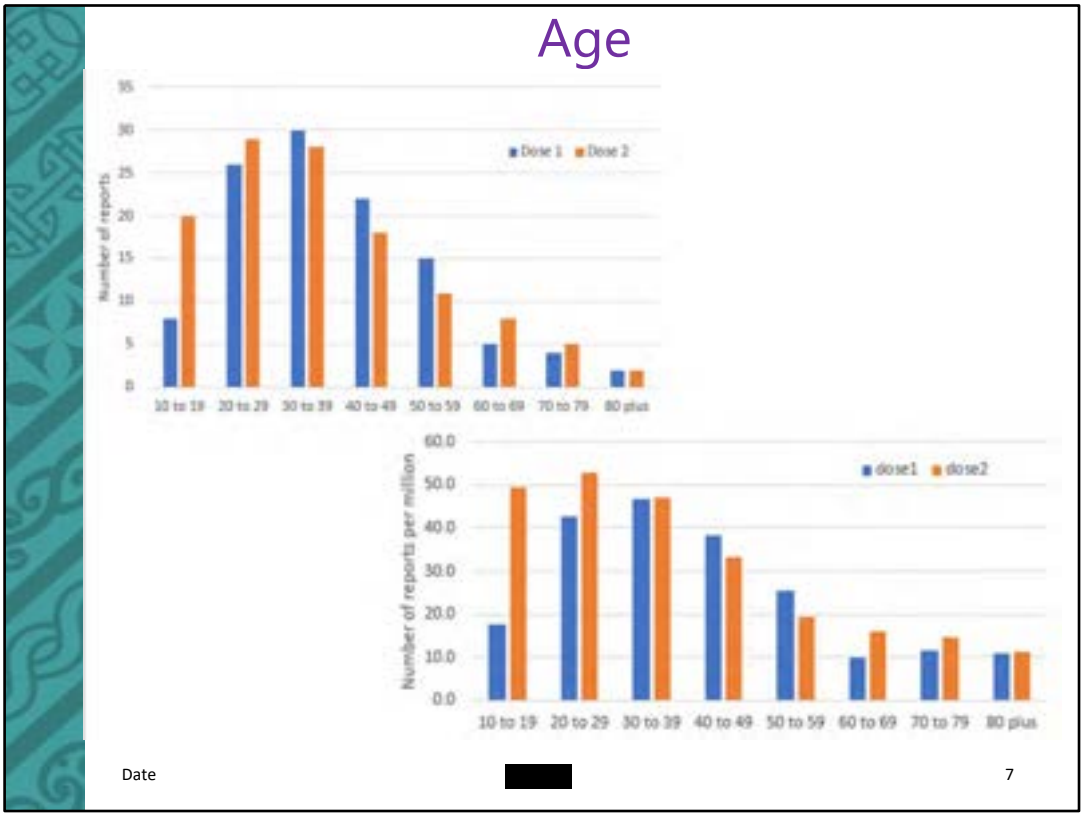
This is 'Cardiologist/healthcare provider assessment of recovery from myocarditis after COVID-19 vaccination by 3 months (n=47)'.

91% of cardiologists or healthcare providers indicated the patient was fully or probably recovered.

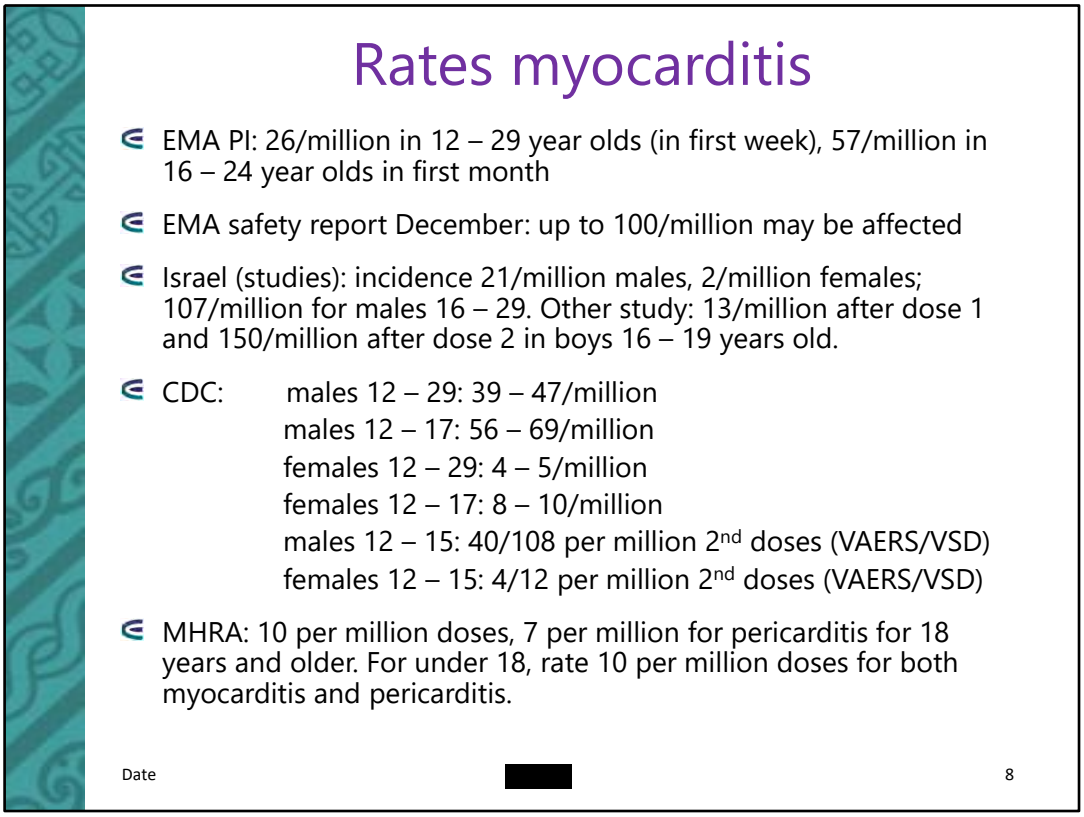


Number of reports

Rate: number of diagnoses per million people had at that time been vaccinated with dose 1 and dose 2 respectively.



We can see that dose 2 is becoming more of an issue in younger age groups when looking at the rate (number of reports per million vaccinated)



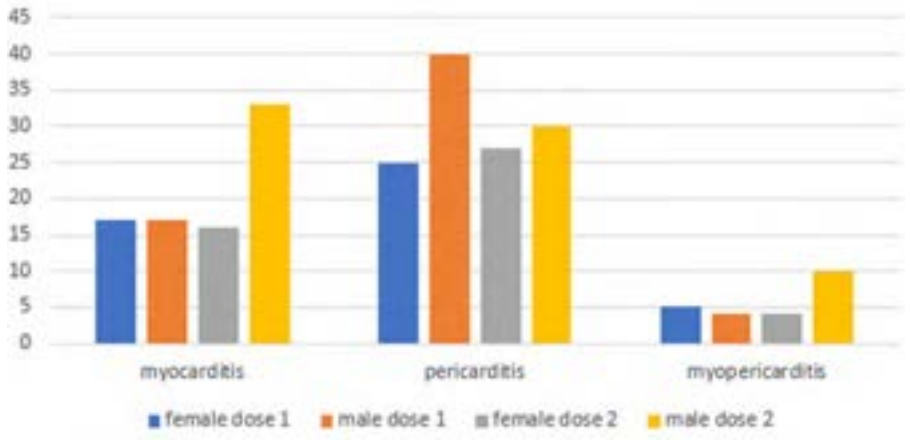
Kaiser study US 5.8 per mille

Larger difference between males and females after dose 2.

Europeans mainly.

This is number of reports on y-axis.

Diagnosis, dose and gender



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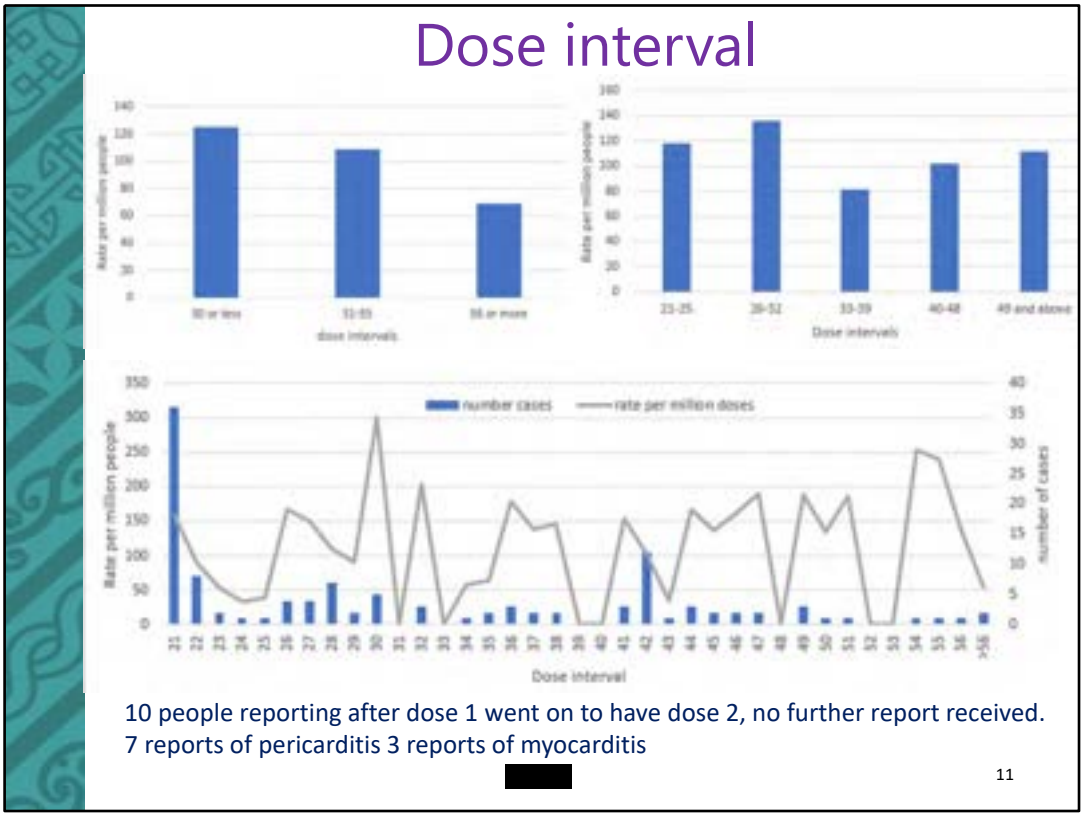
10



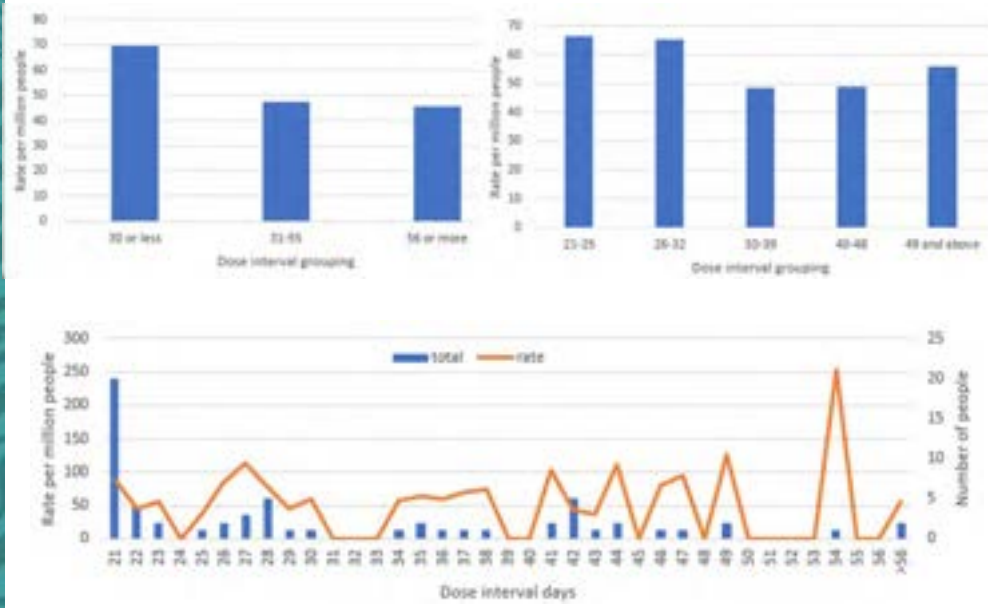
Number of reports with different dose intervals (30 days or less; between 31-55 days; 56 days or more).

Rate per million is number of diagnoses per million people that had that particular interval between their doses. The rate fluctuates a lot, and therefore it matters a lot how you cut the intervals for how many cases you see in that interval.

21-25 approx 3 weeks
26-32 approx 4 weeks
33-39 approx 5 weeks
40-48 approx 6 weeks
49 and above
56 is 8 weeks

Results in the other staple diagram which does not show as much difference

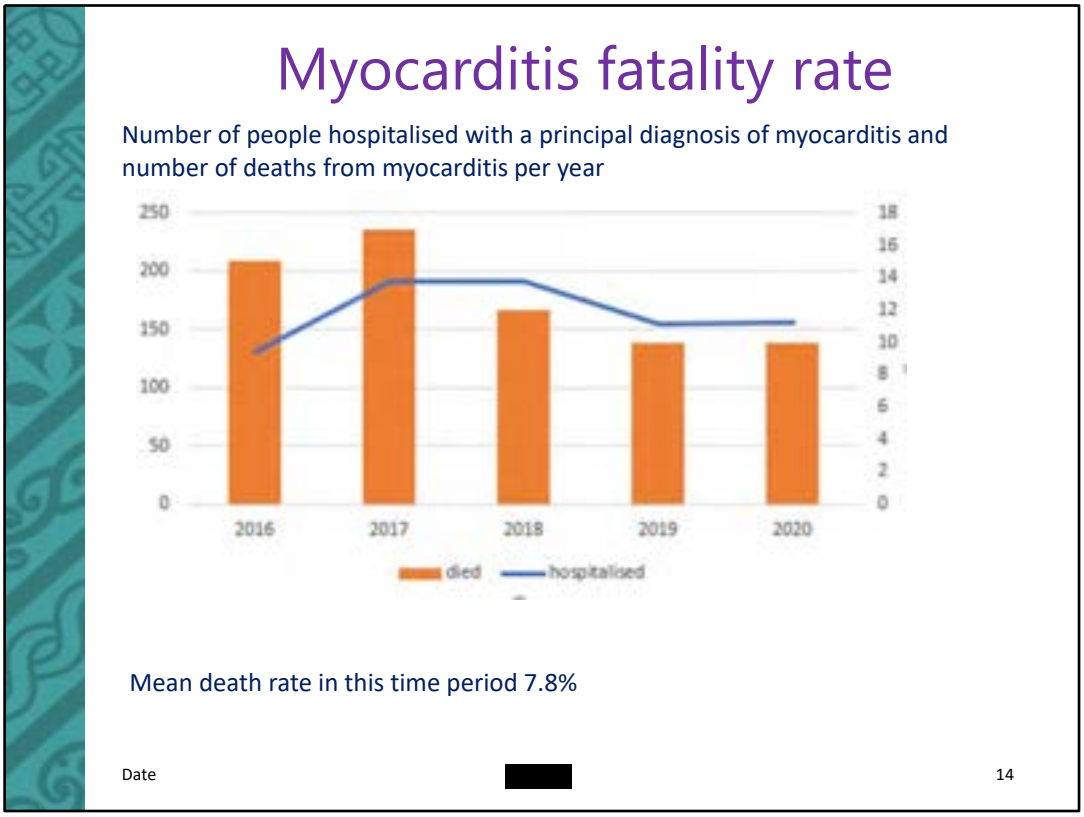
Dose interval- myocarditis



Date [redacted] 12

Fatal Cases - NZ

- 57-y-o-f 3 days after dose 1. Thymoma, UTI, fulminant necrotizing eosinophilic myocarditis.
- 26-y-o-m 12 days after dose 1. Fulminant necrotizing, eosinophilic, lymphocytic with giant cells.
- 13-y-m-11 days after dose 2. No symptoms reported. Lymphocytic myocarditis.



This only captures patients that were hospitalised.

To the left is patients that were hospitalised with myocarditis
To the right is fatalities

No particular trend.

Mean death rate average deaths per year/average hospitalisations per year = 7.8%

Higher than vaccination fatality rates.

8 Dec 2021:

Fatality rate per million doses: per million vaccinated people:	**Fatality rate**
7,762,793 doses administered; fully vaccinated	3,699,639
1 mors – 0.12 fatalities per million doses per million vaccinated people	0.27 fatalities
2 mors – 0.26	0.54
3 mors – 0.39	0.81
4 mors – 0.52	1.08

Comparison: Japan 0.09 fatalities per million doses

Fatality rate per reported myocarditis/myopericarditis cases
Number of reported cases: 110 (87 of them myocarditis)
1 mors – 0.9%
2 mors – 1.8%
3 mors – 2.7%
4 mors – 3.6%

Literature cases

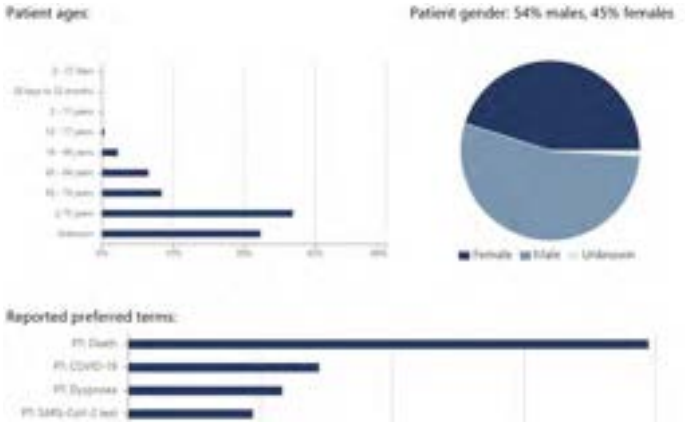
- **Abbate et al (US)-** Approximately 21 h after admission, patient with fulminant myocarditis temporally associated with Comirnaty died due to recurrent cardiac arrest and refractory shock.
- **Choi et al (South Korea)** - A 22-year-old man who developed chest pain 5 days after the first dose of the BNT162b2 mRNA vaccine died 7 hours later.
- **Chouchana et al (Vigibase)** - June 2021 22 fatal myo/pericarditis reports for mRNA vaccines.
- **Ho et al (Singapore)** – One patient with vaccine induced myocarditis died after a total of 9 million doses of mRNA vaccines had been given in Singapore.
- **Lane et al (spontaneous data from UK, EU and US)** - Post-mortem examination revealed myocarditis as the cause of death in one 65-year-old male. This patient had pre-existing cardiac disease, therefore it was not conclusively determined whether exposure to the vaccine resulted in this patient's death.
- **Mevorach et al (Israel)** – from 136 cases of definite or probable myocarditis, one person with fulminant myocarditis died.
- **Pillay et al (systematic review)** - Almost all reports of death are from unverified cases and of unclear cause**.**
- **Schneider et al (Germany) -** In one case (65M) after vaccination with Comirnaty, myocarditis was found to be the cause of death. (likely Lane et al case)

International information

- Regulators who have informed us they have fatal myocarditis cases
  - Japan
  - UK
  - Canada
  - Switzerland
- Regulators without fatal cases
  - Singapore

Total reported cases and fatal cases Vigilyze

- Total number of reported ADR cases for Comirnaty globally, all ages: 1,143,318 on 1.6 billion administered doses
- Of these 20,348 fatal (Pfizer SMSR Oct 9,190)

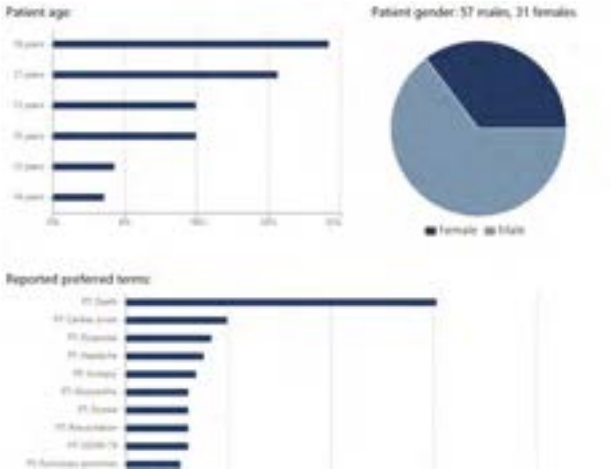


- Myocarditis was reported PT in 132 (0.6% of the fatal cases).

Date [redacted] 17

Year group 12 – 17 Vigilyze

- Total 88 fatal cases in year group 12 - 17.
- Myocarditis was reported PT in 9% (8 reports) of the fatal cases.

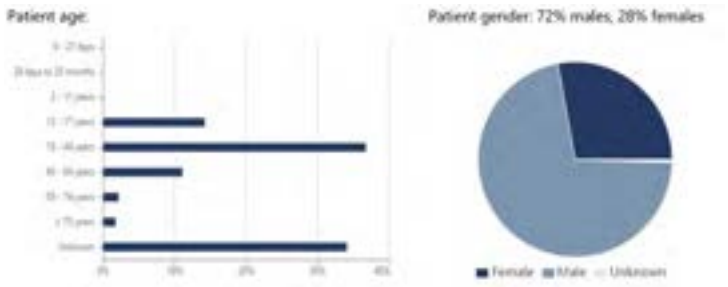


Date

18

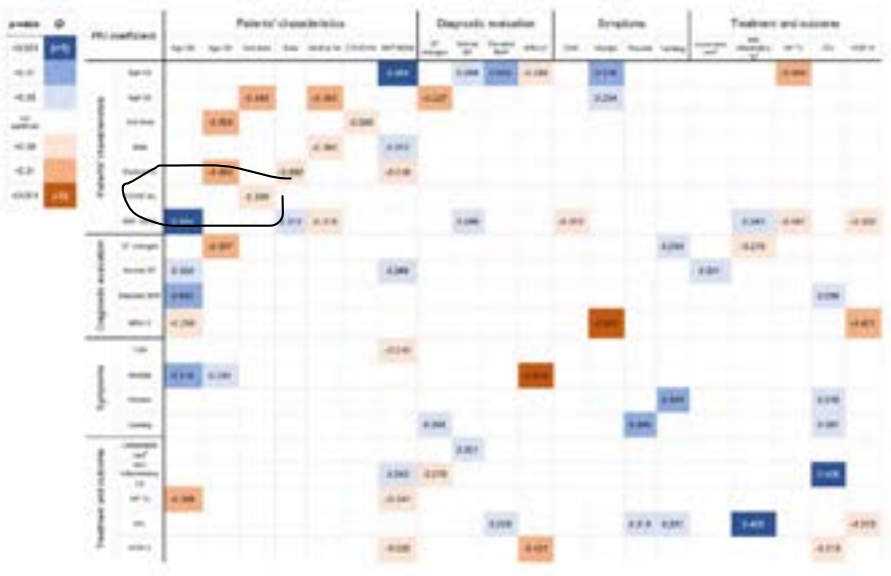
PT Myocarditis Vigilyze

- Total number of reported cases 9,797 (Pfizer SMSR Oct 4,100).



- Fatal reports 132.
- Of those, 8 were in year group 12 – 17.
- Very limited information in the cases.

Why is NZ different?



Correlation among key clinical characteristics and diagnostic findings with Phi(Φ) coefficient. Woo et al doi: 10.1002/jmv.27501

Date [redacted]

20

Medicines Adverse Reactions Committee

Meeting date	**2 December 2021**	Agenda item	
Title	**Update of Risk Management Plan for Comirnaty to include vaccination of children 5 - <12 years of age**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice/ For information
Active constituent	**Medicine**	**Sponsor**	
Tozinameran	Comirnaty	Pfizer BioNTech	
Funding	There is a funded immunisation programme		
Previous MARC meetings	The first Risk Management Plan was discussed at an out of session meeting on 20 January 2021.		
Advice sought	The Committee is asked to advise whether the following questions/requests should be addressed to the company or whether additional questions or amendments are required: • The company should provide more information on how they plan to monitor the safety and efficacy in children post-marketing? • The number of participants for NZ relevant ethnic minorities was very low and use in these populations should be considered to be missing information. The company should provide more information on how they intend to monitor the safety and efficacy in different populations? • Use in patient with previous COVID-19 or other COVID infections is also considered to be missing information. The company should provide more information on how they are intending to monitor safety and effectiveness in this group? • Only one interaction study on co-administration with influenza vaccine is planned. In children many more vaccines have the potential to be co-administered. The company should consider further interaction studies.		

Table of Contents

1.0 PURPOSE

This paper summarises an updated Risk Management Plan (version 3.0) for Comirnaty/ Tozinameran/ BNT162b2, a COVID-19 mRNA vaccine jointly developed by BioNTech and Pfizer. This RMP update was made in conjunction with the extension of the indication to children 5 to <12 years of age.

2.0 PRODUCT OVERVIEW

2.1 Description

Comirnaty COVID-19 mRNA Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

The nucleoside-modified messenger RNA in Comirnaty is formulated in LNPs, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Two new products (see section 2.4) will be introduced containing a new formulation.

Composition of the new formulation:
Nucleoside-modified messenger RNA formulated in LNPs.
White to off-white frozen dispersion (pH:6.9 – 7.9).
Excipients:

- (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
- 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
- 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
- cholesterol
- trometamol
- trometamol hydrochloride
- sucrose
- water for injection

Composition of the currently used product:
Nucleoside-modified messenger RNA formulated in LNPs.
White to off-white frozen dispersion (pH:6.9 – 7.9).
Excipients:

- (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
- 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
- 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
- cholesterol
- potassium chloride
- potassium dihydrogen phosphate
- sodium chloride
- disodium phosphate dihydrate
- sucrose
- water for injection

2.2 Proposed indication

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 years of age and older.

2.3 Proposed dosage

Children 5 to 11 years: Administered intramuscularly after dilution as a course of 2 doses (0.2 mL each / 10 microgram). It is recommended to administer the second dose 3 weeks after the first dose.

From 12 years and above: Administered intramuscularly after dilution as a course of 2 doses (0.3 mL each / 30 microgram) at least 21 days apart. The new formulation will not require dilution, see below.

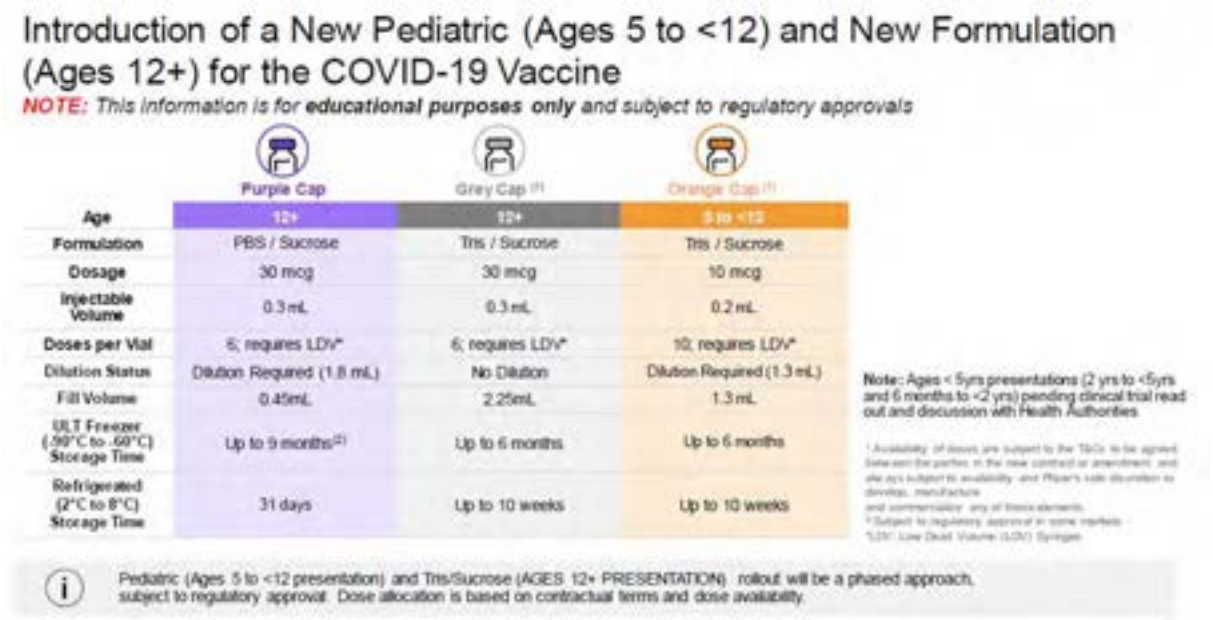
2.4 Proposed pharmaceutical form(s) and strengths

Two new products will be introduced with the new formulation:

Children 5 to 11 years: 10 micrograms/dose concentrate for dispersion for injection. After dilution each vial contains 10 doses of 0.2 mL.

From 12 years and above: Concentrate for dispersion for injection (sterile concentrate). No dilution required for the new formulation. Each vial contains 6 doses of 0.3 mL.

Figure 1. Description of the 2 new products as well as the currently used (purple cap) product



Comments: The currently used suspension of Comirnaty (for 12 years and over) has the concentration 0.5 mg/ml and each dose of 0.3 ml after dilution contains 30 micrograms of BNT162b2. However, this suspension has been reformulated so that dilution is no longer needed. The suspension for use in children 5-11 years old is the same new formulation but it needs dilution, and each dose (0.2 ml) contains 10 micrograms of Comirnaty.

The different vials will, apart from having different labels, be distinguished by different colours of the cap, see figure 1.

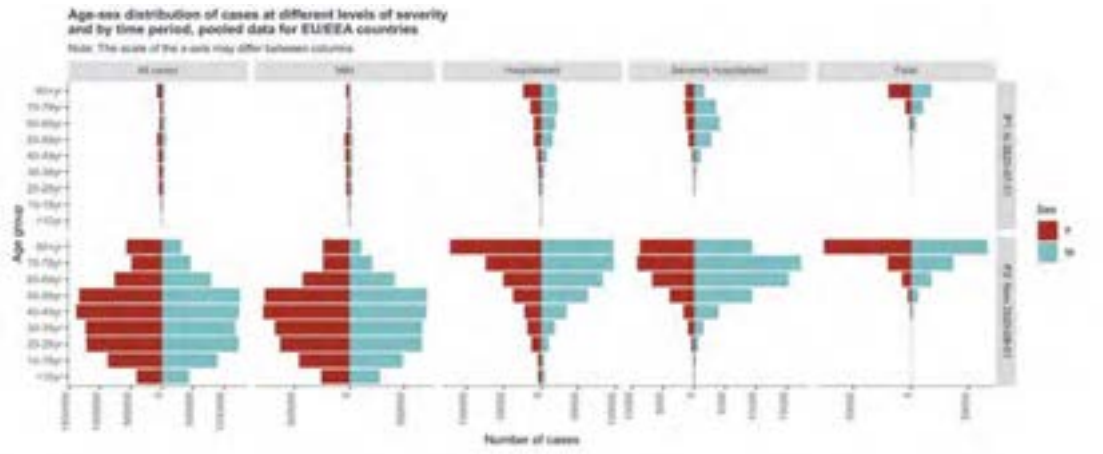
In addition, it is expected that there will be old formulation of 30 microgram/dose (for 12 years and over) that requires dilution still in use during a cross-over period. The risk of medication errors when using the different vials is considered to be high.

3.0 SAFETY SPECIFICATION

3.1 Epidemiology of the Indications with a focus on children

Since the beginning of the Covid-19 pandemic, the ECDC has continuously collected COVID-19 information from all EU/EEA member states. The ECDC's TESSy database, contain over 80% of the official number of cases reported. TESSy data on age and sex distributions by severity of symptoms as posted on 12 August 2021 are shown in Figure 2.

Figure 2. Age-Sex distribution of COVID-19 Cases as Different Levels of Severity, Pooled data for EU/EEA countries. Case-based Data from TESSy produced on 12 August 2021[a]



Note: "mild" = a case that has not been reported as hospitalized or a case that resulted in death.
a. Data from ECDC. COVID-19 Surveillance report. Week 31, 2021, 12 August 2021. "2.2 Age-sex pyramids" Accessed 15 August 2021.

It is noted by the company that cases reported in TESSy have been older than the general population throughout the pandemic, with few cases observed in people aged younger than 20 years. This likely reflects the age distribution of people who met the requirements for being tested and is unlikely to reflect the actual distribution of infections in the population.

In the US in general, Covid disease has been much less severe among ages 0-24 compared to ages ≥25 years, with 2.5% hospitalised, 0.8% admitted to an intensive care unit, and <0.1% dying among ages 0-24, versus 16.6% hospitalised, 8.6% intensive care, and 5% dying among ages ≥25 years. Research from the US has also shown that among the paediatric population, children age 12-17 were more frequently infected than those under age 12 and that COVID-19 cases aged 0-1 and 12-18 years were more likely to develop serious illness than those aged 2-11.

There are several factors increasing the risk of initial infection in children such as:

- infected adult living in the same household
- some ethnic groups. For example: among 121 SARS-CoV-2-associated deaths among persons <21 years of age reported to the American CDC, nearly 80 percent occurred among Hispanic, non-Hispanic Black, and non-Hispanic American Indian/Alaskan Native persons, who account for approximately 40 percent of the population <21 years of age.

- underlying medical conditions, such as asthma, obesity, congenital heart disease, and neurological conditions.

According to a recent meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients 0.1-2%. In a study from January through June 2020 using the National Child Mortality Database (NCMD) in England, 5.7% of 437 children 0-17 years of age who died were SARS-CoV-2 PCR-positive and those who died of COVID-19 were older and were more likely to be non-White ethnicity.

For 'long COVID', a NICE guideline from 2020 included both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more and for which signs and symptoms are not explained by an alternative diagnosis) in that definition. Post-acute COVID symptoms in children with asymptomatic or mild disease appear to be less severe than in adults, with the most common symptoms being a post-viral cough (4%), fatigue (2%), or both symptoms (1%) with the duration of symptoms lasting 3 to 8 weeks. Children who are infected with COVID-19 are at risk of subsequent multisystem inflammatory syndrome (MIS-C) and often develop a rash following resolution of COVID-19. As of August 19, 2021, there were 4,403 cases of MIS-C reported to health departments in the United States.

Comment: The RMP does not include as much information on long COVID and children as expected, and there is a lack of knowledge both regarding rates, duration and symptoms (especially if not related to MIS-C) of this phenomenon.

Current information indicates approximately 4 percent of children with SARS-CoV-2 had symptoms for ≥28 days and <2 percent for ≥56 days. The number of symptoms decreased over time. In a population-based cohort study, 4 of 109 children (median age 11 years) who were seropositive for SARS-CoV-2 had ≥1 caregiver-reported symptom that persisted for >84 days, compared with 2 percent of 1,246 seronegative controls.

3.2 Non-Clinical Summary

Not relevant to this update as no new information presented.

3.3 Clinical Trial Exposure

3.3.1 The three studies that are basis for clinical trial data analysis in the RMP

BioNTech conducted a first-in-human dose level–finding Phase 1/2 study (BNT162-01) in Germany to gather safety and immunogenicity data to enable evaluation of 4 vaccine candidates individually to inform the overall clinical development of a COVID-19 mRNA vaccine, study C4591001.

Phase 3 of the pivotal study C4591001 (which is ongoing) evaluates the efficacy and safety in all participants (including 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort as well as a 12- to 15-year-old cohort). Total number of participants: 46,000.

Follow-up was initially planned for up to 24 months. However, after completing the final efficacy analysis, MAH started to unblind all participants so those randomised to placebo could be offered vaccine in accordance with local authorisation. Therefore, a placebo group for comparison of safety data is only available for up to 6 months post Dose 2.

The initial efficacy analysis on the 16 years and older population was event driven. Analysis of 6-month post Dose-2 data was conducted on 16 years of age and older, and a further efficacy analysis on 12- to 15-year-old cohort participants, were reported by 13 March 2021.

Further evaluation for the paediatric population (5-<12 years of age) has been conducted in study C4591007. Phase 1 is the dose finding portion of the study. The placebo controlled and observer blinded Phase 2/3 part of the study (which is ongoing) was planned to evaluate BNT162b2 at the selected dose levels for each age group for safety and tolerability, immunogenicity, and efficacy (depending on meeting success criteria for immunobridging and accrual of a sufficient number of COVID-19 cases). An immunobridging analysis was designed to compare responses (neutralizing antibodies) in paediatric participants within each age group in Study C4591007 to young adult participants 16 to 25 years of age in the study C4591001.

The population for analysis of clinical trial data in this RMP therefore includes the following 3 trials: C4591007, C4591001 and BNT162-01 (A multi-site, phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy adults).

Comments: The update of the RMP was approved by Pfizer 13 October 2021.

FDA requested a second cohort analysis from study C4591007 to increase the safety population being studied and a report was presented on 18 October 2021. The second cohort consisted of approximately 2,250 newly recruited participants 5 to <12 years of age who were randomized 2:1 to receive Comirnaty 10 µg or placebo. Results were presented up to the data cutoff date of 08 October 2021. Additionally, a summary of new AEs was provided for the initial enrolment group (cohort 1).

3.3.2 Exposure and ethnicity in study C4591001, all ages

The pivotal study C4591001 is a Phase 1/2/3, placebo-controlled, randomised, observer-blind, dose-finding, study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. Exposure by age, gender and ethnicity in this study, all ages are shown in tables 2 to 4.

Table 2: Exposure by age group and gender to proposed dose (30 µg) (blinded part of C4591001)

Dose Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 30 µg				
≥12 years to ≤15 years	567	564	1128	1127
≥16 years to ≤17 years	187	191	373	379
≥18 years to ≤55 years	6456	6249	12770	12373
>55 years to ≤64 years	2231	2177	4421	4328
≥65 years to ≤74 years	1934	1707	3858	3407
≥75 years to ≤84 years	511	391	1020	781
≥85 years	12	11	23	21
Total	11898	11290	23593	22416

Table 3: Exposure by age group and gender to proposed dose (30 µg) (open label follow up, people who first got placebo and received Comirnaty after unblinding in C4591001)

Dose Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 30 µg				
≥12 years to ≤15 years[a]	26	23	36	32
≥16 years to ≤17 years	152	141	250	229
≥18 years to ≤55 years	5424	5708	9450	10101
>55 years to ≤64 years	1973	2012	3602	3713
≥65 years to ≤74 years	1801	1613	3530	3170
≥75 years to ≤84 years	495	311	976	613
≥85 years	13	4	25	8
Total	9884	9812	17869	17866

Note: 30 µg includes data from phase 1 and phase 2/3.
a. Includes subjects who became eligible for unblinding at 16 years of age, confirmed to have received placebo originally and then received BNT162b2 post unblinding.
PFIZER CONFIDENTIAL SDTM Creation: 25MAR2021 (23:24) Source Data: adsl Table Generation: 27MAR2021 (12:46) (Cutoff Date: 13MAR2021, Snapshot Date: 25MAR2021) Output File: /nda2 unblinded/C4591001 PVP BLA/adsl s932 open

Table 4: Ethnicity of participants in study C4591001

Table 28 shows exposure in blinded part of 4591001, all ages:

Table 28. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001) – Blinded Placebo-Controlled Follow-up Period

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
Racial origin		
White	19052	37815
Black or African American	2153	4257
Asian	1026	2040
American Indian or Alaska Native	225	437
Native Hawaiian or other Pacific Islander	61	121
Multiracial	574	1145
Not reported	97	194
Total	23188	46009
Ethnic origin		
Hispanic/Latino	5838	11513
Non-Hispanic/non-Latino	17237	34271
Not reported	113	225
Total	23188	46009

Note: 30 µg includes data from phase 1 and phase 2/3.

3.3.3 Exposure and ethnicity in study C4591007 ages 5 to <12

Exposure, gender and ethnicity in the age group 5 to <12 in study C4591007 is shown in tables 5-7.

Table 5: Exposure and gender in participants 5 to <12 years of age to proposed dose (10 µg) (C4591007)

Part of the study Exposure	Total Number of subjects	Male	Female
Phase 1 Open label 1 dose 2 doses Total	 12 16 28	 11	 17
Phase 2/3 1 dose only 2 doses Total	 3 1,1515 1,1518	 799	 719

* Phase 2/3 Blinded Placebo-Controlled Follow-up Period

Table 6: Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591007) – Phase 2/3 – Blinded Placebo-Controlled Follow-up Period

Age Group Dose Race/Ethnic Origin	Number of Participants Exposed to BNT162b2	Total Number of Vaccine Doses
Participants 5 years to <12 years		
Vaccine 10 µg		
Racial origin		
White	1204	2405
Black or African American	89	178
Asian	90	180
American Indian or Alaska Native	12	24
Native Hawaiian or other Pacific Islander	5	10
Multiracial	109	218
Not reported	9	18
Total	1518	3033
Ethnic origin		
Hispanic/Latino	319	638
Non-Hispanic/non-Latino	1196	2389
Not reported	3	6
Total	1518	3033

PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: (CDISC)\C4591007_RMP_PVP\adsl_s942

Table 7: Exposure to BNT162b2 by Special Population (C4591007) – Phase 2/3 – 5 to <12 Years of Age – Blinded Placebo-Controlled Follow-up Period

Population	Number of Participants Exposed to BNT162b2 (10 µg) (Na=1518) nb	Total Number of Vaccine Doses
Participants with any baseline comorbidityc	312	623
Asthma	119	237
Blood disorders	1	2
Cardiovascular disease	8	16
Chronic lung disease	1	2
Chronic metabolic disease	2	4
Congenital heart disease	15	30
Diabetes mellitus	2	4
Feeding tube dependent	2	4
Immunocompromised condition	1	2
Neurologic disorder	19	38
Obesed	174	348
Sickle cell disease	1	2

Comments: The safety expansion group of C4591007 (cohort 2) included 1,591 vaccinated individuals aged 5-<12 and 1,580 of them also received dose 2. Most of the people in the vaccination group were white (75%), Asian (11%) or multiracial (8%); the median age was 8 years and 51% of participants were male. Obese children made up 11% of the vaccination group. Most reported comorbidities were asthma, neurologic disorders and congenital heart disease. Similar proportions of participants in the Comirnaty group (10%) and placebo group (10%) had baseline SARS-CoV-2 positive status. The children had a medical history profile consistent with the general population.

3.3.4 Summary of exposure with a focus on younger age groups

Participants aged 16-17 years of age: Exposure to 30 µg BNT162b2 for participants aged 16 - 17 years in the blinded part of study C4591001 was 378 subjects Another 293 who originally got placebo received at least one dose BNT162b2 after unblinding.

Participants 12-15 years of age: Clinical study exposure data for the 12- to 15 years of age are provided for the ongoing study C4591001 at the cut-off date of 13 March 2021. Exposure to 30 µg BNT162b2 for participants aged 12-15 years in the blinded part of study C4591001 was 1,131 subjects. Another 49 who originally got placebo got at least one dose BNT162b2 after unblinding.

Participants aged 5 to <12 years of age: As of the cut-off date of 06 September 2021 of the ongoing study C4591007; 1,515 participants had received 2 doses and 3 received 1 dose of 10 µg Pfizer BioNTech COVID-19 Vaccine in the Blinded-Placebo Controlled Follow-up period (Phase 2/3). Another 48 were vaccinated in the Phase 1 part of the study (with 10, 20 or 30 µg dose).

Comment: The number of exposed people in younger age groups in trials is low, especially among the 12-15 years of age. There is no information in the RMP regarding age brackets for the group 5-<12 years old children included in study C4591007, so it is unclear how many of the youngest age groups were exposed.

However, the safety report from 18 October added approximately 1,500 children 5- <12 years old, who were vaccinated with 10 microgram Comirnaty, making the total number of exposed children to approximately 3,100. Immunogenicity was assessed in a subset of 322 participants.

Duration of follow-up varied between cohort and 1 and 2 in study C4591007. The first cohort included approximately 1,500 vaccine recipients and 750 placebo recipients of whom 95% combined had at least 2 months of safety follow up after completing a two dose primary series. Safety data included solicited adverse events, unsolicited adverse events, serious adverse events, and adverse events of special interest.

For cohort 2, the same safety monitoring was included but focusing on SAE and AE of clinical interest due to the shorter follow up time. The cohort size was approximately the same as cohort 1 but the median duration of follow up here was 2.4 weeks post dose 2 at the time of data cut off. Information has been requested from the sponsor for additional safety data with longer follow-up time.

3.3.5 Other ongoing studies

Ongoing Pfizer-BioNTech COVID-19 mRNA vaccine studies also include:

- C4591005: A phase 1/2 study to evaluate the safety, tolerability, and immunogenicity of an RNA vaccine candidate against COVID-19 in healthy Japanese adults. One hundred sixty participants were randomly assigned in a 3:1 ratio to study intervention (candidate vaccine: 120, placebo: 40).
- C4591015: A phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. Approximately **4000 pregnant women** at 24 to 34 weeks gestation are being randomised in a 1:1 ratio to vaccine or placebo.
- C4591020 A phase 3, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of multiple formulations of the vaccine candidate BNT-162B2 against Covid-19 in healthy adults 18 through 55 years of age.
- C4591031 A phase 3 master protocol to evaluate **additional dose(s)** of BNT162B2 in healthy individuals previously vaccinated with BNT162B2.
- BNT162 01 A multi-site, phase I/II, 2-Part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID 19 using different dosing regimens in healthy and **immunocompromised** adults.
- BNT162 033 Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (**BNT162b1**) in Chinese healthy subjects: A phase I, randomized, placebo- controlled, observer-blind study.
- BNT162-04 A multi-site, phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of a prophylactic SARS-CoV-2 RNA vaccine (**BNT162b3**) against COVID-19 using different dosing regimens in healthy adults.
- BNT162-063 Safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population: A phase II, randomized, placebo-controlled, observer-blind study.
- BNT162-14 A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of **one or two boosting** doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.
- BNT162-17 A Phase II trial to evaluate the safety and immunogenicity of a SARS-CoV-2 **multivalent** RNA vaccine in healthy subjects.
- B7471026 A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older.

3.4 Populations not studied in the development programme

3.4.1 Inclusion criteria in the clinical trials, all ages:

- Healthy participants
- Healthy participants with pre-existing stable disease, defined as disease stable during the 6 weeks before enrolment
- Phase 2/3 only: Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (such as using mass transportation, relevant demographics or front-line essential workers)

3.4.2 Exclusion criteria in the clinical trials, all ages:

- Previous vaccination with any coronavirus vaccine.
- Previous clinical or microbiological diagnosis of COVID-19 (phase 1), participants with prior undiagnosed infection were allowed in phase 2/3 (nasal swabs were taken after vaccination).
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study
- Women who are pregnant or breastfeeding.
- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality.

Of the exclusion criteria only Immunocompromised individuals with known or suspected immunodeficiency and Women who are pregnant or breastfeeding were considered to be missing information.

3.4.3 Exposure of Special Populations included or not in Clinical Trial Development Programmes:

- Pregnant women: limited experience. 50 cases of pregnancy in C4591001. Studied in C4591015.
- Breastfeeding women: limited experience. No cases of breastfeeding in C4591001.
- Participants with relevant comorbidities (hepatic/renal impairment, cardiovascular disease, immunocompromised, disease severity different from inclusion): included if stable 6 weeks before inclusion. Participants with potential immunodeficient status were not specifically included in the study population. In the year group 5-<12, most subjects with comorbidities had obesity or asthma. In the year group 12-15, most subjects with comorbidities had obesity or chronic pulmonary disease. In the year group 16 and older, most subjects with comorbidities had obesity, chronic pulmonary disease, diabetes with or without complication or malignancy.
- Ethnicity: mostly white in all age groups. Very, very few Native Hawaiians or other Pacific Islanders.
- Subpopulations carrying relevant genetic polymorphisms: no information.
- Elderly (≥65 years old): 8846 participants 65 years of age and over.

3.5 Post-authorisation exposure

Cumulatively, through 18 June 2021, approximately 774,478,440 doses of Comirnaty were shipped worldwide, corresponding to 642,817,105 estimated administered doses (based on that 83% of the doses were administered (based on data from EEA and US)). Total number of shipped dosed to Australia/New Zealand was 5,681,520 corresponding to 4,715,662 doses administered.

In the EEA countries; 451,547 dose 1 and 113,343 dose 2 had been administered to individuals <18 years of age.

Comment: According to the latest SMSR, approximately 1,958,966,949 doses of Comirnaty were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 October 2021, corresponding to approximately 1,584,774,361 estimated administered doses.

3.6 Identified and potential risks

Table 8 shows the summary of safety concerns for Comirnaty.

Table 8

Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

3.6.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Identified risks not considered to be important: Injection site pain, Injection site swelling and Injection site redness, Pyrexia, Chills, Fatigue, Headache, Myalgia, and Arthralgia.

Reactogenicity in the younger age groups:

- Local reactions: pain at the injection site was reported more frequently in the younger age group (16-55 years), similar after dose 1 and 2. Redness, swelling similar between groups.
- Systemic reactions: generally increased in frequency and severity in the younger group (16-55 years of age) with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2).
- For 5 – <12 years of age: pattern of local reactions reported after each dose generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001 with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site (still within tolerable limits). Pattern of systemic events after each dose generally comparable to, or less than, that observed in Phase 2/3 participants ≥12 years of age in Study C4591001.

Comments: It is accepted that reactogenicity does not need to be included in the summary of safety concerns.

3.6.2 Adverse events of special interest (AESI)

No changes.

3.6.3 Risks considered important for inclusion in the RMP

Anaphylaxis

Through DLP 18 June 2021 there were 3822 cases in 16-year-olds and older, and 5 in individuals 12-15 years old). No significant new safety information.

Myocarditis and Pericarditis

Serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

5 - <12-year-olds: no cases through 18 June 2021 in safety database, and no cases in CT dataset for study 4591007 up to 6 September 2021. No cases in the analysis of cohort 2 of C4591007.

12 – 15-year-olds: no cases in CT dataset up to 18 June 2021. 15 cases (11 myocarditis, 2 pericarditis, 2 myopericarditis) from 1 Dec 2020 to 18 June 2021 in safety dataset. 11 of the myocarditis cases were (Brighton Criteria 4) BC4 and 2 were BC5. 9 had criterion of hospitalisation.

16 years and older: 2 cases of pericarditis in study C4591001, both deemed not related to study treatment. 823 cases (452 myocarditis, 333 pericarditis, 38 myopericarditis) from 1 Dec 2020 to 18 June 2021 in safety dataset. BC level for the myocarditis cases:

Brighton Collaboration Level	Number of cases
BC 1	41
BC 2	44
BC 3	42
BC 4	337
BC 5	26
Total	490

Risk factors: Post-authorization reports have been received for more males than females, over a wide Age range and following dose 1 and dose 2 of the vaccine. Evaluation by the EU and US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine. PI has been updated; public health impact considered by the MAH to be minimal due to low rates compared to risks from the disease.

Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Although not observed or identified in clinical studies, there is a theoretical risk of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time. 584 cases have been reported in 16-year-olds or older in the safety database but none of them could be definitely considered to be VAED/VAERD.

Pregnancy and while breast feeding

One clinical study of the safety and immunogenicity Comirnaty in pregnant women is ongoing (C4591015); 2 non-interventional studies (C4591009 and C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest are approved. Important to obtain long term follow-up on women who were pregnant at or around the time of vaccination.

Use in immunocompromised patients

Excluded from the pivotal clinical study. Efficacy of the vaccine may be lower in immuno-compromised individuals. Safety data will be collected in individuals with compromised immune function due to acquired or genetic conditions or on immunosuppressant treatment. A noninterventional study (C4591024) in immunocompromised participants is approved.

Use in frail patients with co-morbidities

The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity), but not in frail individuals with severe co-morbidities that may compromise immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population.

Use in patients with autoimmune or inflammatory disorders

Limited information and a theoretical concern that the vaccine may exacerbate the underlying disease.

Interaction with other vaccines

One protocol study (C4591030 - Co-administration study with seasonal influenza vaccine) is approved.

Long term safety data

Safety data are being collected in study C4591001 for up to 2 years following second vaccination. Active surveillance studies are planned to follow long-term safety in vaccine recipients for 2 years following dose 2.

4.0 PHARMACOVIGILANCE PLAN

4.1 Routine Pharmacovigilance Activities

For information of the routine activities – see previous RMP assessment.

In addition to routine 6-monthly PSUR production, monthly summary safety reports (SMSRs) are compiled. Topics covered by SMSRs include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women)
- Interval and cumulative number of reports per HLT (high level term) and SOC (system organ class)
- Summary of the designated medical events
- Reports per EU country
- Exposure data (including age-stratified)
- Changes to reference safety information in the interval, and current CCDS (company core data sheet)
- Ongoing and closed signals in the interval
- Potential Medication errors
- AESI reports – numbers and relevant cases
- Fatal reports – numbers and relevant cases
- Risk/benefit considerations.

Comments: the web- based reporting portal for reporting suspected ADRs to Pfizer is available in New Zealand. Medsafe has assessed 9 SMSRs and 1 PSUR for Comirnaty to date. After Christmas the SMSRs will be bi-monthly.

Regarding potential medication errors and the new product for children

Comirnaty for use in children 5 to <12 years of age is a new formulation with a 10 µg dose. For the 10-µg RNA dose, dilution of the vaccine is required as follows: dilute the 1.3-mL filled vial with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume.

This new drug product formulation is referred to as the 'Tris/Sucrose formulation' to emphasize the change in formulation buffer. The new formulation of the 30 µg/dose for ages 12 years and over that does not require dilution is also referred to as the 'Tris/Sucrose formulation'.

The currently used, concentrated formulation of Comirnaty that requires dilution is referred to as the 'PBS/Sucrose formulation'.

Only the Tris/Sucrose formulation can be used to deliver the 10-µg dose of the vaccine.

The vial for the 10 µg dose has an orange plastic cap while the new Comirnaty 30 µg/dose vial has a grey plastic cap. The currently used Comirnaty 30 µg/dose vial has a purple cap.

Various educational resources to inform HCPs on the proper preparation and differentiation will be available.

Comments: As there will be several formulations of Comirnaty co-existing, it is of highest importance to provide training to all staff involved and develop routines to prevent medication errors. The company should confirm that educational resources will be available in New Zealand.

4.2 Additional pharmacovigilance activities

The MAH proposes the following 15 studies, of which 3 global, 5 in Europe only, 6 in US only and 1 (C4591030 co-administration with influenza vaccine) in New Zealand. There are 5 Interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591024 and study C4591030 for vaccine interactions), 2 Low-Interventional studies (WI235284 and WI255886) and 8 Non-Interventional studies (7 safety and 1 effectiveness). The studies are described in table 9 and 10 below.

Table 9. Additional pharmacovigilance activities

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study population	Milestones	
C4591001 Global	A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA vaccine candidates against COVID-19 in healthy individuals Interventional *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2	Phase 1/2/3, randomised, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.	Healthy men and women 18-55 and 65-85 years of age. Male and female, aged ≥ 12 years of age. Stable chronic conditions including stable treated HIV, HBV and HCV allowed, excluding immunocompromising conditions and treatments.	CSR submission upon regulatory request:	Any time
					CSR submission 6 months post Dose 2:	31-May-2021
					Final CSR submission with supplemental follow-up:	31-Aug-2023
C4591009 US	A non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States Non-Interventional *Planned*	To capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System.	Post-approval observational study using real-world data	The general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System	Protocol submission	31 August 2021
					Monitoring report submission:	31 October 2022
					Interim Analysis submission:	31 October 2023
					Final study report submission	31 October 2025

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study populations	Milestones	
C4591011 US	Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense population following Emergency Use Authorization Non-Interventional *Planned*	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, including myocarditis and pericarditis following receipt of the COVID-19 mRNA vaccine.	Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches	Department of Defense military and civilian personnel and their families in the Military Health System	Interim reports submission:	31-Dec-2021* 30-Jun-2022 31-Dec-2022
					Final CSR submission:	31-Dec-2023
C4591012 US	Post-Emergency Use Authorization active safety surveillance study among individuals in the Veteran's Affairs health system receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine Non-Interventional *Ongoing*	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the COVID-19 mRNA vaccine.	Secondary use of real-world data to conduct comparative analyses using self-controlled risk interval and active comparator approaches	US Veterans	Interim reports submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022
					Final CSR submission:	31-Dec-2023
C4591010 EU	A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the	Primary data collection cohort study	EU general population	Final CSR submission:	30-Sep-2024
	Non-Interventional *Planned*	COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.				
C4591015 Global	A phase 2/3, placebo-controlled, randomized, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older Interventional *Ongoing*	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Randomised, placebo-controlled, observer-blind study	Healthy pregnant women 18 years of age or older vaccinated during their 24 to 34 weeks of gestation	Final CSR submission:	30-Apr-2023

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study population	Milestones	
C4591014 US	Pfizer-BioNTech COVID-19 BNT162b2 vaccine effectiveness study - Kaiser Permanente Southern California Non-Interventional (Retrospective database analysis) *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥16 years of age with acute respiratory illness admitted to the emergency department or hospital	Final CSR submission:	30-Jun-2023
WI235284 US	Determining RSV burden and outcomes in pregnant women and older adults requiring hospitalization. COVID-19 Amendment for COVID VE / Sub-study 6 Low-Interventional[a] *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Low-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥18 years of age with acute respiratory illness admitted to the hospital	Final CSR submission:	30-Jun-2023
WI255886 Ex-EU[b]	Avon Community Acquired Pneumonia Surveillance Study. A pan-pandemic acute lower respiratory tract disease surveillance study Low-Interventional[a] *Planned*	To determine the effectiveness of COVID-19 mRNA vaccine when administered outside of the clinical setting. To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Low-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Individuals ≥18 years of age with acute respiratory illness admitted to the hospital	Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 EU	Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses Interventional *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Dose escalating Open uncontrolled	Use in immunocompromised patients	IA submission:	30-Sep-2021
					Final CSR submission:	31-Dec-2022
C4591024 (former Safety and immunogenicity in high-risk adults)	A Phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years:	Open uncontrolled	High risk individuals including frail, those having autoimmune disease, chronic renal	Final CSR submission:	30-Jun-2023[m]

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study population	Milestones	
Global	candidate BNT162b2 in immunocompromised participants ≥2 years of age Interventional *Planned*	NSCLC, CLL, in hemodialysis for end-stage renal disease).		disease and immunocompromising conditions		
C4591021 (former ACCESS/VAC4EU) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine Non-Interventional Ongoing	Assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 mRNA vaccine Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination	Secondary database analysis of observational data to assess potential increased risk of adverse events of special interest (AESI and other clinically significant events among COVID-19 vaccine recipients in the EU.	General population	Final CSR submission:	30 Sep-2024[1]
C4591038 (former C4591021 substudy) EU	Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Sub-study to investigate natural history of post-vaccination myocarditis and pericarditis Non-Interventional *Planned*	Assessment of the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Secondary database analysis of observational data	General population in EU: individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Final protocol submission	31 January 2022
					Final CSR submission:	30 September 2024
C4591036 (former Pediatric Heart Network Study) US	Safety surveillance study of myocarditis and myopericarditis temporally associated with Tozinameran (Comirnaty®) in persons < 21 years of age Non-Interventional *Planned*	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis	Prospective cohort study	Patients <21 years presenting to PHN sites after receiving any dose of BNT162b2 and who were diagnosed with myocarditis / pericarditis as well as individuals not vaccinated with myocarditis/pericarditis	Protocol submission	30-Nov-2021
					Final CSR submission:	31-Oct-2025

Study Number *Country (ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study design	Study population	Milestones	
C4591030 (Co-administration study with seasonal influenza vaccine) NZ	Co-administration of BNT162b2 with seasonal influenza vaccine Interventional *Approved*	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Not available at this time	General population	Protocol submission:	30 -Sep-2021
					Final CSR submission:	31-Dec-2022

Table 10. On-going and planned additional pharmacovigilance activities.

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 2					
C4591001 *Ongoing*	Global	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in frail patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
				CSR submission 6 months post Dose 2:	31-May-2021
				Final CSR submission with supplemental follow-up:	31-Aug-2023

Study (*study short name, and title*) Status (*planned/on-going*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 3					
C4591009 Planned	US	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System.	Myocarditis and pericarditis AESI-based safety events of interest Use in general population Use in pregnancy Use in immunocompromised patients Use in persons with a prior history of COVID-19	Protocol submission	31 August 2021
				Monitoring report submission	31 October 2022
				Interim Analysis submission:	31 October 2023
				Final study report submission:	31 October 2025
C4591011 *Planned*	US	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.	Myocarditis and pericarditis Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	31-Dec-2021
					30-Jun-2022
					31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591012 *Ongoing*	US	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following	Myocarditis and pericarditis Anaphylaxis	Interim reports submission:	30-Jun-2021
					31-Dec-2021
					30-Jun-2022

		receipt of the COVID-19 mRNA vaccine.	AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		31-Dec-2022
				Final CSR submission:	31-Dec-2023
C4591010 *Planned*	EU	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final CSR submission:	30-Sep-2024
C4591015 *Ongoing*	Global	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.	Use in pregnancy and while breast feeding.	Final CSR submission:	30-Apr-2023
C4591014 *Planned*	US	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023
WI235284 *Planned*	US*	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalization for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable.	Final CSR submission:	30-Jun-2023

Study (*study short name, and title*) Status (*planned/ongoing*)	Country	Summary of Objectives	Safety concerns addressed	Milestone	Due date
WI255886 *Planned*	Ex-EU[a,b]	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.	Not Applicable	Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	EU	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission:	30-Sep-2021
				Final CSR submission:	31-Dec-2022
C4591024 (former Safety and immunogenicity in high-risk adults) *Planned*	Global	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).	Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders.	Protocol submission:	30-Jun-2021
				Final CSR submission:	30-Jun-2023[10]
C4591021 (former ACCESS/VAC4EU) *Ongoing*	EU	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.	Myocarditis and Pericarditis Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long term safety data.	Final CSR submission:	30-Sep-2024
C4591038 (former C4591021 substudy) Planned	EU	To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine	Myocarditis and Pericarditis Long term safety data	Protocol submission:	31-Jan-2022
				Final CSR submission:	30-Sep-2024
C4591036 (former Pediatric Heart Network Study) *Planned*	US	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis	Myocarditis/pericarditis Long term safety data	Protocol submission:	30-Nov-2021
				Final CSR submission	31-Oct-2025
C4591050 (Co-administration study with seasonal influenza vaccine) *Approved*	NZ	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
				Final CSR submission:	31-Dec-2022

Non-Interventional Post-Approval Safety Studies Assessing Myocarditis/Pericarditis are planned to:

- describe the incidence of myocarditis/pericarditis following Comirnaty vaccination overall, and stratified by age group, gender, race/ethnicity (if feasible), dose, and risk interval
- estimate Relative risk (RR) from comparative analyses
- evaluate long-term outcomes (1 year) for individuals diagnosed with myocarditis/pericarditis who were previously vaccinated/not vaccinated, and over 5 years in study C4591036.

- estimate the time trend between DHPC letter dissemination and real-world clinical assessments for myocarditis/pericarditis

Comments: Studies involving children are lacking in the list above. The company should state how the proposed studies will address concerns regarding lack of information on use in young people/children. As the company plans to extend the indication into younger age groups additional vaccine-vaccine interaction studies will be needed.

4.3 Risk minimisation activities

The company describes that the product information is sufficient to mitigate the current identified and potential risks of COVID-19 mRNA vaccine. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measures for risk minimisation are considered necessary by the MAA at this time.

The additional risk minimisation measure to address myocarditis and pericarditis is a Direct Healthcare professional communication to inform HCPs about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alerted about the signs and symptoms and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

More information regarding the studies in Post-authorisation development plan is shown in Table 11 and 12.

Table 11: Studies which are Conditions of the Marketing Authorisation

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.

Table 12: Other Studies in Post-Authorisation Development Plan

Study	Purpose of the study
C4591009	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.
C4591011	To assess whether individuals in the US DoD MHS experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.
C4591012	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA vaccine.
C4591010	To estimate the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates.
C4591015	To assess safety and immunogenicity in pregnant women In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to

	breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy.
C4591014	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection.
WI235284	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
WI255886	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
BNT162-01 Cohort 13	To assess potentially protective immune responses in immunocompromised adults.
C4591024 (former Safety and Immunogenicity in highrisk adults)	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).
C4591021 (former ACCESS/VAC4EU)	Assessment of potential increased risk of adverse events of special interest (AESI) after being vaccinated with COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.
C4591038 (former C4591021 substudy)	To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.
C4591036 (former Pediatric Heart Network study)	To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis.
C4591030 (Coadmini-stration study with seasonal influenza vaccine)	Safety and immunogenicity of COVID-19 mRNA vaccine and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

5.0 DISCUSSION AND CONCLUSIONS

It is considered that the safety specification for Comirnaty is generally sufficient but there is information lacking relating to the changed indication to include children 5 - <12 years of age and the changed formulation for this age group.

The RMP should be updated to include how more information will be gathered regarding the safety of vaccination in 5 - 17-year-old individuals. The company should be asked to confirm that risk minimisation measures to decrease the risk of medication errors, such as educational resources, will be available in New Zealand. Additional interaction studies will be needed.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether the following questions/requests should be addressed to the company or whether additional questions or amendments are required:

- The company should provide more information on how they plan to monitor the safety and efficacy in children post-marketing?
- The number of participants for NZ relevant ethnic minorities was very low and use in these populations should be considered to be missing information. The company should provide more information on how they intend to monitor the safety and efficacy in different populations?
- Use in patient with previous COVID-19 or other COVID infections is also considered to be missing information. The company should provide more information on how they are intending to monitor safety and effectiveness in this group?

- Only one interaction study on co-administration with influenza vaccine is planned. In children many more vaccines have the potential to be co-administered. The company should consider further interaction studies.

7.0 ANNEXES

1. BNT162b2 RMP version 3.0

MEDICINES ADVERSE REACTIONS COMMITTEE

MINISTRY OF HEALTH, WELLINGTON

NEW ZEALAND

MINUTES OF THE 188th MEDICINES ADVERSE REACTIONS COMMITTEE MEETING

2 December 2021

MEDSAFE

WELLINGTON

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MINUTES OF THE 188th MEDICINES ADVERSE REACTIONS COMMITTEE MEETING

Thursday 2nd December

The one hundred and eighty-eighth meeting of the Medicines Adverse Reactions Committee (MARC) was held on Thursday 2nd December at 133 Molesworth Street, Wellington, via video conference. The meeting commenced at 9am and closed at 2.09pm.

MARC MEMBERS PRESENT

[redacted]

MARC SECRETARIAT PRESENT

[redacted] (Advisor, Pharmacovigilance)

[redacted] (Advisor, Pharmacovigilance)

[redacted] ((Advisor, Pharmacovigilance)

MEDSAFE STAFF IN ATTENDANCE

[redacted] (Manager, Clinical Risk Management)

[redacted] (Senior Advisor, Pharmacovigilance)

[redacted] (Senior Advisor, Pharmacovigilance)

[redacted] (Senior Advisor, Pharmacovigilance)

[redacted] (Advisor, Pharmacovigilance)

[redacted] (Advisor, Pharmacovigilance)

[redacted] (Medical Advisor, Clinical Assessment)

1.0 MATTERS OF ADMINISTRATION

1.1 Welcome and Apologies

The Chair welcomed the attendees to the meeting. Apologies were received from [redacted].

1.2 Minutes of the 187th MARC Meeting

The minutes of the 187th meeting were accepted as a true and accurate record of the meeting.

1.3 Potential Competing Interests

Committee members submitted their Competing Interest Declaration forms to the Secretary. The Chair reminded the MARC members that in addition to competing interests disclosed in the declaration forms, members should declare competing interests at the commencement of discussion of any relevant agenda item.

There were no potential competing interests which were considered likely to influence the discussions or decisions of the MARC at this meeting.

2.0 MATTERS ARISING FROM THE NEW ZEALAND PHARMACOVIGILANCE CENTRE

2.1 Centre for Adverse Reactions Monitoring (CARM) Quarterly Reports

2.1.1 Fatal Cases (Causal Cases Only)

Members were given a brief description of the fatal reports for which CARM had assessed the causality to be at least possible.

The Committee discussed case 142078. This was a case of pulmonary embolism with Levlen ED. The Committee noted concerns about the potential for patients not being informed about the signs and symptoms associated with deep vein thrombosis (DVT).

Recommendation 1

The Committee recommended that a *Prescriber Update* article be published about the signs and symptoms of DVT that patients who take combined hormonal contraceptives should be informed to monitor for, with reference made to consumer information leaflet available published by Medsafe (Hormonal Contraceptives and Blood Clots).

Recommendation 2

The Committee recommended to provide a letter to the Health Quality & Safety Commission to increase public awareness about the signs and symptoms of DVT to monitor for people who take combined hormonal contraceptives

The Committee discussed case 142282. This was a case of Bicalutamide and renal failure.

Recommendation 3

The Committee recommended that Medsafe review the signal of Bicalutamide and renal failure.

The Committee did not consider other reports required further action.

2.1.2 Special Populations: Serious Cases Associated with Medicines in Children under 18 years (Causal Cases Only)

Reports of serious cases associated with medicines in children under 18 years were briefly outlined for the Committee.

The Committee did not consider any of the reports required further action.

2.1.3 Special Populations: Serious Cases Reporting Adverse Events Following Immunisation Terms with Vaccines in Children under 18 years

Reports of events occurring in children under 18 years were briefly outlined for the Committee.

The Committee did not consider any of the reports required further action.

2.1.4 Special Populations: Serious Non-Fatal Cases Causally Associated with Critical Terms in Patients Over 80 Years

Reports of events occurring in patients over 80 years were briefly outlined for the Committee.

The Committee did not consider any of the reports required further action.

2.1.5 Causal and Serious Cases in Patients Aged 18 to 80 Years

The Committee did not consider any of the reports required further action.

2.1.6 Special Populations: Cases in patients aged 65 years and over – Ethnicity Māori

Reports of events occurring in patients aged 65 years and over (ethnicity Māori) were briefly outlined for the Committee.

The Committee did not consider any of the reports required further action.

2.1.7 Special Populations: Cases in patients aged 65 years and over – Ethnicity Pacific Peoples

Reports of events occurring in patients aged 65 years and over (ethnicity Pacific Peoples) were briefly outlined for the Committee.

The Committee did not consider any of the reports required further action.

3.0 PHARMACOVIGILANCE ISSUES

3.1 Matters Referred to the MARC under Section 36 of the Medicines Act 1981

3.1.1 Dihydrocodeine: benefit-risk review

Background

At the MARC June 2021 meeting, the Committee queried the clinical benefits of dihydrocodeine (DHC) in pain management. The Committee noted that while the prescribing of DHC was low in New Zealand, the proportion of patients hospitalised from substance abuse and poisoning, associated with this medicine, was high compared to other weak opioids. The Committee expressed that the literature showed safety concerns with DHC use and the benefits in pain management were questionable. The Committee recommended Medsafe undertake a benefit-risk review of DHC.

On 12 July 2021, Medsafe issued a section 36(1) of the Medicines Act 1981 (the Act) notice to the sponsors of DHC products. Under this section of the Act, the Director – General of Health may request the sponsor to provide evidence that a product is safe and effective for the therapeutic purpose for which it is sold. If the sponsor is unable to satisfy the Director – General that the product is safe and effective for its therapeutic purpose, conditions on the use of the medicine may be imposed or the consent for distribution of the product may be revoked.

On 12 August 2021, Medsafe published a monitoring communication seeking feedback from consumers and healthcare professionals regarding the risks and benefits of DHC.

In this meeting, Medsafe presented a risk-benefit review of DHC and referred two DHC products to the Committee under section 36 (2) of the Act. The Committee was asked to advise whether the benefit-risk balance is favourable for the use of DHC for pain treatment and if any regulatory action is required to improve the balance of benefits and risks.

Discussion

The Committee commented initially on the hospitalisation data that had triggered this review. The Committee discussed potential confounding factors that may be present, rather than the drug itself, for the increased hospitalisations. The Committee highlighted that patient factors, such as the presence of other medicines (e.g., CNS depressants), may have the potential to exacerbate the side effects of DHC, and pre – dispose patients to harm.

The Committee agreed that it was difficult to review its net benefit versus other opioids.

The Committee discussed that it was difficult to review the harms associated with DHC. It was noted that the term 'weak opioid' may mean the DHC is seen as having less potential to cause harm.

The Committee considered that restricting access to DHC by revoking its consent would mean that there are fewer options for pain management.

The Committee noted that there are low numbers of patients in NZ currently using DHC, and that its use is not increasing. The Committee considered that there may be prescribers that may prefer prescribing DHC over other agents or who use it in certain clinical situations.

The Committee discussed the current inequities to access specialist pain services.

The Committee agreed that there was insufficient evidence to recommend revoking consent of the approved DHC products in New Zealand. However, they recommended that regulatory action was needed to improve information about DHC for prescribers and patients.

Recommendation 4

The Committee recommended that conditions be imposed on the indications of use of DHC to align with indications in the Australian Product Information for modified release opioid products:

[Product] is indicated for the management of severe pain where:

- ***other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and***
- ***the pain is opioid-responsive, and***
- ***requires daily, continuous, long term treatment***

[Product] is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

[Product] is not indicated as an as-needed (PRN) analgesia.

Recommendation 5

The Committee recommended that sponsors of DHC products in New Zealand supply a Consumer Medicines Information (CMI) sheet for publication on the Medsafe website.

Recommendation 6

The Committee recommended that the MARC write a letter to the Chief Medical Officer at the Ministry of Health to highlight inequities in access to pain services and of the need for leadership in the correct use of opioids.

3.2 Matters Referred to the MARC by Medsafe

3.2.1 Buccaline benefit-risk review

Background

Buccaline *(Haemophilus influenzae, pneumococci (I, II, III), streptococci, staphylococci),* is a restricted (pharmacist only) product that has been marketed in New Zealand for several decades. It is, indicated for the oral antibacterial prophylaxis of complications of colds and marketed with the claim 'natural active oral vaccine'. Considering the limited evidence of efficacy or effectiveness of this product, a review of the benefits and risks of Buccaline was undertaken. The efficacy and safety of bacterial lystates for respiratory conditions, including Buccaline, was also recently reviewed by the European Medicines Agency (EMA) (27 June 2019).

The Committee was asked to advise whether the benefits of treatments outweigh the risks and advise on other potential issues associated with the medicine identified by Medsafe.

Discussion

The Committee noted that the use of the word 'vaccine' in association with Buccaline was concerning, and potentially misleading, as it can imply that Buccaline is comparable to other registered vaccines in terms of effectiveness and evidence base.

The Committee discussed concerns about the efficacy of the product and agreed there was lack of efficacy and safety data. It was acknowledged that the European Medicines Agency has required a randomised controlled trial for Buccaline, but the results will not be available until the year 2026. It was considered necessary to make any recommendations based on the currently available information.

The Committee agreed that public perception of the product may be incorrect. This could lead to harm if consumers delay or chose not to get the influenza vaccine and use Buccaline as an alternative.

The Committee discussed the implications associated with potential changes to the classification of Buccaline, including reclassification from a pharmacist only medicine to a prescription only medicine. The Committee did not see a benefit to reclassification of Buccaline as a prescription only medicine.

The Committee reinforced that approved medicines in New Zealand are endorsed by Medsafe as having a positive benefit risk balance. It was felt that if the product was to be evaluated against current requirements, there would be insufficient data to approve the product.

The Committee considered the harms that may be potentially associated with Buccaline use. These included using Buccaline as an alternative to well-studied vaccines or medicines, reduced uptake of the influenza vaccine, cost of product that may lack efficacy to the consumer, delay in seeking treatment and adverse reactions.

The Committee recommended that Medsafe undertakes a statutory risk-benefit review of Buccaline under section 36 of the Medicines Act 1981.

([redacted] left the meeting at this time.)

Recommendation 7

The Committee recommended that Medsafe request a review of the safety and efficacy of Buccaline under section 36 of the Medicines Act 1981.

3.2.2 Tocopherol and the risk of bleeding

Background

Medsafe were notified of a signal of tocopherol and intracranial haemorrhage at recommended doses of tocopherol.

Tocopherol (vitamin E) is a lipid-soluble antioxidant that reduces the state of oxidative stress. Alpha-tocopherol is the most biologically active form of tocopherol and the form known for its role in human health. The main oxidation product of alpha-tocopherol is tocopherylol quinone. Alpha-tocopherol is generally considered to have very modest anticlotting activity, however in contrast tocopherylol quinone is an anticoagulant.

This paper reviewed the potential safety concern of bleeding with tocopherol.

The Committee was asked to advise if the evidence presented supports there being an increased risk of bleeding with tocopherol, and if so, is further action required.

Discussion

The Committee discussed approved tocopherol-containing products that are currently available in New Zealand. It was noted that there are a range of general sale and pharmacy only products of which some are used in hospital.

The Committee discussed the evidence presented and noted that the information was more related to stroke, rather than all bleeding complications. It was noted that the information presented corresponded mostly to what is already known about topic.

The Committee discussed that it would be difficult to advise from the data presented about the risk of bleeding. It was also noted that there are different vitamin E compounds and the data presented talked about alpha-tocopherol specifically.

The Committee felt that possibly there is an association between tocopherol and the risk of bleeding, however there was insufficient evidence provided to support this and the clinical significance is not known.

The Committee agreed it may be helpful to check if there is an interaction with medicines that are known to cause bleeding such as oral anticoagulants.

Recommendation 8

The Committee recommended that Medsafe contact the sponsors of warfarin, dabigatran, rivaroxaban and apixaban, to ask them to review a possible interaction between vitamin E and their products regarding the risk of bleeding.

3.2.3 Update of Risk Management Plan for Comirnaty to include vaccination of children 5 - < 12 years of age

Background

This paper summarises an updated Risk Management Plan (version 3.0) for Comirnaty/Tozinameran/BNT162b2, a Covid-19 mRNA vaccine jointly developed by BioNTech and Pfizer. This RMP update was made in conjunction with the extension of the indication to children 5 to < 12 years.

The first Risk Management Plan was discussed at an out of session meeting on 20 January 2021.

The Committee was asked to advise whether any changes to the suggested questions on the RMP were required.

Discussion:

The Committee discussed the proposed formulation, noting the change in formulation of the two new products (Paediatric and > 12 years). It was noted that the different products would have different cap and label colours to distinguish between the adult and children's products. The Committee commented on the need for very clear information to be communicated by the company about these new products.

The Committee noted that within the New Zealand population, there are varying weights of children across the same age. It was noted that the development programme had examined several different doses and had selected the most appropriate for the age range.

The Committee suggested that the company could be asked about the appropriate dosing schedule for children who are 11 years old for their 1st dose, then subsequentially turn 12 before their 2nd dose.

The Committee agreed with the proposed requests for amendments to the Risk Management Plan and for confirmation that new safety information will be provided to Medsafe as it becomes available.

4.0 MEDSAFE PHARMACOVIGILANCE ACTIVITIES

4.1 Report on Standing Agenda Items from Previous Meetings of the MARC

The Committee reviewed the list of outstanding recommendations made by the MARC at previous meetings. Background information on these issues can be found in the minutes of previous MARC meetings on the Medsafe website:

www.medsafe.govt.nz/profs/MARC/Minutes.asp

There were no other standing agenda items for which the MARC made further recommendations.

4.2 Medsafe Pharmacovigilance Activities

The Committee noted the report detailing Medsafe's recent pharmacovigilance activities.

4.3 *Prescriber Update* Volume 42, Number 4, December 2021

The Committee noted the latest edition of *Prescriber Update*. The Committee noted they were very impressed with the quality of the publication.

4.4 Quarterly Summary of Medsafe Safety Communications

The Committee noted the quarterly summary of Medsafe safety communications.

([redacted] re-joined the meeting at 2pm)

5.0 OTHER BUSINESS

5.1 <u>Oral updates on Covid – 19 vaccine signals</u>

<u>Discussion</u>

Medsafe provided an update on Covid – 19 vaccine signals.

The Committee had no further comments.

The Chair thanked members, the Secretariat and Medsafe staff for their attendance and closed the meeting at 2:09pm.

Date 14 January 2022

Chair, Medicines Adverse Reactions Committee

Memo

Date:	10 December 2021
To:	Chris James, Minister's Delegate, Group Manager, Medsafe
Copy to:	[redacted] Team Leader – Medicines Assessment, Product Regulation [redacted] Manager, Clinical Risk Management [redacted] Secretariat, Medicines Assessment Advisory Committee
From:	[redacted] Manager, Product Regulation
Subject:	**New medicine application: Comirnaty solution for injection 30 µg/0.3 mL (TT50-10853/1) and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-1053/1a) – Referral to the Medicines Assessment Advisory Committee**
For your:	Decision

Purpose

On 4 November 2021, Pfizer New Zealand Limited (Pfizer) submitted information to Medsafe relating to an application for approval to distribute two new medicines based on a parent product, their COVID-19 vaccine Comirnaty concentrate for injection 0.5 mg/mL (30 µg/0.3 mL dose delivered) (TT50-10853) (**Comirnaty**). On 12 November 2021, the application was complete and formally received by Medsafe. These products represent an additional dosage form, Comirnaty solution for injection 30 µg/0.3 mL (TT50-10853/1) (**Comirnaty 30 µg**), and an additional strength, Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-10853/1a) (**Comirnaty 10 µg**), compared to the parent product. Comirnaty has provisional consent under section 23 of the Medicines Act 1981 (the Act). Therefore, Pfizer's application, being based on that approval, is also considered for provisional consent under section 23 of the Act.

This memo seeks your decision on whether to grant provisional consent to distribute Comirnaty 30 µg and/or Comirnaty 10 µg under section 23 of the Act, or refer Pfizer's application in relation to one or both of those new medicines to the Medicines Assessment Advisory Committee (MAAC). The Minister of Health (the Minister) has previously delegated decision making under sections 20, 22 and 23 of the Act to you.[1]

Background

Comirnaty 30 µg and Comirnaty 10 µg are both based on the parent product Comirnaty. The parent product was given provisional consent under section 23 of the Act on 3 February 2021 and renewed provisional consent under section 23(4A) of the Act on 28 October 2021.

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[1] Delegation made by the Minister of Health 11 September 2013 under section 28 of the State Sector Act 1988; and sub-delegated by Director-General of Health on 20 September 2013 under section 41 of the State Sector Act 1988.

Comirnaty 30 µg has a different dosage form (solution for injection, rather than concentrate for injection) and a different formulation to the parent product. The difference in formulation is related to a change in the buffering ingredients used, largely intended to support the stability of a more diluted solution. It is indicated for use in individuals aged 12 years and over and has been specifically developed to allow for use without prior dilution.

Comirnaty 10 µg has the same qualitative formulation as Comirnaty 30 µg but a different strength per dose compared to Comirnaty 30 µg and the parent product. It has been specifically developed for use in children aged between five and 11 years old, an indication which is not currently approved for the parent product.

A comparison of all three Comirnaty presentations is shown in the table below. The product names refer to the following medicines:

Original PBS/Sucrose (current indication/purple) = **Comirnaty (parent product)**
Tris/Sucrose (current indication/grey) = **Comirnaty 30 µg**
Tris/Sucrose (new indication/orange) = **Comirnaty 10 µg**

	Original PBS/Sucrose (current indication)	Tris/Sucrose (for current indication)	Tris/Sucrose (for new indication)
Vial cap colour	Purple	Grey	Orange
Age range	Over 12 Years	Over 12 Years	5 to <12 Years
Pharmaceutical form	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
Fill Volume	0.45 mL	2.25 mL	1.3 mL
Volume/dose	0.3 mL	0.3 mL	0.2 mL
µg RNA/dose	30 µg	30 µg	10 µg
Dilution required	Yes (1.8 mL saline)	No	Yes (1.3 mL saline)
Doses/vial	6	6	10
Strength (RNA) in vial	500 µg/mL	100 µg/mL	100 µg/mL
Pack size	195	10, 195	10, 195

All three products have been developed in response to the global pandemic of SARS-COR-2 virus that causes COVID-19.

Statutory framework

Under section 23 of the Act, you may, in your capacity as the Minister's delegate, give provisional consent to the sale or supply or use of a new medicine if you consider it is desirable that medicine be sold, supplied, or used.

Therapeutic value weighed against the risk of injuriously affecting a person

In deciding whether to give provisional consent under section 23 of the Act, you must follow the procedure set out in section 22 which requires you to:[2]

(a) consider all of the particulars and information required to be submitted by an applicant, and such other matters as appear to be relevant to you; and

(b) as far as practicable, weigh the likely therapeutic value of the medicine against the risk (if any) of the use of the medicine injuriously affecting the health of any person.

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2 Medicines Act 1981, section 22(1).

Desirable

Section 23 provides no explicit guidance on the circumstances when it would be desirable to give provisional consent to a medicine. However, the legislative history of section 23 indicates that it may be desirable to give provisional consent to a medicine:[3]

(a) where limited information means that a full consent process under section 20 of the Act is not feasible;
(b) there is an identified public health need for the medicine;
(c) if, having followed the process in section 22, you are satisfied that the assessment of therapeutic benefits and risks supports New Zealanders having timely access to the medicine.

Referral to a committee

If, after undertaking the above assessment, you are not satisfied that you should give consent, you are required to refer the application to an appropriate committee. In this case, that would be the MAAC. The MAAC would consider the application and will provide you with a recommendation as to the decision you should make.[4]

If you decide to refer to MAAC, you would not be bound by MAAC's recommendation – it is open to you to make a different decision. However, if the recommendation is to refuse consent you must notify the applicant of the terms of the recommendation and the reasons for it. The applicant may then object to the recommendation. If this occurs you must refer the application to the Medicines Review Committee who will review the application and provide a further recommendation as to the decision you should make.[5]

Conditions

On giving provisional consent, you may impose conditions as you see fit.[6] These can be:

(a) conditions relating to the persons to whom the medicine may be sold or supplied;
(b) conditions relating to the area in which the medicine may be distributed; or
(c) any other conditions (provided such other conditions are not inconsistent with the purpose of section 23 of the Act).[7]

Time limited

The default position is that every provisional consent shall have effect for two years, however, you have the discretion to grant a shorter provisional consent. [8] Upon the expiry of the provisional consent, the provisional consent can be renewed for a period not exceeding two years.

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3 See the Medicines Amendment Bill, 41-1, explanatory note.
4 Medicines Act 1981, section 22(2).
5 Medicines Act 1981, section 22(5).
6 Medicines Act 1981, section 24(3).
7 There is no explicit purpose statement in section 23. However, the legislative history of section 23 indicates that the purpose of section 23 is to ensure that New Zealanders have timely access to safe and effective medicines where there is a public health need (see the explanatory note in the Medicines Amendment Bill, 41-1).
8 Medicines Act 1981, section 23(4).

Information

An applicant seeking consent under section 23 is required to provide with their application certain information set out in section 21(2)(a) – (h).

Pfizer's application

On 4 November 2021, Pfizer New Zealand Limited (Pfizer) submitted information to Medsafe relating to an application for approval to distribute Comirnaty 30 µg and Comirnaty 10 µg as extensions to the provisional consent for Comirnaty under section 23 of the Act. On 12 November 2021, the application was complete and formally received by Medsafe. These two new products are considered new medicines as they are materially distinct (different strength of active ingredient, different qualitative and quantitative formulation) from Comirnaty and have not been previously available in New Zealand.

By this application Pfizer has applied for provisional consent under section 23 for two new medicines: Comirnaty 30 µg, and Comirnaty 10 µg. The application for these two new medicines has been assessed and progressed together, because the quality and manufacturing information for both products is the same and has been submitted in the same dossier. However, the application relates to two new medicines and you are required to make a separate decision on each new medicine. It would be open to you to give one of the new medicines provisional consent, and refer the other new medicine to the MAAC.

Pfizer's application included all information required by section 21(2)(a) – (p) for both Comirnaty 30 µg and Comirnaty 10 µg.

All three Comirnaty COVID-19 vaccines have been developed in response to the global pandemic of the SARS-CoV-2 virus that causes COVID-19. Specifically, Comirnaty 30 µg has been developed as "ready-to-use" formulation for use in the currently approved age group of individuals aged 12 years and older. Comirnaty 10 µg has been developed as a lower-dose formulation to be administered to a paediatric population of individuals aged 5 to 11 years old.

Pfizer's application for provisional consent under section 23 for Comirnaty 30 µg has been considered for the following indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

Pfizer's application for provisional consent under section 23 of the Act for Comirnaty 10 µg has been considered for the following indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in children aged 5 to 11 years.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

The application has been submitted via an expedited priority review process and has been assessed under urgency due to the significant clinical need for a COVID-19 vaccine that can be administered to children. The availability of COVID-19 vaccines is important to protect the health of all New Zealanders in light of the risk of serious health consequences requiring hospitalisation, sometimes resulting in death, posed by the COVID-19 pandemic. The need for a paediatric COVID-19 vaccine does not directly relate to Comirnaty 30 µg. However, Comirnaty 30 µg has been developed to have the same qualitative formulation as Comirnaty 10 µg (Comirnaty 10 µg is diluted before use). Accordingly, the quality and manufacturing information for both products is the same and has been submitted in the same dossier. Therefore, it is appropriate for both products to be evaluated together as they have been in this instance.

The initial application was formally accepted on 12 November 2021. Following assessment of the initial data submission, requests for additional information related to each of the aspects of the application (quality, clinical and Pfizer's risk management plan) were issued between 24 November and 7 December 2021. Responses from Pfizer were received on 7 December 2021. A second request for additional information related to product information and quality aspects was issued on 7 December 2021 and a response was received on 9 December 2021. The information Pfizer provided in response resolved all critical clinical and quality issues and addressed the majority of the information requested. If provisional consent is granted, it is proposed that remaining questions for which Pfizer advised that supporting information was not yet available be captured as conditions of consent, requiring Pfizer to provide this information within specified timeframes.

Medsafe's evaluation

Medsafe's assessment of the therapeutic value and the risks of Comirnaty 30 µg and Comirnaty 10 µg are set out in Medsafe's evaluation reports (attached at Appendix One). A summary of this assessment of the quality and clinical aspects is outlined below.

Quality

Formulation development studies and analytical data performed by the company provide a reasonable level of assurance of comparability to the parent product to justify the proposed new formulation of Comirnaty 30 µg and 10 µg. Both products are manufactured and tested at sites currently approved for the parent product. The currently available stability data for Comirnaty 30 µg and 10 µg support storage of the drug product at -90 to -60°C for up to 6 months, and 10 weeks at 2 – 8°C at the point of use. The 6-month shelf-life for the unopened drug product is less than that currently approved for the parent vaccine but may be extended via submission of a changed medicine notification post-approval once further stability data is available. The 10-week shelf-life at 2 – 8°C is longer than currently approved for the parent product (1 month refrigerated shelf-life), which will facilitate ease of handling and storage at the point of use.

The drug product batches used in the paediatric clinical study C4591007 are the same formulation as the parent product. There is no clinical data for Comirnaty 30 µg. In alignment with other international regulators such as the EMA and TGA, Medsafe considers the absence of clinical bridging and bioequivalence data for Comirnaty 30 µg to be justified on the basis of the nature of the change in formulation, the analytical comparability data provided and high clinical need for these medicines.

Clinical

This application related to Comirnaty 10 µg is supported by the results from the ongoing clinical study C4591007. In addition, there is general support for the efficacy and safety of the Comirnaty vaccine through the study programme for individuals ≥12 years of age, and through the accumulating post-marketing experience

For children at risk of COVID-19, the vaccine provides a high level of immunogenecity against this disease and is generally well tolerated. Clinical efficacy was also demonstrated with an observed vaccine efficacy of 91% among participants in this study following two doses of 10 µg, which is consistent with real-world data from individuals aged 12 years and older who receive two doses of 30 µg, including an observed efficacy of 88% against the delta variant of SARS-CoV-2.

The observed safety profile in this study did not suggest any new safety concerns for Comirnaty vaccination in children 5 to <12 years of age. Overall, the safety and tolerability profile of Comirnaty 10 µg reflects age-appropriate events that are consistent with a paediatric general population and the known reactogenicity profile of the parent product. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

Note that no clinical data was submitted to support the safety and efficacy Comirnaty 30 µg. As discussed above, this was demonstrated via analytical comparability studies with the parent product.

Data sheet

The proposed data sheet provided with this application has been based of the currently approved data sheet for the parent product. A single data sheet including all three Comirnaty products was initially proposed, however upon request from Medsafe, Pfizer has produced a separate data sheet for each product and has made other revisions to increase readability and reduce the risk of confusion for healthcare professionals. The product details, indications and dosage instructions have been updated accordingly, and appropriate descriptions of clinical data related to use in children aged 5 to 11 years old has also been included.

Risk Management Plan

Medsafe has assessed Pfizer's proposed updates to the Comirnaty RMP to include use in children aged 5 to 11 years old. The RMP was also considered by the Medicines Adverse Reactions Committee (MARC) at the meeting on 2 December 2021. Following these reviews, Pfizer has been asked to make several revisions, such as to include more information on how they plan to monitor safety and efficacy in children post-approval. This request is currently outstanding, however it is recommended that this application proceed in the meantime and that the outstanding requests are resolved prior to a decision being made regarding approval. Note that a single RMP is proposed for all three Comirnaty products and no changes are required that specifically related to Comirnaty 30 µg.

Recommendation

The quality data provided to support the formulation, manufacture and quality control of Comirnaty 30 µg is sufficient to provide reasonable assurance of comparability between this vaccine and the parent product. However, it is noted that the differences in formulation and other quality aspects between the two products are substantial and are not supported by specific clinical data, with some quality data yet to be provided. Notwithstanding this, in light of the ongoing risk posed by COVID-19 to individuals aged 12 years and older, and the quality data provided to date, Medsafe's evaluation is that it is likely desirable to give provisional consent to Comirnaty 30 µg.

In relation to Comirnaty 10 µg, there is evidence that it provides short-term protection to children aged five to 11 years old from COVID-19 with two doses. While there are some reported side effects most of these are minor and temporary. It is noted that children between the ages of 5 to 11 in New Zealand are potentially at risk of infection with SARS-CoV-2 and the associated COVID-19. While the disease-burden of COVID-19 is concentrated in the elderly, there is morbidity and mortality in children.

Notwithstanding the reported side effects, in light of the ongoing risk posed by COVID-19 to children and the evidence Comirnaty 10 µg is effective at preventing COVID-19 Medsafe's evaluation is that it is likely desirable to give provisional consent to Comirnaty 10 µg.

However, given the rapid development of Comirnaty 30 µg and Comirnaty 10 µg in order to meet the public health need posed by COVID-19, there is some data not yet available on the quality, safety and efficacy of these vaccines. This includes clinical data from future analysis cut-off dates and additional stability data.

Medsafe's recommendation is that if provisional consent is granted for either or both of Comirnaty 30 µg and Comirnaty 10 µg, Pfizer be required to provide any outstanding information as part of the conditions of consent. The proposed conditions are outlined in Medsafe' evaluation reports (attached at Appendix One). This will ensure Medsafe is kept up-to-date with the latest available information, particularly as the manufacturing process continues to be upscaled to meet global demand and as clinical trials progress. Also, if provisional consent is granted for either or both of Comirnaty 30 µg and Comirnaty 10 µg, it is recommended that the period of consent be aligned with that of the parent product, such that the provisional consents for all Comirnaty COVID-19 vaccines be valid until 3 November 2023. This approach is considered appropriate to enable consistency in the lifecycle management of all Comirnaty COVID-19 vaccines.

Medsafe considers that the benefit/risk assessment for both Comirnaty 30µg and Comirnaty 10 µg is likely to be positive in the context of a provisional consent with the proposed information conditions. However, Medsafe recommends that you refer Pfizer's new medicine application for both Comirnaty 30 µg and Comirnaty 10 µg to the MAAC. Due to the timeframes in which the Comirnaty 30 µg and Comirnaty 10 µg have been developed, there are several aspects of data to support the quality, safety and efficacy of the vaccine that are not yet available. As noted above, the Comirnaty 10 µg product is intended for use in five to 11 year olds, a population group that is not indicated for the parent product. Due to these data limits and the public interest in a proposed COVID-19 vaccine for use in a paediatric population, Medsafe considers it would be beneficial for the MAAC to review Pfizer's application in relation to both new medicines and to provide a recommendation before you make a decision on provisional consent for either medicine. It is also recommended that as

part of their consideration, MAAC provide advice regarding Medsafe's proposed conditions and duration of provisional consent.

Decision required

As set out above, before making a decision on whether to grant provisional consent for the sale, supply or use of Comirnaty 30 µg and Comirnaty 10 µg you must consider all of the particulars and information submitted by Pfizer, and such other matters as appear to be relevant to you, and you must weigh the likely therapeutic value of the medicine against the risk.

While Pfizer has submitted one application, you are required to make separate decisions in relation to each new medicine. It is possible that you could be satisfied that you should grant provisional consent to one of the medicines and not the other.

If you are not satisfied that you should grant provisional consent to one or both of the new medicines, you are required to refer that medicine or medicines, as the case may be, to the MAAC.

For the reasons given above, I recommend that you refer Pfizer's application in relation to both the Comirnaty 30 µg and the Comirnaty 10 µg to the MAAC for a recommendation. In particular, I recommend that you seek MAAC's recommendation regarding the granting of provisional consent for both new medicines valid until 3 November 2023 and with the proposed conditions outlined in Medsafe's evaluation reports (attached at Appendix One).

Recommendations
It is recommended that you:

1.	Note	Medsafe's evaluation reports (Appendix One).	Yes/No
2.	Agree	to refer Pfizer's application for consent for Comirnaty solution for injection 30 µg/0.3 mL (TT50-10853/1) and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-10853/1a) to the MAAC under section 22(2) of the Act for a recommendation	Yes/No
3	Sign	the attached letter to Pfizer informing of the referral to MAAC for Comirnaty solution for injection 30 µg/0.3 mL (TT50-10853/1) and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-10853/1a) (Appendix Two).	Yes/No

Signature [redacted] Date: 10 Dec 2021

[redacted]
Manager, Product Regulation

In light of the data limitations and the public interest involved, I am not satisfied that I should give my consent or provisional consent to the distribution of Comirnaty solution for injection 30 µg/0.3 mL (TT50-10853/1) and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-10853/1a) without first seeking a recommendation from the Medicines Assessment Advisory Committee.

Signature _____ Date: 10/12/2021

Chris James
Group Manager, Medsafe

Appendix One

Medsafe's evaluation reports

Refer attached.

Contents

Abbreviation	Definition
ADR	adverse reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ARDS	acute respiratory distress syndrome
BiPaP	bilevel positive airway pressure
BLA	(US FDA) Biologics License Application
BMI	body mass index
BNP	B-type natriuretic peptide
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	(US) Centers for Disease Control and Prevention
CFR	case fatality rate
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CPaP	continuous positive airway pressure
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	cerebrovascular accident
DART	developmental and reproductive toxicity
ECMO	extracorporeal membrane oxygenation
e-diary	electronic diary
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
EUA	Emergency Use Application
FDA	(US) Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean-fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
ICU	intensive care unit
IFNγ	interferon-gamma
IL-6	Interleukin 6
IM	intramuscular(ly)
IND	Investigational New Drug application
iPSP	initial Pediatric Study Plan
IRC	(US Study) Internal Review Committee
IRR	illness rate ratio
LDH	lactate dehydrogenase
LLN	lower limit of normal

Abbreviation	Definition
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger RNA
mRNA	messenger RNA
NAAT	nucleic acid amplification testing
NHP	non-human primate
P2 S	SARS-CoV-2 full-length, P2 mutant, "heads up," prefusion spike glycoprotein
PaO_2	partial pressure of oxygen
PDCO	Paediatric Committee
PCR	polymerase chain reaction
PIP	Paediatric Investigational Plan
PSP	Pediatric Study Plan
PT	Preferred Term
RBD	receptor binding domain
RNA-LNP	RNA lipid nanoparticle
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS Coronavirus-2; virus causing the disease COVID-19
SBP	systolic blood pressure
S glycoprotein, S	spike glycoprotein
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System Organ Class
SpO_2	peripheral oxygen saturation
SRC	(German Study BNT162-01) Safety Review Committee
TME	targeted medical event
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAE(R)D	vaccine-associated enhanced (respiratory) disease
VE	vaccine efficacy
WHO	World Health Organization

MEDICAL ADVISORS REPORT

1 TYPE

NMA (New Medicine Application) – additional strength (with extension of indication)

2 MEDICATION

Comirnaty (tozinameran) COVID-19 vaccine 0.1 mg/mL (10 µg/0.2 mL dose) concentrate for injection (TT50-10853/1a)

3 SPONSOR / MANUFACTURER

Pfizer New Zealand Limited

4 BACKGROUND

This application seeks provisional consent for new strength (10 µg/0.2 mL dose) of of Comirnaty COVID-19 vaccine (TT50-10853), with an extension to the approved indication of the parent product to include use in children 5 to <12 years of age.

The proposed indication is:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.

The use of this vaccine should be in accordance with official recommendations."

Comirnaty 0.5 mg/mL (30 µ/0.3 mL dose) concentrate for injection currently has provisional consent for the indication:

"Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations."

Renewal of the provisional consent for Comirnaty was granted on 28 October 2021 for two years from 3 November 2021.

This application to extend the indication to include children 5 to <12 years of age is accompanied by Module 3 updates to register a new drug product formulation in two strengths using a tromethamine (Tris) buffer instead of a phosphate-buffered saline (PBS). This new Comirnaty drug product formulation is referred to as the Tris/Sucrose formulation. The current registered formulation under TT50-10853 is now referred to as the PBS/Sucrose formulation.

The new Tris/Sucrose formulation will be supplied in two strengths and two fill volumes to support vaccination of different age groups.

• Individuals 12 years of age and older: The 30 µg/0.3 mLdose is filled at 2.25 mL fill volume and is administered without dilution, providing 6 doses.

• Children age 5 to <12 years: The 10 µg/0.2 mLdose is filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration, providing 10 doses.

The Tris/Sucrose formulation has been developed to provide an improved stability profile and greater ease of use at administration sites, compared to the current PBS/Sucrose formulation

4.1 Clinical Rationale

Since the initial outbreak of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, SARS-CoV-2 infections and the resulting disease, coronavirus disease 2019 (COVID-19), have spread globally with over 243 million confirmed COVID-19 cases and over 4.9 million deaths being reported to the World Health Organization as of 25 October 2021. [https://covid19.who.int/]

COVID-19 is highly contagious, serious, and potentially fatal or life-threatening disease, and can lead to hospitalisation and serious illness in children, including Multisystem Inflammatory Syndrome in Children (MIS-C). The emergence of COVID-19 variants such as Delta, that have been shown to be more contagious than the original Alpha variant (https://www.unicef.org/coronavirus/what-you-need-know-about-delta-variant), has heightened the need for protection of a broader spectrum of the community using efficacious COVID-19 vaccines.

The existing PBS/Sucrose formulation would require only 0.1 mL to administer the 10 µg dose in individuals aged 5 to <12 years which is difficult to measure accurately with standard syringes. Vaccination of this patient population is better supported by the 1.3 mL presentation of the new Tris/sucrose formulation which provides an easier-to-measure 0.2 mL dose.

Current Therapies
Currently available therapies have different benefit-risk profiles depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet need for a licensed prophylactic vaccine during the ongoing pandemic, that has been demonstrated to be safe and efficacious in the paediatric population.

In New Zealand there are three vaccines currently registered for the prevention of COVID-19 including Comirnaty. The other two vaccines are indicated for adults aged 18 years and older only. This application for Comirnaty presents the only COVID-19 vaccine with data supporting use in children as young as 5 years of age.

5 REGULATORY STATUS

Applications to register the new indication and new formulation/strength of Comirnaty have been filed in other jurisdictions. The tables below provide dates of submission and the regulatory status of these applications, in countries or jurisdictions of interest to Medsafe. A similar application has not been deferred, withdrawn or rejected in any of the below countries/jurisdictions.

Table 1 Foreign regulatory status for A. New Indication and B. New formulation

New Indication (5 < 12 Yrs)

Country/Jurisdiction	Submission Date	Status	Approved Indications
[redacted]			
United States of America	6/10/21	Approved 29/10/21 (Emergency Use Application)	Prevention of COVID-19 to include children 5 through 11 years of age.

New Formulation (Tris/sucrose)

Country/Jurisdiction	Submission Date	Status	Approved Indications
[redacted]			
United States of America	6/10/21	29/10/21	N/A

6 DATA SHEET SIMILARITIES AND DIFFERENCES

As stated above, similar applications have been submitted to the respective regulatory authorities in [redacted]

The data submitted in support of this Application to seek approval of the proposed new indication and the new formulation are identical to that submitted in the [redacted]

7 SUPPORTING DOCUMENTATION

In support of this application, a dossier is provided in NeeS format via Medsafe's electronic file transfer (EFT) system.

The sponsor has provided complete dossier Modules 1 to 5, including copies of the proposed draft NZ Data Sheet. The DS submitted with this application is a new and separate version specifically for the Tris/Sucrose Comirnaty drug product formulation in support of the expanded proposed indication for individuals 5 years of age and older. The new 1.3 mL vial for Tris/Sucrose is required to administer Comirnaty to children aged 5 to <12 years. Pfizer considers a separate DS for the Tris/Sucrose presentations will facilitate a smooth transition for the introduction of supply of the new Tris/Sucrose formulation and eventual depletion of stock of the PBS/Sucrose formulation that supports the existing 12 years of age and older indication. The tracked changes are prepared based on the clean copy Comirnaty DS that was submitted by e-mail to Medsafe on 28 October 2021, incorporating the amendments requested by Medsafe for the 6-month post Dose 2 Booster application

This submission is supported by a one pivotal clinical trial, Study C4591007. Commencing with a Phase 1 dose-finding study, Phase 2/3 of Study C4591007 evaluated both the safety and immunogenicity of Comirnaty as a vaccine against COVID-19. Additional safety data from a safety expansion cohort is provided, as well as reports showing efficacy data and delta neutralisation.

Whilst the study included 4 different age groups, only the 5 to <12 years age group is analysed in the submitted application. The doses examined in Phase 1 were 10 µg, 20 µg and 30 µg, and the 10 µg dose was selected for the Phase 2/3 part of the study.

All studies in the clinical development program were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. They were designed, performed, and analysed in accordance with all applicable regulations, laws, and guidelines in effect at the time they were conducted from the US FDA, EU Directive 2001/20/EC, and local regulatory agencies in countries where the study was conducted. The study design reflects recommendations from local review boards/committees, and other local regulatory authorities.

7.1 Tozinameran Development

Pfizer and BioNTech developed an investigational vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

The vaccine is based on SARS-CoV-2 spike glycoprotein (S) antigens encoded in RNA formulated in lipid nanoparticles (LNPs) and was perviouslyreferred to as BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048). Recently, the active ingredient INN tozinameran has been adopted. The structural elements of the vector backbones of BNT162 vaccines are optimized for prolonged and strong translation of the antigen-encoding RNA. The potency of RNA vaccines is further optimized by encapsulation of the RNA into LNPs, which protect the RNA from degradation by RNAses and enable transfection of host cells after IM delivery.

7.2 Formulation Development

In the present submission, data are submitted in support of a new presentation for use in children 5 to <12 years of age: the tozinameran (10 µg) Tris/Sucrose vaccine is provided in a 10-dose multi-dose vial (MDV) that contains a frozen concentrate solution and must be thawed and diluted prior to administration. The tozinameran concentrate must be diluted in its original vial using 0.9% Sodium Chloride Injection resulting in an off-white suspension. The tozinameran Tris/Sucrose solution is a preservative-free, sterile concentrate for dispersion of LNPs in aqueous cryoprotectant buffer for IM administration.

To provide a vaccine with an improved stability profile and greater ease of use at administration sites, Pfizer/BioNTech have developed a new drug product formulation using tromethamine (Tris) buffer instead of phosphate-buffered saline (PBS) and exclusion of sodium chloride and potassium chloride. Additionally, due to the lower concentration of mRNA, this formulation enables administration of smaller doses necessary for paediatric patients.

This new drug product formulation is referred to as the ‘Tris/Sucrose formulation’ to emphasize the change in formulation buffer. The current registered, concentrated formulation is referred to as the ‘PBS/Sucrose formulation’.

The Tris/Sucrose drug product is a preservative-free, sterile dispersion of LNPs in aqueous cryoprotectant buffer for IM administration and is formulated at 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4. The presentations of the vaccine are anticipated as:

- 30 µg tozinameran dose for individuals ≥12 years of age, same as current PBS/Sucrose formulation
- 10 µg tozinameran dose for individuals 5 to <12 years of age

The 30 µg and 10 µg tozinameran doses are prepared by filling the identically formulated drug product with different volumes: either 2.25 mL or 1.3 mL, respectively. The Tris/Sucrose formulation is currently manufactured at the Pfizer Puurs site using facilities already authorized for manufacture of the PBS/Sucrose formulation.

For the 30-µg tozinameran dose, a multi-dose vial (MDV) format (6 doses) using 2.25 mL is planned to maintain supply capacity. A single-dose vial (SDV) with a 0.48 mL for single dose vials is possible for a future time where demand may be diminished and preventing waste of extra doses in a vial may become more important. All vials are filed into a 2-mL glass vials. The vaccine is administered without dilution for the 30-µg presentation. For the 10-µg tozinameran dose, dilution of the vaccine with 0.9% sodium chloride for injection is required, as follows: dilute the 1.3-mL filled vial with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg tozinameran / 0.2 mL Injection volume.

Only the Tris/Sucrose formulation is proposed for use to deliver the 10-µg dose of the vaccine. Therefore, this change in formulation is critical to support an extension enabling dosing individuals 5 to <12 years of age.

Details of formulation development and storage conditions are out of the scope of this clinical evaluation and will be reviewed separately by the quality evaluator.

8 DOSE FINDING

8.1 Phase 1 Study C4591007

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. The study was designed to evaluate tozinameran vaccination in an age de-escalation Phase 1 dose finding part and Phase 2/3 selected dose part, in protocol defined age groups: 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age. Initiation of the paediatric study with the oldest paediatric group (5 to <12 years of age) was based on acceptable safety and tolerability demonstrated in adolescents in Study C4591001.

Phase 1 is the dose-finding portion of the study. Dose levels were tested in sentinel cohorts of children by age de-escalation, starting with the lowest dose level in the oldest age group. For each age group, the dose level identified as safe and tolerable and immunogenic in C4591007 Phase 1 was advanced for further evaluation in Phase 2/3. Phase 1 of Study C4591007 was conducted in the US. Starting with the oldest age group (5 to <12 years of age), sentinel cohorts in that age group received the lowest dose level (N=16 per dose level) followed by either the progression to subsequent a higher dose level cohort or termination of a dose level based upon the safety evaluation by the IRC. The intent was to evaluate doses up to 30 µg in each age cohort if the safety was acceptable for all the lower doses.

Terminated dose cohorts were not to be evaluated further in the age cohort that received the dose and in younger age cohorts. Progression to a subsequent younger age cohort occurred if a dose was judged safe in an older cohort, based upon the safety evaluation of the IRC.

Following this schema, the doses tested and selected in each age group during Phase 1 were:

- 5 to <12 years of age: dose levels 10, 20, 30 µg
- 2 to <5 years of age: dose levels 3 and 10 µg
- 6 to <2 years of age: dose level 3 µg

After the initial 4 participants in the 5 to <12 years of age group received the second dose of the highest dose level of tozinameran 30 µg, the IRC recommended that a second dose of 30 µg not be administered for the remaining participants due to reactogenicity after the second dose for these 4 participants. The remaining 12 participants in this group instead received a second dose of tozinameran at the 10-µg dose level based on the dose selected for Phase 2/3, and the 30-µg dose level was discontinued (i.e., not administered to any further participants in any age group).

The Sponsor/agent study team was not blinded in Phase 1. Participants who enrolled in Phase 1 are followed for cases of COVID-19 but do not contribute to the planned supportive efficacy assessments. Safety follow-up will continue for at least 2 years and/or end of study.

Based upon review of safety and immunogenicity from the Phase 1 part of the study, the final tozinameran dose levels selected were 10 µg for the 5 to <12 years and 3 µg for the 2 to <5 years of age and 6 months to <2 years of age groups.

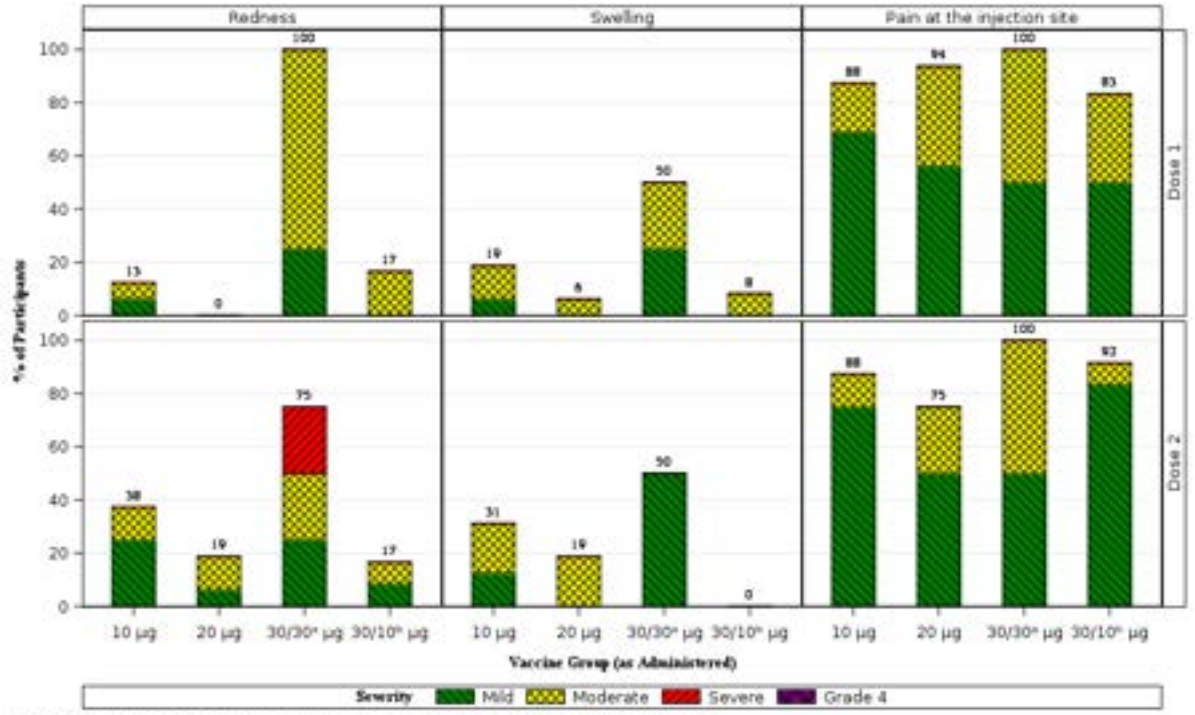
8.2 Evaluator's comments

The phase 1 dose finding portion of the study evaluated safety and immunogenecity of three dose levels: 10, 20 and 30 µg. The formulation used in study C4591007 was the currently approved formulation PBS/Sucrose diluted in saline to the appropriate dose level to administer the 10, 20 and 30 µg dose levels. The phase I component took place in the USA and enrolled children that were not at high risk of SARS-CoV-2 exposure or severe disease and who did not have evidence of previous SARS-CoV-2 infection.

Doses were evaluated sequentially with sixteen participants per dosage beginning with the ten microgram dose. SARS-CoV-2 50% neutralising geometric mean tires were assessed at 7 days after dose 2. A total of 48 participants were enrolled in this phase I portion of the study.

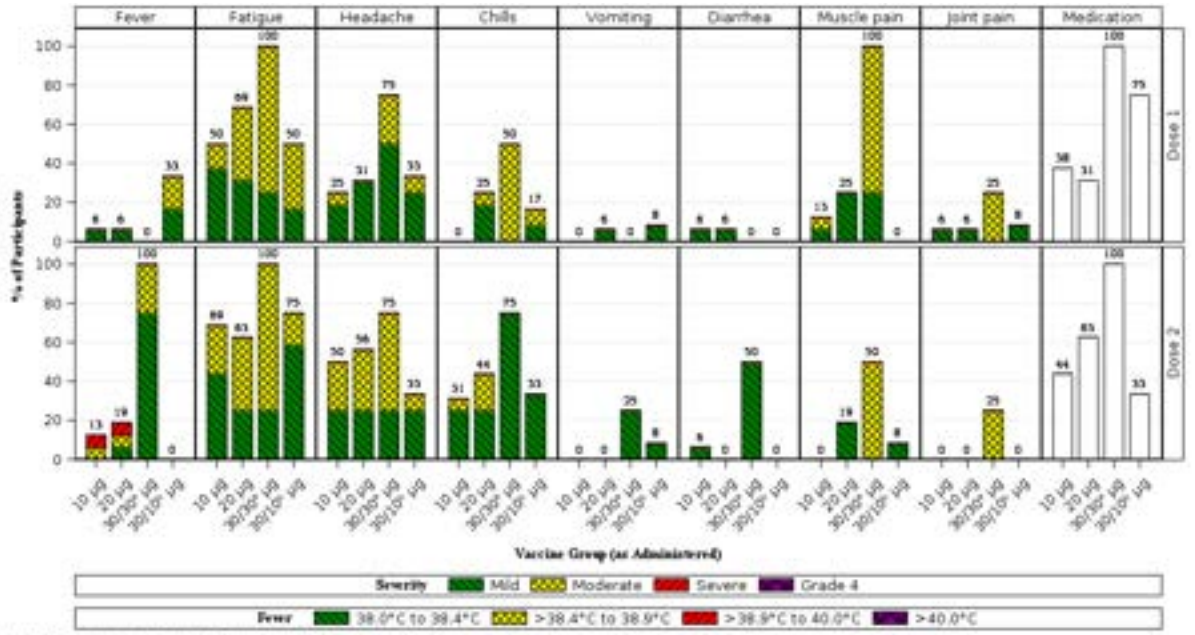
Safety review of reactogenecity data from the initial 4 participants who received the 30 microgram dose for both doses found that all participants developed mild to moderate redness at the injection and fever to 37.8c.

A higher frequency of solicited adverse events in participants receiving the 30 and 20 µg doses, the favourable AE profile at the 10 µg dose and the immunogenecity results demonstrating similar neutralising antibodies at the 10 and 20 µg doses informed the internal review committee's decision to discontinue the 30 µg dosage and proceed to the phase II/III study at the 10 µg dose. There were no SAEs or deaths and no participants from phase I withdrew or were discontinued from the study. The phase I safety study and decision to select the 10 µg dose for the 5 - <12 population is consequently clinically acceptable from a safety perspective.



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: /sdsi/C4591007_Phase1_EUA/adce_fl901_lr_p1_12

Figure 1 Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose - Phase 1 - 5 to <12 years of Age – Safety Population



Note: Severity was not collected for use of antipyretic or pain medication.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
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(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: /sdsi/C4591007_Phase1_EUA/adce_fl901_re_p1_12

Figure 2 Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose - Phase 1 - 5 to <12 Years of Age - Safety Population

9 CLINICAL EFFICACY

9.1 Phase 1/2/3 Study C45910017

9.1.1 Study Design

Study C4591007 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 paediatric study in healthy children from 6 months to <12 years of age. The study was designed to evaluate tozinameran vaccination in an age de-escalation Phase 1 dose finding part and Phase 2/3 selected dose part, in protocol defined age groups: 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age. Initiation of the paediatric study with the oldest paediatric group (5 to <12 years of age) was based on acceptable safety and tolerability demonstrated in adolescents in Study C4591001.

The initial Phase 2/3 enrolment into the 5 to <12 years of age group included N~2250 (N~1500 active and N~750 placebo). Immunobridging results and safety follow-up data with at least 2 months after Dose 2 from this initial enrolment group were submitted in the EUA. This report includes a summary of updated safety from the initial enrolment group, from the time of EUA submission to the current data cut-off date, representing approximately 3 months of follow-up after Dose 2.

An additional N~2250 participants 5 to <12 years of age were enrolled and also randomized 2:1 (1500 active and 750 placebo) as a safety expansion group in the Phase 2/3 part of Study C4591007, to obtain a larger safety database to support the EUA and a future application for licensure for this age group. This report includes Phase 2/3 interim safety data from this 5 to <12 years of age safety expansion group, with safety follow-up data up to at least 2 weeks after Dose 2 for most participants.

9.1.2 Study Eligibility Criteria

In Phase 1, the protocol defined age groups were studied separately: 5 to <12 years of age, 2 to <5 years of age, and 6 months to <2 years of age. The study population includes male and female participants deemed healthy as determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with clinically important prior medical or psychiatric illness or laboratory abnormalities, past diagnosis of multisystem inflammatory syndrome in children (MIS-C), serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

In Phase 2/3, participants were enrolled into protocol defined age groups to evaluate the dose level of tozinameran selected for each age group in the Phase 1 dose-finding part of the study. Eligibility in Phase 2/3 permitted enrolment of participants with medical conditions such as stable Type 1 diabetes or hypothyroidism; stable and controlled HIV, HCV, or HBV infection; and past serological or microbiological evidence of prior (not active) SARS-CoV-2 infection

Phase 2/3 of Study C4591007 commenced with the selected vaccine dose for each age group, who were randomized 2:1 to receive vaccine or placebo.

Phase 2/3 is being conducted at sites in the US, Finland, Poland, and Spain. Phase 2/3 (which is ongoing) was planned to evaluate BNT162b2 at the selected dose levels for each age group for safety and tolerability, immunogenicity, and efficacy (depending on meeting success criteria for immunobridging and accrual of a sufficient number of COVID-19 cases). An immunobridging analysis was designed to compare SARS-CoV-2 neutralizing antibody responses in paediatric participants within each age group in Study C4591007 to a group of

young adult participants 16 to 25 years of age in the C4591001 efficacy study. A supportive vaccine efficacy analysis is planned to be conducted when at least 22 confirmed cases of COVID-19 had accrued in the 5 to <12 years of age group among participants without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection and if success criteria for immunobridging in this age group had also been met. Additional objectives are designed to explore lower dose levels and other vaccine immunogenicity evaluations subsets of participants.

9.1.3 Overview of Efficacy (Including Immunogenicity)

The basis of tozinameran effectiveness in children is immunobridging: demonstration that the immune response to tozinameran 10 µg at 1 month after Dose 2 in children 5 to <12 years of age is within the prespecified margin of that observed at 1 month after Dose 2 of BNT162b2 30 µg in young adults 16 to 25 years of age, based on SARS-CoV-2 50% neutralizing titers in participants without prior evidence of SARS-CoV-2 infection.

Efficacy analyses for the 5 to <12 years of age group were prespecified to be conducted when at least 22 confirmed COVID-19 cases had accrued in participants without serological or virological evidence of past SARS-CoV-2 infection prior to 7 days post-Dose 2, and only if immunobridging success criteria had first been met

9.1.4 Immunogenicity Endpoints

In Phase 1, immunogenicity was analysed and reported for SARS-CoV-2 50% neutralizing titers for C4591007 participants 5 to <12 years of age by dose level at 7 days after Dose 2. These results were used to inform dose level selection to proceed to Phase 2/3 evaluation. Phase 1 data are presented to the 7 days post-Dose 2 time point, for participants without serological or virological evidence of SARS-CoV-2 infection up to 7 days post-Dose 2.

In Phase 2/3, the primary immunogenicity objective was to demonstrate immunobridging of the immune response elicited by prophylactic tozinameran in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing children in the 5 to <12 years of age group who received tozinameran 10 µg to young adult participants 16 to 25 years of age from Phase 2/3 of the C4591001 study who received tozinameran 30 µg. Phase 2/3 immunogenicity results were reported as:

- SARS-CoV-2 neutralizing geometric mean titers (GMTs) by vaccine/age group
- Geometric mean ratio (GMR) of SARS-CoV-2 neutralizing titers for children vs young adults
- Percentages/difference in percentages of children vs young adults with seroresponse
- Geometric mean-fold rises (GMFRs) of SARS-CoV-2 neutralizing titers by vaccine/age group

9.1.5 Immunogenicity Analysis Methods

In Phase 1, SARS-CoV-2 50% neutralizing titers were assessed to 7 days after Dose 2 and summarized as GMTs.

In Phase 2/3, immunobridging was based on SARS-CoV-2 50% neutralizing titers (GMTs) at 1 month after Dose 2, comparing Phase 2/3 C4591007 participants 5 to <12 years of age to Phase 2/3 C4591001 participants 16 to 25 years of age, for GMR and seroresponse assessed sequentially. Immunobridging based on seroresponse was evaluated only after the pre-specified criteria for immunobridging based on the GMR were met.

- GMR was calculated as the mean of the difference of logarithmically transformed titers and exponentiating the mean. The associated 2-sided 95% confidence intervals (CIs) were obtained by constructing CIs using Student's t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits. Immunobridging success for the GMR was declared if the lower bound of the 2-sided 95% CI for the GMR was >0.67 and the GMR point estimate was >0.8 (as prespecified in the protocol) or ≥1 (as requested by FDA)*.
  * Note that the FDA requested GMR point estimate was considered in a post hoc manner for this analysis as the database release was in progress at the time of the FDA request.
- Seroresponse was defined as achieving a ≥4-fold rise in SARS-CoV-2 neutralizing titers from before Dose 1. If the baseline measurement was below the LLOQ, the postvaccination measure of ≥ 4 × LLOQ was considered seroresponse. The difference in percentages and the associated 2-sided 95% CI calculated using the Miettinen and Nurminen method were provided. Immunobridging success for seroresponse was declared if the lower limit of the 2-sided 95% CI for the difference in seroresponse rate was greater than -10%, provided that the immunobridging success criterion based on the GMR was achieved.

GMTs and GMFRs were also provided, with associated 2-sided 95% CIs calculated with reference to Student's t-distribution. Comparative analyses of immunogenicity data were performed for participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2. Two-sided 95% CIs were obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits. The exact 2-sided 95% CI for binary endpoints for each group was computed using the F distribution (Clopper-Pearson). Titers below the LLOQ were set to 0.5 × LLOQ for all other analyses except for seroresponse.

9.1.6 Immunogenicity Subset Sample Size

The immunogenicity subset for the Phase 2/3 primary immunobridging assessment was comprised of a sample size of 225 evaluable participants in Study C4591007 (5 to <12 years of age) and in the corresponding randomly selected comparator group in Study C4591001 (16 to 25 years of age), providing a power of 90.4% and 92.6% to declare immunobridging success based on GMR and seroresponse difference, respectively. Assuming a 25% non-evaluable rate with a 2:1 randomization ratio, this would require approximately 450 participants (300 in the active vaccine group and 150 in the placebo group) with 1-month post-Dose 2 blood sample collection to achieve 225 evaluable participants in the active vaccine group.

9.1.7 Subgroup analyses

In Phase 2/3, subgroup analyses of immunogenicity endpoints were conducted based on demographics (sex, race, ethnicity) and SARS-CoV-2 baseline status (positive or negative).

9.1.8 Immunogenicity results

C4591007 Immunogenicity Results – 5 to <12 Years of Age – Phase 2/3:

Immunogenicity data from Phase 2/3 paediatric participants 5 to <12 years of age in Study C4591007 (who received tozinameran at the 10-µg dose level or placebo) were compared with Phase 2/3 young adults 16 to 25 years of age in Study C4591001 (who received

tozinameran at the 30-µg dose level or placebo). Samples for comparison from each age group/study were tested contemporaneously in the same assay.

In Phase 2/3, immunogenicity data were evaluated for children 5 to <12 years of age who had had the protocol-specified blood draws for immunogenicity testing (i.e., the immunobridging subset: approximately 300 participants in the tozinameran group and 150 participants in the placebo group). Data for comparison in immunobridging analyses were from a randomly selected subset of participants 16 to 25 years of age from Study C4591001 (approximately 300 participants in the BNT162b2 group and 50 participants in the placebo group).

The evaluable immunogenicity population for children 5 to <12 years of age included 294 participants in the tozinameran group and 147 participants in the placebo group, and for young adults 16 to 25 years of age included 273 participants in the BNT162b2 group and 47 participants in the placebo group. Exclusions from the evaluable immunogenicity population were generally balanced across vaccine groups, and the most common reason for exclusion was participants not having at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2.

The evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2 for the group of children 5 to <12 years of age was comprised of 264 participants in the tozinameran group and 130 participants in the placebo group, and for young adults 16 to 25 years of age was comprised of 253 participants in the tozinameran group and 45 participants in the placebo group.

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) n[a] (%)	30 µg 16-25 Years (C4591001) n[a] (%)	5 to <12 Years (C4591007) n[a] (%)	16-25 Years (C4591001) n[a] (%)
Randomized[b]	322 (100.0)	300 (100.0)	163 (100.0)	50 (100.0)
All-available immunogenicity population	311 (96.6)	286 (95.3)	156 (95.7)	49 (98.0)
Participants excluded from all-available immunogenicity population	11 (3.4)	14 (4.7)	7 (4.3)	1 (2.0)
Reason for exclusion				
Did not have at least 1 valid and determinate immunogenicity result after vaccination	11 (3.4)	13 (4.3)	7 (4.3)	1 (2.0)
Unreliable data due to lack of PI oversight	0	1 (0.3)	0	0
Evaluable immunogenicity population	294 (91.3)	273 (91.0)	147 (90.2)	47 (94.0)
Without evidence of infection up to 1 month after Dose 2[c]	264 (82.0)	253 (84.3)	130 (79.8)	45 (90.0)
Participants excluded from evaluable immunogenicity population	28 (8.7)	27 (9.0)	16 (9.8)	3 (6.0)
Reason for exclusion[d]				
Did not receive 2 doses of the vaccine as randomized	3 (0.9)	0	1 (0.6)	0
Did not receive Dose 2 within the 19-42 days after Dose 1	3 (0.9)	3 (1.0)	2 (1.2)	1 (2.0)
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after Dose 2	13 (4.0)	21 (7.0)	14 (8.6)	3 (6.0)
Did not have blood draw at 1 month after Dose 2 visit	7 (2.2)	8 (2.7)	6 (3.7)	0
1 Month after Dose 2 blood draw outside of window (28-42 days after Dose 2)	6 (1.9)	8 (2.7)	8 (4.9)	2 (4.0)
Had blood draw within the window but no valid and determinate immunogenicity result obtained in lab	0	5 (1.7)	0	1 (2.0)
Had important protocol deviation(s) as determined by the clinician	10 (3.1)	4 (1.3)	1 (0.6)	0
Unreliable data due to lack of PI oversight	0	1 (0.3)	0	0

Figure 3 Immunogenicity populations – Immunobridging subset – Phase 2/3 – 5 to <12 years of age and Study C4591001 Phase 2/3 – 16 through 25 years of age.

9.1.8.1 Vaccine Administration and Timing

Among C4591007 Phase 2/3 participants 5 to <12 years of age in the immunobridging subset, almost all (>99%) participants were administered study intervention as randomized.

Altogether, 100% received Dose 1 of either tozinameran or placebo, and 99.1% and 99.4% received Dose 2 of tozinameran and placebo, respectively.

Among C4591001 Phase 2/3 participants in the 16 to 25 years of age group in the immunobridging subset, all participants were administered study intervention (Dose 1 and Dose 2) as randomized.

The majority of C4591007 participants in the immunobridging subset (N=322 randomized to tozinameran and N=163 randomized to placebo) received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the tozinameran (94.7%) and placebo (95.7%) groups. Second doses administered outside of the protocol specified window included 0.9% and 1.2% of the BNT162b2 and placebo groups, respectively, who received Dose 2 at <19 days after Dose 1 and 3.4% and 2.5% of the tozinameran and placebo groups, respectively, who received Dose 2 at >23 days after Dose 1.

Longer time intervals reported for Dose 2 administration after Dose 1, in C4591007 participants in the tozinameran and placebo groups of the immunobridging subset, were:

- 28 to 34 days: 1.6% vs 0.6%
- 35 to 41 days: 0.9% vs 1.8%

The majority of C4591001 participants in the immunobridging subset (N=300 randomized to tozinameran and N=50 randomized to placebo) received Dose 2 in the protocol defined window of 19 to 23 days after Dose 1 in the tozinameran (94.7%) and placebo (86.0%) groups. Second doses administered outside of the protocol specified window included 0.3% and none of the tozinameran and placebo groups, respectively, who received Dose 2 at <19 days after Dose 1 and 5.0% and 14.0% of the tozinameran and placebo groups, respectively, who received Dose 2 at >23 days after Dose 1.

Longer time intervals reported for Dose 2 administration after Dose 1, in C4591001 participants in the tozinameran and placebo groups of the immunobridging subset, were:

- 28 to 34 days: 2.3% vs 2.0%
- 35 to 41 days: 0.7% vs 2.0%
- 49 to 55 days: none vs 2.0%
- >55 days: 0.7% vs none

The total range for timing of Dose 2 administration after Dose 1 of tozinameran or placebo for paediatric participants in C4591007 was 14 to 41 days. For young adult participants in C4591001, the total range for timing of Dose 2 administration after Dose 1 was 14 day to >55 days

9.1.8.2 Demographics

In C4591007 Phase 2/3 paediatric participants 5 to <12 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after Dose 2, in the tozinameran group 53.0% of participants were male; 78.0% were White, 6.4% were Black or African American, 8.0% were Asian; 14.8% were Hispanic/Latino; the median age was 8.0 years. Baseline SARS-CoV-2 status was positive for 7.1% and 8.8% of participants in the tozinameran and placebo groups, respectively. Obese children (based on age- and sex-

specific indices) made up 8.0% and 11.5% of participants in the tozinameran and placebo groups, respectively.

In C4591001 Phase 2/3 young adult participants 16 to 25 years of age in the evaluable immunogenicity population without evidence of infection up to 1 month after Dose 2, in the tozinameran group 49.8% of participants were male; 76.7% were White, 10.7% were Black or African American, 6.3% were Asian; 37.5% were Hispanic/Latino; the median age was 21.0 years. Baseline SARS-CoV-2 status was positive for 4.8% and 2.1% of participants in the tozinameran and placebo groups, respectively. Obese adults made up 15.8% and 31.1% of participants in the tozinameran and placebo groups, respectively.

Demographics of participants without evidence of infection up to 1 month after Dose 2 in the evaluable immunogenicity population were similar to those for all participants in the evaluable immunogenicity population and all-available immunogenicity population. Likewise, the immunogenicity population demographics were generally similar to those in the safety population

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N^a=264) n^b (%)	30 µg 16-25 Years (C4591001) (N^a=253) n^b (%)	5 to <12 Years (C4591007) (N^a=130) n^b (%)	16-25 Years (C4591001) (N^a=45) n^b (%)
Sex				
Male	140 (53.0)	126 (49.8)	72 (55.4)	16 (35.6)
Female	124 (47.0)	127 (50.2)	58 (44.6)	29 (64.4)
Race				
White	206 (78.0)	194 (76.7)	103 (79.2)	29 (64.4)
Black or African American	17 (6.4)	27 (10.7)	5 (3.8)	11 (24.4)
American Indian or Alaska Native	0	3 (1.2)	0	1 (2.2)
Asian	21 (8.0)	16 (6.3)	14 (10.8)	2 (4.4)

	Vaccine Group (as Randomized)			
	BNT162b2		Placebo	
	10 µg 5 to <12 Years (C4591007) (N[a]=264) n[b] (%)	30 µg 16-25 Years (C4591001) (N[a]=253) n[b] (%)	5 to <12 Years (C4591007) (N[a]=130) n[b] (%)	16-25 Years (C4591001) (N[a]=45) n[b] (%)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	0	0
Multiracial	16 (6.1)	11 (4.3)	6 (4.6)	1 (2.2)
Not reported	3 (1.1)	2 (0.8)	2 (1.5)	1 (2.2)
Ethnicity				
Hispanic/Latino	39 (14.8)	95 (37.5)	20 (15.4)	12 (26.7)
Non-Hispanic/non-Latino	223 (84.5)	158 (62.5)	110 (84.6)	32 (71.1)
Not reported	2 (0.8)	0	0	1 (2.2)
Age at vaccination (years)				
Mean (SD)	8.3 (1.85)	20.9 (3.02)	8.3 (2.04)	20.8 (3.10)
Median	8.0	21.0	9.0	22.0
Min, max	(5, 11)	(16, 25)	(5, 11)	(16, 25)
Obese[c]				
Yes	21 (8.0)	40 (15.8)	15 (11.5)	14 (31.1)
No	243 (92.0)	213 (84.2)	115 (88.5)	31 (68.9)

Abbreviations: COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart for 5 to <12 years of age or BMI ≥30 kg/m² for 16 to 25 years of age.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 16SEP2021 (15:29)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File:
./nda2_ubped/C4591007_P23_5_12_Bridging/adsl_s005_demo_p2_12_weoi_evl

Figure 4 Demographic Characteristics – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

9.1.8.3 Immunobridging Analysis – Geometric Mean Ration (GMR) in Neutralisation Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of the SARS-CoV-2 50% neutralizing GMT in children 5 to <12 years of age (who received the 10-µg dose level) to that of young adults 16 to 25 years of age (who received the 30-µg dose level) was 1.04 (2-sided 95% CI: 0.93, 1.18).

The lower bound of the 2 sided 95% CI for GMR was >0.67 and the GMR point estimate was ≥0.8, which meets the prespecified 1.5-fold margin and success criteria. Therefore, immunobridging based on GMR was achieved. Note that the observed GMR point estimate

meets the requested criterion from the FDA of ≥1 (which was considered in a post hoc manner, as the database release was in progress at the time of the FDA request).

		Vaccine Group (as Randomized)								
		BNT162b2								
		10 µg 5 to <12 Years (C4591007)			30 µg 16-25 Years (C4591001)			5 to <12 Years/16-25 Years		
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d]	(95% CI[d])	Met Immunobridging Objective[e] (Yes/No)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	1197.6	(1106.1, 1296.6)	253	1146.5	(1045.5, 1257.2)	1.04	(0.93, 1.18)	Yes

Abbreviations: COVID-19 = coronavirus disease 2019; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([5 to <12 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).

e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.8.

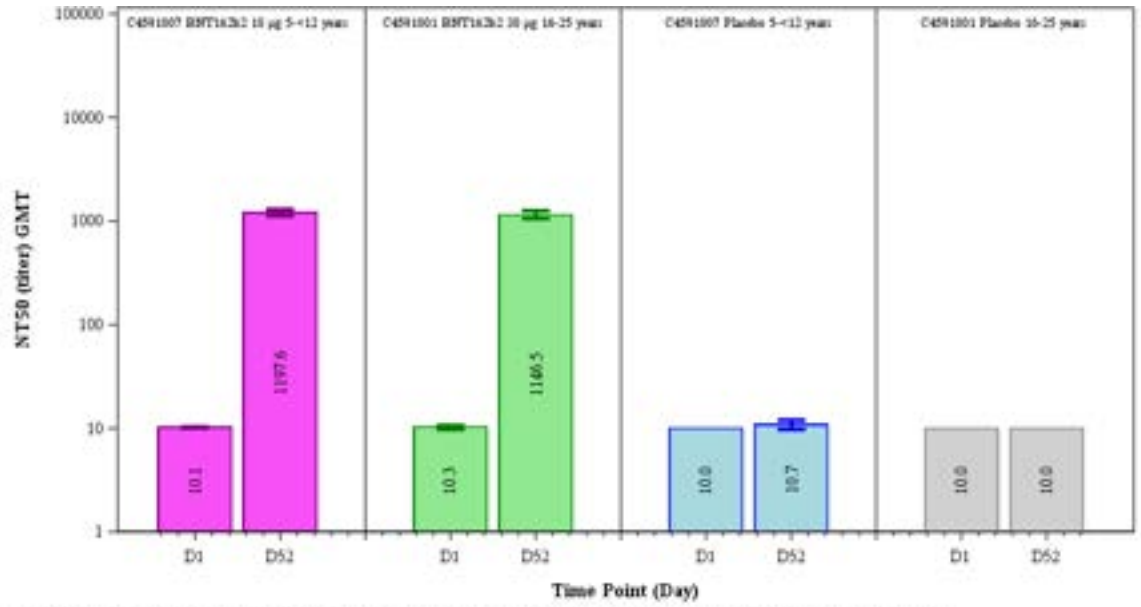
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (18:27)

(Cutoff Date: C4591001 [24MAR2021]/C4591007 [08SEP2021]) Output File: /sda2_ubped/C4591007_P23_5_12_Bridging/adva_v004_gmr_p2_12_evl

Figure 5 Summary of Geometric Mean Ratios – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population Vaccine Group (as Randomized)

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, at 1 month after Dose 2 (Day 52) of tozinameran vaccination there were substantial and comparable increases in SARS-CoV-2 50% neutralizing GMTs in both children 5 to <12 years of age (who received the 10-µg dose level) and young adults 16 to 25 years of age (who received the 30-µg dose level).

The neutralizing GMTs observed at 1 month after Dose 2 was 1197.6 in children 5 to <12 years of age compared to 1146.5 in young adults 16 to 25 years of age. Neutralizing GMTs were very low in placebo groups for both age groups.



Abbreviations: COVID-19 = coronavirus disease 2019; D = day; GMT = geometric mean titer; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Number within each bar denotes geometric mean.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

PFIZER CONFIDENTIAL Source Data: adva Date of Generation: 16SEP2021 (16:11)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021])
Output File: /nda2_ubpe4/C4591007_P23_5_12_Bridging/adva_f002_sars_50_p2_12_evt

Figure 6 Geometric Mean Titers and 95% Confidence Intervals: SARS-CoV-2 Neutralization Assay – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

Assay	Dose/ Sampling Time Point[a]	Subgroup	Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
			n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])
SARS-CoV-2 neutralization assay - NT50 (titer)	1/Prevax	All	294	11.5 (10.7, 12.3)	272	11.4 (10.6, 12.3)	147	12.4 (11.0, 14.0)	47	10.0 (10.0, 10.0)
		Sex								
		Male	153	10.8 (10.1, 11.6)	133	11.4 (10.1, 12.9)	84	12.6 (10.7, 14.8)	17	10.0 (10.0, 10.0)
		Female	141	12.3 (10.9, 13.8)	139	11.5 (10.4, 12.6)	63	12.2 (10.2, 14.6)	30	10.0 (10.0, 10.0)
		Race								
		White	232	11.8 (10.9, 12.9)	204	10.4 (9.9, 11.0)	120	13.0 (11.3, 15.0)	29	10.0 (10.0, 10.0)
		Black or African American	18	10.0 (10.0, 10.0)	32	16.4 (10.5, 25.6)	5	10.0 (10.0, 10.0)	12	10.0 (10.0, 10.0)
		American Indian or Alaska Native	0	NE (NE, NE)	4	22.1 (1.8, 277.4)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Asian	23	11.0 (9.5, 12.8)	17	13.0 (7.5, 22.5)	14	10.0 (10.0, 10.0)	3	10.0 (10.0, 10.0)
		Native Hawaiian or other Pacific Islander	1	10.0 (NE, NE)	1	42.0 (NE, NE)	0	NE (NE, NE)	0	NE (NE, NE)
		Multiracial	17	10.0 (10.0, 10.0)	12	12.3 (7.8, 19.2)	6	10.0 (10.0, 10.0)	1	10.0 (NE, NE)

Assay	Dose/ Sampling Time Point[a]	Subgroup	Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
			n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])	n[b]	GMT[c] (95% CI[d])
		Not reported	3	10.0 (10.0, 10.0)	2	10.0 (10.0, 10.0)	2	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Ethnicity								
		Hispanic/Latino	46	14.3 (10.8, 19.0)	98	10.6 (9.7, 11.6)	26	19.4 (11.6, 32.5)	12	10.0 (10.0, 10.0)
		Non-Hispanic/non-Latino	246	11.0 (10.4, 11.7)	174	11.9 (10.6, 13.3)	121	11.3 (10.3, 12.3)	34	10.0 (10.0, 10.0)
		Not reported	2	10.0 (10.0, 10.0)	0	NE (NE, NE)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Baseline SARS-CoV-2 Status[e]								
		POS	21	59.8 (33.5, 106.5)	13	91.3 (45.1, 184.7)	13	114.5 (71.6, 183.0)	1	10.0 (NE, NE)
		NEG	273	10.1 (9.9, 10.3)	259	10.3 (9.8, 10.8)	134	10.0 (10.0, 10.0)	46	10.0 (10.0, 10.0)
	2/1 Month	All	294	1300.3 (1195.9, 1413.8)	273	1192.6 (1089.7, 1305.2)	147	13.5 (11.6, 15.8)	47	10.3 (9.7, 10.9)
		Sex								
		Male	153	1218.5 (1102.8, 1346.3)	133	1081.8 (939.2, 1245.9)	84	14.5 (11.5, 18.3)	17	10.0 (10.0, 10.0)
		Female	141	1395.3 (1216.4, 1600.6)	140	1308.3 (1168.1, 1465.5)	63	12.3 (10.2, 14.8)	30	10.4 (9.6, 11.4)
		Race								

Assay	Dose/ Sampling Time Point[a]	Subgroup	Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
			n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])
		White	232	1299.4 (1178.8, 1432.4)	205	1225.6 (1120.7, 1340.3)	120	14.5 (12.0, 17.4)	29	10.0 (10.0, 10.0)
		Black or African American	18	1171.2 (823.7, 1665.4)	32	1010.3 (857.3, 1552.9)	5	10.0 (10.0, 10.0)	12	11.2 (8.8, 14.2)
		American Indian or Alaska Native	0	NE (NE, NE)	4	1905.7 (724.8, 5011.0)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Asian	23	1219.4 (918.6, 1618.6)	17	967.9 (641.0, 1461.3)	14	10.0 (10.0, 10.0)	3	10.0 (10.0, 10.0)
		Native Hawaiian or other Pacific Islander	1	3921.0 (NE, NE)	1	1063.0 (NE, NE)	0	NE (NE, NE)	0	NE (NE, NE)
		Multiracial	17	1435.8 (1086.7, 1896.9)	12	1236.8 (649.5, 2354.8)	6	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Not reported	3	1659.9 (616.0, 4472.4)	2	2028.7 (715.8, 5749.2)	2	10.0 (10.0, 10.0)	1	10.0 (NE, NE)
		Ethnicity								
		Hispanic/Latino	46	1412.3 (1118.1, 1783.9)	98	1179.2 (1046.6, 1328.6)	26	20.0 (11.7, 34.3)	12	10.0 (10.0, 10.0)
		Non-Hispanic/non-Latino	246	1276.9 (1166.4, 1397.9)	175	1200.2 (1059.4, 1359.6)	121	12.4 (10.7, 14.4)	34	10.4 (9.6, 11.2)
		Not reported	2	1823.3 (432.2, 7691.5)	0	NE (NE, NE)	0	NE (NE, NE)	1	10.0 (NE, NE)
		Baseline SARS-CoV-2 Status[b]								

Assay	Dose/ Sampling Time Point[a]	Subgroup	Vaccine Group (as Randomized)							
			BNT162b2				Placebo			
			10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
			n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])	n[c]	GMT[d] (95% CI[d])
		POS	21	3270.0 (2032.1, 5261.8)	13	2253.8 (1497.7, 3391.5)	15	133.2 (81.0, 219.0)	1	37.0 (NE, NE)
		NEG	273	1211.3 (1121.1, 1308.7)	259	1151.2 (1050.5, 1261.5)	134	10.8 (9.8, 12.0)	46	10.0 (10.0, 10.0)

Abbreviations: COVID-19 = coronavirus disease 2019; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NE = not estimable; NEG = negative; NT50 = 50% neutralizing titer; POS = positive; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Protocol-specified timing for blood sample collection.

b. POS = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. NEG = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19. Participants whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included.

c. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:33)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: /ada2_ubped/C4591007_P23_5_12_Bridging/adva_s001_gmt_sub_p2_12_evl

Figure 7 Summary of Geometric Mean Titers, by Subgroup – NT50 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

9.1.8.4 Geometric Mean Fold-Rise (GMFR) in Titers

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1 month after Dose 2 of tozinameran were robust. There was a similar magnitude of rise in the paediatric 5 to <12 years of age group (118.2) compared with the young adult 16 to 25 years of age group (111.4) for tozinameran group. GMFRs for placebo participants in either age group were very low (1.0 to 1.1).

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized)							
		BNT162b2				Placebo			
		10 µg 5 to <12 Years (C4591007)		30 µg 16-25 Years (C4591001)		5 to <12 Years (C4591007)		16-25 Years (C4591001)	
		n[b]	GMFR[c] (95% CI)	n[b]	GMFR[c] (95% CI)	n[b]	GMFR[c] (95% CI)	n[b]	GMFR[c] (95% CI)
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	118.2 (109.2, 127.9)	253	111.4 (101.2, 122.7)	130	1.1 (1.0, 1.2)	45	1.0 (1.0, 1.0)

Abbreviations: COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both pre-vaccination time points and at the given dose/sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: ./nda2_ubped/C4591007_P23_5_12_Bridging/advas_s001_gmfr_p2_12_weos_evl

Figure 8 Summary of Geometric Mean Fold Rises From Before Vaccination to Each Subsequent Time Point – NT50 – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – 5 to <12 Years of Age and Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

9.1.8.5 Seroresponse

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, high and equal proportions (99.2% each of children 5 to <12 years of age and young adults 16 to 25 years of age) achieved a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the two age groups (children – young adults) was 0.0% (2-sided 95% CI: -2.0%, 2.2%.

Since immunobridging based on GMR was achieved, hypothesis of immunobridging based on seroresponse rate was tested subsequently (refer to analysis methods in Section 2.5.4.1.2). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which is greater than the prespecified margin of -10%. Therefore, immunobridging based on seroresponse rate was achieved.

Seroresponse rates were evaluated by demographic and baseline SARS-CoV-2 status subgroups. Subgroups of paediatric participants 5 to <12 years of age and young adults 16 to 25 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2) had similar patterns of seroresponse rates at 1 month after Dose 2 with regard to the tozinameran and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Seroresponse rates in the tozinameran groups were overall high with no meaningful differences between any subgroups. These subgroups are summarized below.

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized) BNT162b2 10 µg 5 to <12 Years (C4591007) N[b]	n[c] (%)	(95% CI[d])	BNT162b2 30 µg 16-25 Years (C4591001) N[b]	n[c] (%)	(95% CI[d])	Difference %[e]	(95% CI[f])
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	264	262 (99.2)	(97.3, 99.9)	253	251 (99.2)	(97.2, 99.9)	0.0	(-2.0, 2.2)

Abbreviations: COVID-19 = coronavirus disease 2019; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (5 to <12 years – 16-25 years).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (15:31)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: /ada2 ubped/C4591007 P23 5 12 Bridging/adva s003 diff sero p2 12 evl

Figure 9 Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 to <12 Years of Age to Study C4591001 Phase 2/3 – 16 Through 25 Years of Age – Evaluable Immunogenicity Population

9.1.8.6 Supplementary data October 2021: Paediatric (5 to <12 Years of Age) Delta Neutralization Immunogenicity Data in Phase 2/3 Study C4591007

The two-dose primary series of tozinameran 10 µg administered 3 weeks apart to children 5 to <12 years of age elicited high neutralizing titers to both the USA-WA1/2020 (reference) and B.1.617.2 (Delta) recombinant SARS-CoV-2 strains at 1 month after Dose 2.

Some SARS-CoV-2 variants have been associated with more rapid transmission, and potentially, greater pathogenicity, leading to concerns about the potential for reduced vaccine-mediated protection. Studies of in vitro neutralization of a number of SARS-CoV-2 variants have found that tozinameran -immune sera neutralize all SARS-CoV-2 variants tested to date, including B.1.351 (Beta) and B.1.617.2 (Delta) variants. Real-world data from individuals ≥12 years of age also indicate that two doses of tozinameran are 75%, 88%, and 90% effective against B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.7 (Alpha) variants, respectively.

To date, results from the global Phase 1/2/3 efficacy study of tozinameran (C4591001) indicate robust protection from COVID-19 lasting at least 6 months.

The present data from Study C4591007 participants 5 to <12 years of age show that, at 1 month after receipt of two doses of tozinameran at the 10-µg dose level selected for paediatric administration, tozinameran -immune sera effectively neutralize both the USA-WA1/2020 (reference) strain of SARS-CoV-2 and the highly transmissible B.1.617.2 (Delta) variant of concern. These data are aligned with similar results previously obtained for adults in the Phase 1 part of Study C4591001.

Assay	Dose/ Sampling Time Point[a]	Vaccine Group (as Randomized)			
		BNT162b2 10 µg		Placebo	
		n[b]	GMR[c] (95% CI[c])	n[b]	GMR[c] (95% CI[c])
SARS-CoV-2 plaque reduction neutralization assay - strain B.1.617.2 (delta) NT50 (titer) to reference strain USA-WA1/2020 - NT50 (titer)	1/Prevaccination	34	1.00 (1.00, 1.00)	4	1.00 (1.00, 1.00)
	2/1 Month	34	0.81 (0.65, 1.00)	4	1.00 (1.00, 1.00)

Abbreviations: GMR = geometric mean ratio; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visits 1 and 4, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 1-month post-Dose 2) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for both the specified assays at the given dose/sampling time point.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean differences in the logarithms of the assays and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
PFIZER CONFIDENTIAL SDTM Creation: 12OCT2021 (22:42) Source Data: adva Table Generation: 13OCT2021 (09:12)
(Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File:
./nda2 ubped/C4591007 P23 CBER OCT2021 5 11/adva s004 gmr p2 12 evl

Figure 10 Summary of Geometric Mean Ratios – Delta Neutralization Subset – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Phase 2/3 – 5 to <12 Years of Age – Evaluable Immunogenicity Population.

9.1.8.7 Immunogenicity conclusions

Based on immune response to the 10-µg dose level of tozinameran in SARS-CoV-2 50% neutralizing titers in participants without prior evidence of SARS-COV-2 infection up to 1 month after Dose 2, children 5 to <12 years of age met success criteria for immunobridging to young adults 16 to 25 years of age who received tozinameran at the 30-µg dose level, for both GMR and difference in seroresponse rates. The success criteria for GMR comparing children 5 to <12 years of age to young adults 16 to 25 years of age included a lower bound of the 2-sided 95% CI for GMR >0.67 and GMR point estimate ≥0.8, and for seroresponse rate was the lower limit of the 2-sided 95% CI for the difference in seroresponse rate of greater than -10%. Criteria for both endpoints were met with a GMR of 1.04 (2-sided 95% CI: 0.93, 1.18) and difference in seroresponse rate of 0.0% (2-sided 95% CI: -2.0%, 2.2%), therefore, immunobridging based on both GMR and difference in seroresponse rates was achieved for the 5 to <12 years of age group in C4591007. Note that the observed GMR point estimate meets the post hoc criterion requested by the FDA of ≥1.

Substantial and comparable increases over baseline (pre-vaccination) in neutralizing GMTs, GMFRs, and high seroresponse rates were observed at 1 month after Dose 2 of tozinameran in both age groups. The vast majority of tozinameran recipients in both age groups achieved a seroresponse 1 month after Dose 2.

Subgroup analyses of GMTs and seroresponse rates suggested no meaningful differences in neutralizing immune response based on participant demographics, within either age group, given that some subgroups included a limited number of participants. Participants who were baseline SARS-CoV-2 status positive had higher SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, and those who were baseline status negative had a greater magnitude of rise in titers from before vaccination to 1 month after Dose 2; seroresponse was high and not differentiated by baseline SARS-CoV-2 status.

Overall, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2, children 5 to <12 years of age had a similar immune response to the two-dose primary series of tozinameran 10 µg compared to young adults 16 to 25 years of age who received two doses of tozinameran 30 µg.

9.1.8.8 Evaluator's comments

C4591001 was used for the immunobridging analysis to support vaccine effectiveness in the 5-11 year age group. This was the study in which vaccine clinical efficacy against Covid-19 was established for individuals 16 years of age or older. The comparator group was a subset of 300 randomly selected participants enrolled in study C4591001 phase II/III who received the vaccine at 30mcg dose level in a two dose primary series 21 days apart.

The effectiveness of the Pfizer BioNTech paediatric Covid-19 vaccine is being inferred by comparing the neutralising antibody responses against USA_WA1/2020 one month post dose 2 in children 5-11 years enrolled in study C4591007 and comparing that to a subset of study participants 16-25 years of age enrolled in the separate study C4591001. Participants in both studies had no evidence of prior Sars-CoV2 infection.

Immunobridging criteria comparing 5-<12-year-olds compared to 16–25-year-olds were met both for the geometric mean ratio and for seroresponse towards SARS-CoV-2 neutralisation titer. There were no significant differences in immunobridging on subgroup analysis.

The International Coalition of Medicines Regulatory Authorities (ICMRA) convened a workshop on 24 June 2021 to consider the development of COVID-19 vaccines. The ICMRA focused on immunobridging, the design and use of controlled trials (placebo or other controls) and correlates of protection.

Access Consortium members agree that well-justified and appropriately designed immunobridging studies are an acceptable approach for authorising COVID-19 vaccines.

The Consortium provides additional considerations for cross-platform immunobridging. These include extending previous points of consideration for variant-based vaccines that was limited to currently authorised COVID-19 vaccines.

Consensus positions from the ICMRA meeting relevant to this statement include:

- *Study designs for pivotal trials to demonstrate the efficacy of COVID-19 vaccines must provide robust data for authorisation*
- *Immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible*
- *Study designs can be based on either:*

- *non-inferiority immunogenicity if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or*
- *superiority if the comparator vaccine has demonstrated modest efficacy*

• *Based on the specifics of the product under consideration, neutralising antibody titre may be justified as immune marker to predict vaccine effectiveness*

• *Neutralising antibody titres should be determined using World Health Organization (WHO)-certified reference standards*

• *Other parameters to be justified include:*

- *choice of appropriate vaccine comparators considering the platform*
- *statistical criteria*
- *population comparator groups (for example, matched by age, gender, prior vaccination/infection status)*

• *Applicant support for sharing information between regulators would help build global convergence.*

The ACESS Consortium considers that the weight of evidence from studies with authorised COVID-19 vaccines is sufficient to support using neutralising antibody titres as a primary endpoint in cross-platform immunobridging trials.

Applicants are to provide a clear rationale regarding the:

• *Suitability of neutralising antibody as a primary endpoint in immunobridging studies, considering data that support the mechanism of action for the candidate vaccine*

• *Proposed comparator and an appropriate design (for example, comparability margin).*

The Consortium also recommends that applicants follow WHO standards in neutralisation assays and consult with the relevant authority early in the study process.

Medsafe aligns with ICMRA position statement regarding immunobridging for authorising new COVID-19 vaccines. The present data from participants 5 to <12 years of age in Study C4591007 demonstrate that children who received a lower dose of tozinameran 10 µg had comparable immune responses to older participants who received a higher dose of tozinameran 30 µg and the non-clinical and clinical data provided in the gazette meets ICMRA requirements. The immunogenicity endpoint and the findings of this study are therefore clinically acceptable.

9.1.9 Efficacy endpoints

Efficacy analyses were conducted on the evaluable efficacy population (participants who received both doses within the protocol defined window and had no important protocol deviations prior to 7 days post-Dose 2), and the all-available efficacy (modified intent-to-treat [mITT] populations (all participants who received vaccination).

Efficacy endpoints are: confirmed COVID-19 incidence from 7 days after Dose 2 per 1000 person-years of follow-up in participants (1) without or (2) with or without serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection.

COVID-19 cases are summarized by vaccine group for participants 5 to <12 years of age according to the case criteria below. Case narratives were generated for confirmed COVID-19 cases. A validated SARS-CoV-2 PCR was used to obtain confirmed COVID-19 case data

9.1.9.1 Case Surveillance and Criteria

Efficacy against confirmed COVID-19 was assessed by continuous surveillance for potential cases of COVID-19 (overall and those meeting criteria as severe or MIS-C). If a study participant developed an acute illness, it was considered to potentially be COVID-19 and the participant's parent/legal guardian was to contact the site to arrange an in-person or telehealth visit. Per protocol, illness visit assessments included nasal (anterior nares) swab sample collection either by site staff personnel (clinical visit) or by a participant's parent/legal guardian, for RT-PCR test [redacted] or other equivalent nucleic acid amplification–based test (i.e., NAAT), to detect SARS-CoV-2. Clinical information and results from local standard-of-care tests were also assessed. The central laboratory NAAT result was used for case definition; if no central laboratory result was available then a local NAAT result could be used if it was obtained using one of the following assays:

[redacted]

Two definitions (first and second definitions) of SARS-CoV-2–related cases and SARS-CoV-2– related severe cases, and CDC-defined MIS-C, were considered in case assessments. In all cases, the onset date of the case was the date that symptoms were first experienced by the participant; if new symptoms were reported within 4 days after resolution of all previous symptoms, they were considered as part of a single illness.

First definition (per protocol criteria): Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggered a potential COVID-19 illness visit:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhoea, as defined by ≥3 loose stools/day
- Vomiting

Second definition (per CDC criteria): Could include the following additional symptoms defined by the Centers for Disease Control and Prevention (CDC), but did not trigger a potential COVID-19 illness visit unless deemed necessary in the opinion of the investigator: fatigue, headache, nasal congestion or runny nose, nausea or abdominal pain, and/or lethargy.

SARS-CoV-2–related severe cases per protocol definition: Confirmed COVID-19 and presence of <u>at least 1</u> of the following which triggered a potential COVID-19 illness visit:

- Clinical signs at rest indicative of severe systemic illness:
  − Respiratory rate (breaths/min) and heart rate (beats/min) outside normal

range
− SpO2 ≤92% on room air, >50% FiO2 to maintain ≥92%, or PaO2/FiO2 <300 mm Hg
- Respiratory failure: defined as needing high-flow oxygen, including CPaP, BiPaP, non-invasive ventilation, mechanical ventilation, or ECMO
- Evidence of shock or cardiac failure
  − SBP (mm Hg); <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years
  − Requiring vasoactive drugs to maintain blood pressure in the normal range
- Significant acute renal failure: defined as serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine
- Significant gastrointestinal/hepatic failure: defined as total bilirubin ≥4 mg/dL or ALT 2 times ULN for age
- Significant neurological dysfunction: defined as Glasgow Coma Scale score ≤11, or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline
- Admission to an intensive care unit (ICU)
- Death

SARS-CoV-2–related severe cases per CDC definition: Included the following additional outcomes defined by the CDC: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death.

Confirmed MIS-C per CDC definition: Met all below criteria:
- An individual <21 years of age presenting with fever (≥38.0 °C for ≥24 hours or report of subjective fever lasting ≥24 hours)
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement: − Cardiac (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) − Renal (e.g., acute kidney injury) − Respiratory (e.g., pneumonia, ARDS, pulmonary embolism) − Hematologic (e.g., elevated D-dimers, thrombophilia, or thrombocytopenia) − Gastrointestinal/hepatic (e.g., elevated bilirubin, elevated liver enzymes, or diarrhoea) − Dermatologic (e.g., rash, mucocutaneous lesions) − Neurological (e.g., CVA, aseptic meningitis, encephalopathy)
- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR COVID-19 exposure within the 4 weeks prior to the onset of symptoms

9.1.9.2 Efficacy Analysis Methods

Descriptive vaccine efficacy (VE) analyses within the 5 to <12 years of age group were conducted after immunobridging success was first declared to provide available efficacy data (in addition to the completed immunogenicity and safety analyses described above) to facilitate the (VRBPAC overall assessment of benefit-risk when the EUA for this age group is being considered. With <21 cases (protocol specified number for formal evaluation of vaccine efficacy) accrued by the time of this analysis, there is an increased risk of observing by chance a lower VE than the true VE compared to the same risk when ≥21 cases have

been accrued. To inform VRBPAC's decision on whether to recommend approving the vaccine for this age group, Pfizer has provided the most comprehensive and up-to-date data available, despite the potential risk of a higher 'type II error' for this descriptive efficacy analysis. The protocol specified hypothesis testing efficacy analysis for this age group will be performed when ≥21 cases are accrued.

The VE analyses were conducted among those without evidence of past SARS-CoV-2 infection and among those with or without evidence of past SARS-CoV-2 infection.

VE against confirmed COVID-19 from 7 days after Dose 2 is estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the active vaccine group to the corresponding illness rate in the placebo group. VE and the associated 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time are included with efficacy analyses (noting the participants were randomized 2:1 to receive vaccine: placebo). VE estimation for confirmed COVID-19 uses the first definition (per protocol criteria). A supplemental analysis using the same assessment of VE and associated Clopper-Pearson 95% CI was performed for confirmed COVID-19 illness using the second definition (CDC criteria).

Subgroup Analyses

Subgroup analyses of efficacy endpoints were planned to be conducted based on demographics (sex, race, and ethnicity), country, SARS-CoV-2 status (positive or negative), and risk status (comorbidities that increase the risk for severe COVID-19 illness, categorized based on medical history terms previously reported with safety analyses).

9.1.9.3 Efficacy results

Among randomized participants, the Phase 2/3 evaluable efficacy population for children 5 to <12 years of age included 1450 participants in the tozinameran group and 736 participants in the placebo group, which reflects the 2:1 randomization. Exclusions from the evaluable efficacy population occurred for 5.1% of the tozinameran group and 2.8% of the placebo group, due to receipt of Dose 2 outside the protocol defined window of 19-42 days after Dose 1 (2.0% in tozinameran and 2.4% in placebo) or due to other important protocol deviations on or prior to 7 days after Dose 2 (3.1% in tozinameran and 0.5% in placebo), as previously reported in the EUA being primarily related to vaccine thawing, dilution, and/or administration issues that are not applicable to placebo.

	Vaccine Group (as Randomized)		
	BNT162b2 10 µg n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	1528 (100.0)	757 (100.0)	2285 (100.0)
Dose 1 all-available efficacy population	1517 (99.3)	751 (99.2)	2268 (99.3)
Participants without evidence of infection before Dose 1	1384 (90.6)	686 (90.6)	2070 (90.6)
Participants excluded from Dose 1 all-available efficacy population	11 (0.7)	6 (0.8)	17 (0.7)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	11 (0.7)	6 (0.8)	17 (0.7)
Dose 2 all-available efficacy population	1514 (99.1)	747 (98.7)	2261 (98.9)
Participants without evidence of infection prior to 7 days after Dose 2	1362 (89.1)	671 (88.6)	2033 (89.0)
Participants excluded from Dose 2 all-available efficacy population	14 (0.9)	10 (1.3)	24 (1.1)
Reason for exclusion[c]			
Did not receive 2 vaccinations	14 (0.9)	10 (1.3)	24 (1.1)
Evaluable efficacy population	1450 (94.9)	736 (97.2)	2186 (95.7)
Participants without evidence of infection prior to 7 days after Dose 2	1305 (85.4)	663 (87.6)	1968 (86.1)
Participants excluded from evaluable efficacy population	78 (5.1)	21 (2.8)	99 (4.3)
Reason for exclusion[c]			
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	31 (2.0)	18 (2.4)	49 (2.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	47 (3.1)	4 (0.5)	51 (2.2)

Figure 11 Efficacy Populations – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age

9.1.9.4 Demographics

The demographics of Phase 2/3 paediatric participants 5 to <12 years of age were similar in the evaluable efficacy population of participants without prior evidence of SARS-CoV-2 infection as in the safety population for the tozinameran and placebo groups. In total, 51.9% of participants were male; 77.8% were White, 6.3% were Black or African American, 6.7% were Asian, 7.5% were multiracial, and other racial groups included <1% of participants; 19.0% were Hispanic/Latino. The median age was 8.0 years. Most children (73.4%) were enrolled in the US, with 11.9% in Finland, 8.7% in Spain, and 6.0% in Poland.

Obese children (based on age- and sex-specific indices) made up 10.9% of the total evaluable efficacy population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease were present in 20.1% of participants.

In the evaluable efficacy population of participants with or without prior evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, baseline positive status for prior evidence of SARS-COV-2 infection was reported for 8.7% of the tozinameran group and 8.4% of the placebo group. The overall demographics of Phase 2/3 paediatric participants 5 to <12 years of age were similar for the tozinameran and placebo groups in the evaluable efficacy population of participants with or without prior evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, and in the all-available (mITT) efficacy populations.

9.1.9.5 Confirmed COVID-19 per Protocol Criteria (First Definition)

The observed VE from at least 7 days after Dose 2 for tozinameran 10 µg administered to children 5 to <12 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, per protocol case criteria was 90.7% (2-sided 95% CI:

67.7%, 98.3%) based on 3 cases in the tozinameran group and 16 cases in the placebo group after adjusted for surveillance time (noting the 2:1 randomization of vaccine: placebo)

No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. Hence, in this case, the observed VE from at least 7 days after Dose 2 in evaluable participants in this age group with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was essentially the same: 90.7% (2-sided 95% CI: 67.4%, 98.3%) based on the same number of observed cases (3 cases in the tozinameran group and 16 cases in the placebo group). The earliest reported and confirmed COVID-19 case in this analysis was in July 2021, with most cases occurring in August and September 2021.

	Vaccine Group (as Randomized)					
	BNT162b2 10 µg (N[a]=1305)		Placebo (N[a]=663)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2	3	0.322 (1273)	16	0.159 (637)	90.7	(67.7, 98.3)

Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory
syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding
antibody [serum] negative at Visit 1, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any
unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 13OCT2021 (23:06) Source Data: adc19ef Table Generation: 14OCT2021 (19:43) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File:
./nda2_ubped/C4591007_P23_SAF_EXP_5_11/adc19ef_woe_7pd2_ep3_eval

Figure 12 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

9.1.9.6 Confirmed COVID-19 per CDC Criteria (Second Definition)

In a supportive analysis including the CDC criteria for case confirmation, the observed VE from at least 7 days after Dose 2 for tozinameran 10 µg administered to children 5 to <12 years of age without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was 88.4% (2-sided 95% CI: 64.5%, 97.2%) based on 4 cases in the tozinameran group and 17 cases in the placebo group after adjusted for surveillance time (noting the 2:1 randomization of vaccine: placebo).

No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. Hence, in this case, when including the CDC criteria for case confirmation, the observed VE from at least 7 days after Dose 2 in evaluable participants in this age group with or without prior evidence of SARS-

CoV-2 infection before or during the vaccination regimen was essentially the same: 88.3% (2-sided 95% CI: 64.2%, 97.1%) based on the same number of observed cases (4 cases in the tozinameran group and 17 cases in the placebo group).

	Vaccine Group (as Randomized)					
	BNT162b2 10 µg (N[a]=1305)		Placebo (N[a]=663)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence based on CDC-defined symptoms from 7 days after Dose 2	4	0.322 (1273)	17	0.158 (635)	88.4	(64.5, 97.2)

Abbreviations: CDC = Centers for Disease Control and Prevention (United States); NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
PFIZER CONFIDENTIAL SDTM Creation: 13OCT2021 (23:06) Source Data: adc19ef Table Generation: 14OCT2021 (19:44) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File: ./nda2_ubped/C4591007_P23_SAF_EXP_5_11/adc19ef_woe_cdc_7pd2_ep3_eval

Figure 13 Vaccine Efficacy – First COVID-19 Occurrence Based on CDC-Defined Symptoms From 7 Days After Dose 2 – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

9.1.9.7 Vaccine Efficacy Subgroup Analyses

Vaccine efficacy was evaluated for subgroups of participants by sex, race, ethnicity, country, and at-risk status among participants without evidence of prior infection before and during the vaccination regimen. At-risk participants were those with at least one specified comorbidity or who were obese. Subgroup analyses were based on per protocol case criteria.

All subgroups had observed VE >85%, taking into account that some subgroups contain very few participants with evaluable cases and the 2-sided 95% CIs were wide, limiting the precision of these estimates, and should be interpreted with caution. These data, nevertheless, do not provide evidence to suggest that any subgroup is disadvantaged with regard to efficacy based on demographics (sex, race, ethnicity), country (noting that cases were reported only in Spain and the US), and presence of baseline comorbidities. None of the cases in the tozinameran group occurred in children with reported baseline comorbidities. In general, it is noteworthy that all cases in the tozinameran group were associated with fewer and milder symptoms than cases in the placebo group reported over the same period, suggesting an overall less burdensome symptomatic illness when COVID-19 does occur after vaccination.

The observed VE results by subgroup were similar for participants with or without evidence of prior infection before and during the vaccination regimen. All participants with confirmed cases in this analysis had baseline negative status for prior SARS-CoV-2 infection.

Results for the all-available efficacy populations were similar; with no clinically meaningful differences observed in VE on the basis of subgroups of these populations.

9.1.9.8 Signs and Symptoms of COVID-19

The criteria for COVID-19 case determination are described in Section 9.1.9.1. Signs and symptoms were summarized according to the protocol criteria for case confirmation.

In the evaluable efficacy population, confirmed cases occurring at least 7 days after Dose 2 among participants in the evaluable efficacy population without evidence of SARS-CoV-2 infection before or during the vaccination regimen had signs and symptoms associated with 3 cases in the tozinameran group and 16 cases in the placebo group.

In the tozinameran group, 1 participant each (33.3%) with a confirmed COVID-19 case reported 2, 3, or 4 signs and symptoms of COVID-19. Importantly, fever was not reported in the children with confirmed COVID-19 who received tozinameran. The reported signs and symptoms in the tozinameran group were:

- New or increased cough: all 3 participants (100%)
- Sore throat: all 3 participants (100%)
- Headache: 1 participant (33.3%)
- Nasal congestion or runny nose: 1 participant (33.3%) Nausea or abdominal pain: 1 participant (33.3%)

In the placebo group, the majority of participants (56.2%) with a confirmed COVID-19 case reported 4 or more signs and symptoms of COVID-19, including 8 participants each (50.0%) with 5 or more symptoms. The reported signs and symptoms in the placebo group order of highest to lowest frequency were:

- Fever: 10 participants (62.5%)
- Nasal congestion or runny nose: 9 participants (56.3%)
- New or increased cough: 8 participants (50.0%) New or increased muscle pain: 8 participants (50.0%)
- Sore throat: 8 participants (50.0%)
- Fatigue: 5 participants (31.3%)
- Chills: 4 participants (25.0%)
- New loss of taste or smell: 4 participants (25.0%)
- Headache: 4 participants (25.0%)
- Diarrhoea: 3 participants (18.8%)
- Nausea of abdominal pain: 3 participants (18.8%)
- New or increased shortness of breath: 1 participant (6.3%)

Overall, COVID-9 cases reported in the placebo group reflected a higher incidence of multiple concurrent signs and symptoms for most participants. The signs and symptoms associated with cases in the tozinameran group were mostly mild respiratory tract symptoms. This may be particularly important with regard to children with baseline

comorbidities that increase their risk of severe COVID-19 who made up approximately 20% of the evaluable efficacy population in this study.

No cases of COVID-19 were observed in either the vaccine or placebo groups in participants with evidence of prior SARS-CoV-2 infection. Hence, the same results (based on same number of reported cases) were reported for the evaluable efficacy population with or without evidence of SARS-CoV-2 infection before or during the vaccination regimen, and results were similar for the all-available efficacy populations.

	Vaccine Group (as Randomized)		
Signs and Symptoms	BNT162b2 10 µg (N[a]=3) n[b](%)	Placebo (N[a]=16) n[b](%)	Total (N[a]=19) n[b](%)
Participants with specific signs and symptoms of COVID-19	3 (100.0)	16 (100.0)	19 (100.0)
Fever	0 (0.0)	10 (62.5)	10 (52.6)
New or increased cough	3 (100.0)	8 (50.0)	11 (57.9)
New or increased shortness of breath	0 (0.0)	1 (6.3)	1 (5.3)
Chills	0 (0.0)	4 (25.0)	4 (21.1)
New or increased muscle pain	0 (0.0)	8 (50.0)	8 (42.1)
New loss of taste or smell	0 (0.0)	4 (25.0)	4 (21.1)
Sore throat	3 (100.0)	8 (50.0)	11 (57.9)
Diarrhea	0 (0.0)	3 (18.8)	3 (15.8)
Additional CDC-defined symptoms			
Fatigue	0 (0.0)	5 (31.3)	5 (26.3)
Headache	1 (33.3)	4 (25.0)	5 (26.3)
Nasal congestion or runny nose	1 (33.3)	9 (56.3)	10 (52.6)
Nausea or abdominal pain	1 (33.3)	3 (18.8)	4 (21.1)
Participants with specific number of signs and symptoms			
1	0 (0.0)	2 (12.5)	2 (10.5)
2	1 (33.3)	3 (18.8)	4 (21.1)
3	1 (33.3)	2 (12.5)	3 (15.8)
4	1 (33.3)	1 (6.3)	2 (10.5)
5	0 (0.0)	4 (25.0)	4 (21.1)
>5	0 (0.0)	4 (25.0)	4 (21.1)

Figure 14 Summary of Signs and Symptoms for First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 Initial Enrolment Group – 5 to <12 Years of Age – Evaluable Efficacy Population

9.1.9.9 Efficacy Against Severe COVID-19 and MIS-C

No severe COVID-19 cases (per protocol definition or per CDC definition) were reported in children 5 to <12 years of age as of the data cut-off date (08 October 2021). No cases of MIS-C (per CDC definition) were reported as of the data cut-off date.

9.1.9.10 Efficacy Conclusions

Based on the available number of accrued cases of confirmed COVID-19 confirmed among the initially enrolled N~2250 participants in the 5 to <12 years of age group of Study C4591007 from whom immunobridging data and safety data for this group were previously submitted to the EUA as of the data cut-off date (08 October 2021), these descriptive efficacy data show tozinameran 10 µg is protective against COVID-19 in children 5 to <12 years of age. These analyses included confirmed cases from at least 7 days after Dose 2,

either without or with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, as well as all cases confirmed from Dose 1 onwards.

Among participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen, the observed VE for tozinameran 10 µg against any confirmed COVID-19 from at least 7 days after Dose 2 was 90.7% (2-sided 95% CI: 67.7%, 98.3%) which included 3 cases in the tozinameran group and 16 cases in the placebo group as of the data cut-off date (noting the 2:1 randomization of vaccine: placebo). As no participants with confirmed cases were baseline positive for prior SARS-CoV-2 infection, the analysis of individuals with or without prior infection yielded the same observed efficacy result.

For COVID-19 cases confirmed from Dose 1 onwards in the Dose 1 all-available (mITT) population, the observed VE for tozinameran 10 µg was 91.4% (2-sided 95% CI: 70.4, 98.4%) based on 3 cases in the tozinameran group and 17 cases in the placebo group as of the data cut-off date (noting the 2:1 randomization of vaccine: placebo).

It is notable that the earliest reported and confirmed COVID-19 case in this analysis was in July 2021 (first symptom observed on 05 July 2021 and PCR-confirmed on 07 July 2021), with most occurring in August and September 2021; therefore all confirmed cases have been reported during a time that the highly transmissible B.1.617.2 (Delta) has been the predominant SARS-CoV-2 strain in circulation in the US and globally. A supportive analysis of Delta neutralizing immune responses from a subset of vaccinated and placebo recipients' sera in the 5 to <12 years of age group in Study C4591007 was conducted (submitted separately), which showed robust neutralizing titers against the Delta variant, and was predictive of high efficacy. Therefore, it can be inferred from these efficacy and supportive immunogenicity data that vaccination with tozinameran 10 µg in children 5 to <12 years of age is highly effective against COVID-19 caused by the still-prevalent Delta variant of concern. Confirmatory case sequencing data for COVID-19 cases in this analysis will be reported at a later time, when the sequencing analysis is completed. The observed efficacy in children 5 to <12 years of age in this present VE analysis is in line with real-world data from individuals ≥12 years of age who received two doses of tozinameran 30 µg and had observed efficacy of 88% against the Delta variant.

All subgroups had observed VE >85%, though these results should be interpreted with caution as some subgroups contain very few participants with evaluable cases and the 2-sided 95% CIs are very wide and therefore point estimates are not precise. However, there is no evidence to suggest that any subgroup of children 5 to <12 years of age has a disadvantage with regard to efficacy of the two-dose series of tozinameran 10 µg on the basis of demographics (sex, race, ethnicity), country, and presence of comorbidities. All participants with confirmed cases in this analysis had baseline negative status for prior SARS-CoV-2 infection, so no evaluation of baseline positive status was possible.

Overall, COVID-9 cases reported in the placebo group reflected a higher incidence of multiple concurrent signs and symptoms, with most participants 56.2% reporting 4 or more signs and symptoms of COVID-19, among whom 8 participants (50.0%) had 5 or more symptoms, including fever and chills, nasal congestion or runny nose and new or cough, muscle pain and fatigue, and a case associated with shortness of breath, as compared to the tozinameran group. The most common signs and symptoms associated with cases in the tozinameran group generally were mostly consistent with mild upper respiratory tract

symptoms, such as nasal congestion or runny nose and sore throat. Notably, the cases in the tozinameran group were not associated with any fever or chills, muscle pain or fatigue, diarrhoea, loss of taste or smell, or shortness of breath.

The limited number of cases of COVID-19 in the tozinameran vaccinated group, associated with fewer and milder symptoms, compared with placebo is reassuring for the general paediatric population. Children 5 to <12 years of age are currently in school and potentially frequently exposed to SARS-CoV-2, by virtue of it being a near-daily congregant setting. The vaccine protection from symptomatic illness that was limited to a few confirmed cases with mostly mild upper respiratory tract symptoms compared with the cases in the placebo group may be particularly important for children with baseline comorbidities that have increased risk of severe COVID-19.

No severe COVID-19 cases or MIS-C were reported in the 5 to <12 years of age group, per protocol definition or per CDC definition, as of the date cut-off date (08 October 2021).

Overall, tozinameran administered as a primary series of two doses of 10 µg given 3 weeks apart to children 5 to <12 years of age is highly protective against symptomatic COVID-19, including a substantial blunting of the reported signs and symptoms when COVID-19 cases do occur.

9.1.9.11 Evaluator's comments

In this descriptive supportive efficacy analysis, vaccine efficacy against symptomatic COVID-19 after 7 days post dose 2 up to the date of cut off was 90.7% in participants without prior SARS-CoV2 infection. A total of 3 cases of COVID-19 occurred in the vaccine group, 16 in the placebo group with most cases occuring during July and August during 2021 when the delta variant was present in the US. At the the time that the data was cut off none of the vaccine cases met the criteria for severe COVID-19. All cases occurred in children without prior history of COVID-19 infection. All cases of Covid-19 were confirmed by PCR lab testing at least 7 days or more post dose 2. There were no cases of COVID-19 in participants with prior history of SARS-CoV2 infection.

In the COVID-19 cases, vaccinated participants had less symptoms of COVID-19 compared to unvaccinated participants. Only one case occurred in a child with underlying comorbidities (asthma).

10 CLINICAL SAFETY

10.1 Safety end points

10.1.1 Reactogenicity

Phase 1 and Phase 2/3 participants or their parent/legal guardian were to monitor and record reactogenicity for 7 days after each dose; in the 5 to <12 years of age group, events included:24

- Local reactions: pain, redness, swelling at the injection site
- Systemic events: fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain

Antipyretic/pain medication usage was also to be recorded for 7 days after each dose. Reactogenicity and antipyretic use was to be recorded each evening for 7 days after each

dose administration using prompts from an electronic diary (e-diary). This allowed recording only within a fixed time window to provide an accurate representation of the participant's experience.

10.1.2 Adverse Events

For Phase 1 and Phase 2/3, adverse events (AEs) were collected from the Dose 1 to 1 month after Dose 2 and serious AEs (SAEs) were collected from Dose 1 to 6 months after Dose 2. AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to MedDRA. Deaths are recorded to the end of study.

Myocarditis and pericarditis were designated in the C4591007 protocol as AEs of special interest (AESIs). For other events of specific clinical interest that were not designated as AESIs, Pfizer utilizes a list of Targeted Medical Events (TMEs) of clinical interest that are highlighted during clinical safety data review and signal detection. TMEs are a dynamic list of MedDRA AE terms that are reviewed on an ongoing basis throughout the clinical study; the TMEs are based on review of known pharmacology, toxicology findings, possible class effects, published literature, and potential signals arising from safety data assessments. The list of TMEs includes events of interest due to their association with COVID-19 and terms of interest for vaccines in general; it takes into consideration the CDC list of AESIs for COVID-19 that include events potentially indicative of severe COVID-19 or autoimmune and neuroinflammatory disorders.

10.1.3 Other Assessments

Prior SARS-CoV-2 infection was determined by virological testing via nucleic acid amplification test (NAAT) on anterior nares swab and serological testing for IgG to the SARS-CoV-2 N-antigen at baseline, and via NAAT at Dose 2. Participants were surveilled for potential COVID-19 illness from Visit 1 onwards.

10.2 Safety Analysis Methods

Safety data were analysed and reported using descriptive summary statistics for the safety population. Phase 1 and Phase 2/3 safety were assessed from Dose 1 to 1 month after Dose 2. Data are also provided through the relevant data cut-off date: 16 July 2021 for Phase 1 and 06 September 2021 for Phase 2/3.

10.2.1 Reactogenicity

Descriptive statistics were provided for each reactogenicity endpoint after each dose for participants who completed an e-diary. Local reactions and systemic events from Day 1 through Day 7 after vaccination are presented by severity and cumulatively across severity levels. Descriptive summary statistics included counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs. Missing reactogenicity e-diary data were not imputed.

10.2.2 Adverse Events

AE data were summarized descriptively for the safety population. Descriptive summary statistics including counts, percentages, and associated Clopper-Pearson 2-sided 95% CIs were provided for AEs reported from Dose 1 through 1 month after Dose 2.

10.2.3 Subgroup Analyses

In Phase 2/3, subgroup analyses of safety endpoints were conducted based on demographics (sex, race, ethnicity) and SARS-CoV-2 baseline status (positive or negative).

10.3 Safety Results C4591007 Phase 1

High frequencies of reactogenicity to the 20 and 30 µg dose levels in participants 5 to <12 years of age contributed to the decision to select a lower dose of 10 µg as the final dose level of tozinameran to proceed to Phase 2/3 for this age group. The dose level selection decision for this age group was based on Phase 1 safety and immunogenicity results. tozinameran at 10 µg was well tolerated in participants 5 to <12 years of age based on available Phase 1 safety results representing follow-up to approximately 3 months after Dose 2.

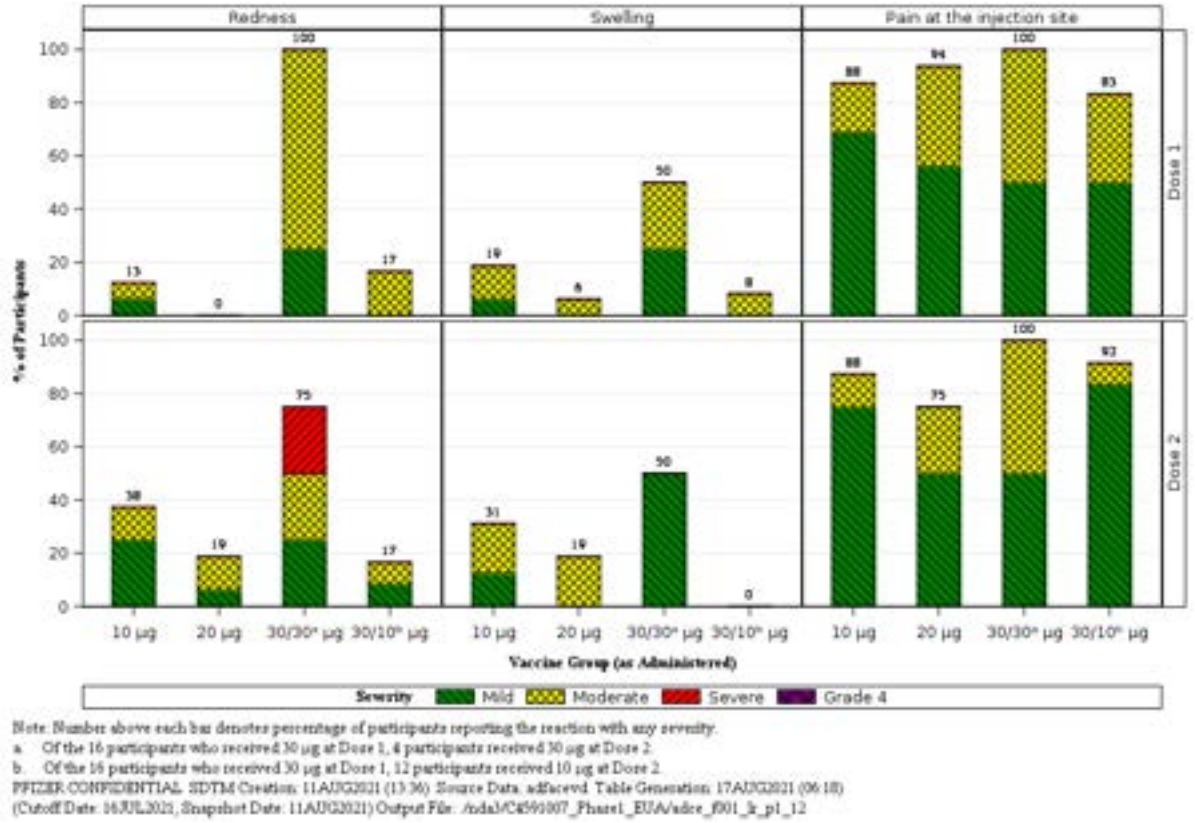
10.3.1 Local Reactions

Reactogenicity in the 5 to <12 years of age group tended to increase in a dose level- and dose number-dependent manner with regard to incidence and/or severity of local reactions at 10, 20, and 30 µg dose levels. Local reactions were mostly mild to moderate and short-lived.

For 10 and 20 µg groups, pain at the injection site was the most commonly reported local reaction within 7 days after any dose (range: 87.5% to 93.8%) with the highest frequency in the 20 µg dose level after Dose 1. Redness and swelling were reported in the 10 and 20 µg dose level groups without a clear dose level or dose number effect on incidence or severity. In the 4/16 participants who received both doses in the 30-µg dose level group as assigned, pain at the injection site was reported in all 4 participants after Doses 1 and 2. Redness was reported in all 4 participants after Dose 1 and 3/4 participants after Dose 2 with 1 participant reporting severe redness. Swelling was reported in 2/4 participants after each dose and was mild to moderate. The high frequency of local reactions for these first 4 sentinel participants at Dose 2 contributed to the IRC decision to discontinue the 30-µg dose level for Dose 2 in the remaining of the 30-µg group.

The remaining 12/16 participants assigned to the 30-µg group who received 10 µg for Dose 2 (the 30/10-µg dose regimen) had a local reaction profile similar to groups that received 10 or 20 µg as assigned. All local reactions were mild or moderate in severity, except for 1 severe event of redness within 7 days after Dose 2 in the 30/30-µg dose regimen.

Across dose levels, the median onset day for most local reactions was within 1 to 2 days after Dose 1 or Dose 2, and the majority of events resolved within 1 or 2 days of onset



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
a. Of the 16 participants who received 30 µg at Dose 1, 4 participants received 30 µg at Dose 2.
b. Of the 16 participants who received 30 µg at Dose 1, 12 participants received 10 µg at Dose 2.
PFIZER CONFIDENTIAL. SDTM Creation: 11AUG2021 (13:36). Source Data: adfacevd. Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021; Snapshot Date: 11AUG2021) Output File: /ada3/C4591007_Phase1_EUA/adce_fl301_lk_p1_12

Figure 15 Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 1 – 5 to <12 Years of Age Group – Safety Population

10.3.2 Systemic Effects

Reactogenicity generally increased in an increasing dose level- and dose number-dependent manner with regard to incidence and/or severity of systemic events at 10, 20, and 30 µg dose levels. Systemic events were mostly mild to moderate and short-lived.

For 10 and 20 µg groups, fatigue was the most commonly reported systemic event within 7 days after either dose (range: 50.0% to 68.8%) which did not show a clear dose number effect for incidence or severity. Headache, muscle pain, and chills were reported in the 10 and 20 µg dose level groups with increasing incidence and/or severity associated with dose number and/or dose level. Vomiting, diarrhea, and joint pain were uncommon or absent after any dose in these dose level groups.

In the 4 participants who received both doses in the 30-µg group as assigned, 4/4 developed fevers up to 38.9 °C after the second dose of vaccine. These 4 participants also reported mild to moderate fatigue and muscle pain after Dose 1; after Dose 2 fatigue was reported in all 4 participants while muscle pain became moderate in severity in 2/4 participants. Headache was mild to moderate in 3/4 participants after Dose 1 and Dose 2. Diarrhea and vomiting were absent after Dose 1 but were reported in 1 to 2 participants after Dose 2. This systemic event profile, particularly occurrence of fevers, in these first 4 sentinel participants contributed to the IRC decision to discontinue the 30-µg dose level.

The remaining 12/16 participants assigned to the 30-µg group who received the 30/10-µg dose regimen had a systemic event profile similar to groups that received 10 or 20 µg as assigned, with the exception of fever which was reported with greater incidence and severity

after Dose 1 of 30 µg (33.3%, up to 38.9 °C) compared to the 10 or 20 µg dose level groups (6.3% each, up to 38.4 °C). The reverse was observed after Dose 2, with no fevers reported in the 30/10-µg group after receipt of 10 µg compared with the 10-µg as assigned dose level (12.5%; n=1 up to 38.9 °C and n=1 >38.9 to 40.0 °C) and the 20-µg as assigned dose level (18.8%; n=2 up to 38.9 °C and n=1 >38.9 to 40.0 °C).

Antipyretic or pain medication use was dose number dependent, reported by 31.3% to 37.5% participants after Dose 1 and 43.8% to 62.5% after Dose 2 in the 10 and 20 µg groups. The 4/16 participants who received both doses in the 30-µg group as assigned all reported medication use after both doses; the remaining 12/16 participants who received the 30/10-µg dose regimen reported medication use in 75.0% after Dose 1 (30 µg) and 33.3% after Dose 2 (10 µg). All systemic events were mild or moderate in severity within 7 days after Dose 1 and Dose 2, with the exception of fevers reported in 1 participant each in the 10 and 20 µg groups, occurring after Dose 2. The participant in the 10-µg group had a high temperature of 39.0 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. The participant in the 20-µg group had a high temperature of 39.7 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. No Grade 4 events were reported at any dose levels.

Across dose levels, the median onset day for most systemic events was 1 to 2 days after Dose 1 or Dose 2, and the majority of events resolved within 1 day of onset.

10.3.3 Adverse Events

From Dose 1 to 1 month after Dose 2, AEs were reported by 7 participants (43.8%) who received tozinameran at 10 µg and 5 participants (31.3%) who received 20 µg. Of these, the AEs were considered related to study intervention for 4 participants (25.0%) and 2 participants (12.5%) participants in the 10 µg and 20 µg dose groups, respectively.

In 4/16 participants who received both doses in the 30-µg group as assigned, AEs were reported by 2 participants with both considered by the investigator as related to study intervention (lymphadenopathy and arthralgia, n=1 each). In the remaining 12/16 participants who received the 30/10-µg dose regimen, 3 participants reported 4 AEs (injection site pain, n=2; injection site erythema and vomiting, n=1 each). Of these, the 3 AEs localized to the injection site were considered related to study intervention.

No SAEs, deaths, or AEs leading to withdrawal were reported in Phase 1 participants 5 to <12 years of age as of the data cut-off date of 16 July 2021, which represents up to approximately 3 months of follow-up.

Overall, no change in the AE profile was reported in any dose level group up to the data cut-off date.

10.3.3.1 Analysis of Adverse Events

All AEs through the data cut-off date of 16 July 2021 were mild to moderate, with the exception of AE of Grade 3 pyrexia, reported in the 20 µg group on Day 1 post-Dose 2. This participant had a high temperature of 39.7 °C on Day 2 that fell to <38.0 °C and resolved by Day 3. The investigator considered the event related to study intervention.

Immediate AEs (reported within 30 minutes post dose) after Dose 1 included injection site discomfort and presyncope in 1 participant each in the 10-µg group and injection site pain in

2 participants in the 30/10-µg dose regimen group. After Dose 2, 1 participant in the 10-µg group reported immediate injection site pain.

10.3.3.2 Adverse Events of Clinical Interest

No Phase 1 participants 5 to <12 years of age had any cases reported of anaphylaxis, appendicitis, Bell's palsy, myocarditis/pericarditis, or MIS-C. One participant who received two doses of tozinameran 30 µg as assigned had an AE of Grade 2 arthralgia (right hip pain) that was judged by the investigator as related to study intervention. This participant was a [redacted]years of age with no relevant medical history or concomitant vaccinations. The event was reported with an onset of 7 days after Dose 1 and was reported as involving no limitation in movement of the extremity, no accompanying fever, no injection site abnormality, and no other symptoms; the event resolved the same day after administration of ibuprofen.

Lymphadenopathy

Two participants 5 to <12 years of age had cases of lymphadenopathy up to the data cut-off date.

- 1 [redacted]participant [redacted] years of age in the 20-µg group had Grade 1 bilateral cervical and inguinal lymphadenopathy with onset at 21 days post-Dose 2 and reported as ongoing at the time of the data cut-off. This event was considered by the investigator as not related to study intervention.
- 1 [redacted]participant [redacted] years of age in the 30-µg group as assigned (i.e., received both doses of 30 µg), had Grade 1 left axillary lymphadenopathy with onset at 3 days post-Dose 2 and reported as resolved 17 days after onset. This event was considered by the investigator to be related to study intervention

10.4 Safety Results C4591007 Phase 2/3 (First Cohort)

The safety population for Phase 2/3 paediatric participants 5 to <12 years of age reflected the 2:1 randomization in the tozinameran (N=1518) and placebo (N=750) groups. The only exclusions from the safety population were due to 17 participants (0.7%) not receiving study vaccine. No participants 5 to <12 years of age included in the safety population were HIV

	Vaccine Group (as Administered)		
	BNT162b2 10 µg n[a]	Placebo n[a]	Total n[a] (%)
Randomized[b]			2285
Vaccinated	1518	750	2268 (99.3)
Safety population	1518	750	2268 (99.3)
HIV-positive	0	0	0
Excluded from safety population			17 (0.7)
Reason for exclusion			
Participant did not receive study vaccine			17 (0.7)

Abbreviation: HIV = human immunodeficiency virus.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 16SEP2021 (06:12) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adsl_s008_saf_pop_p2_12

Figure 16 Safety Population – Phase 2/3 – 5 to <12 Years of Age

10.4.1 Duration of Follow-Up – Phase 2/3

The duration of follow-up for Phase 2/3 paediatric participants 5 to <12 years of age was at least 2 months after Dose 2 for most participants. Almost all (95.1%) of the participants had 2 to <3 months of follow-up after Dose 2.

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Month	7 (0.5)	4 (0.5)	11 (0.5)
≥1 Month to <2 months	67 (4.4)	32 (4.3)	99 (4.4)
≥2 Months to <3 months	1444 (95.1)	714 (95.2)	2158 (95.1)
≥3 Months	0	0	0

Note: Follow-up time was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (23:25) Source Data: adsl Table Generation: 15SEP2021 (11:51) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adsl_s005_fup_time_12

Figure 17 Follow-up Time After Dose 2 - Phase 2/3 - 5 to <12 Years of Age – Safety Population

10.4.2 Disposition – Phase 2/3

The disposition of Phase 2/3 paediatric participants 5 to <12 years of age is summarized. In total, 1528 participants were randomized to receive tozinameran 10 µg and 757 participants were randomized to placebo, reflecting the 2:1 randomization ratio. Most participants randomized to either group (≥98.7%) received Dose 1 and Dose 2.

Two participants (0.1%) in the tozinameran group and 2 participants (0.3%) in the placebo group discontinued from the vaccination period and are continuing in the study for safety follow-up. Most participants across both groups completed the visit at 1 month after Dose 2 (≥98.5%). Among participants who discontinued from the vaccination period but continued in the study up to the 1-month post-Dose 2 visit, none of the discontinuations were reported as due to an AE.

Two participants (0.1%) in the tozinameran group and 2 participants (0.3%) in the placebo group withdrew from the study before the 1-month post-Dose 2 visit. None of these withdrawals were reported as due to an AE.

During the course of the study, 3 participants in the 5 to <12 years of age group turned 12 years of age and became eligible to receive a COVID-19 vaccine outside of the study. These participants were unblinded to their treatment assignment per protocol to seek vaccination with a COVID-19 vaccine (e.g., tozinameran 30 µg) that is authorized for individuals ≥12 years of age under EUA or conditional approval. Of these, 2 participants received both doses of tozinameran 10 µg prior to being unblinded and 1 participant received both doses of placebo before being unblinded and withdrew to receive a COVID-19 vaccine outside of the study. Data from these participants are included in endpoint analyses up to the point at which they were unblinded.

10.4.3 Protocol Deviations

Important protocol deviations were reported in 48 participants (3.1%) in the tozinameran group and 4 participants (0.5%) in the placebo group. Nearly all protocol deviations in the tozinameran group (47 [3.1%]) were related to investigational product, most (38 [2.5%]) due to being unsuitable for use (as tozinameran requires thawing/dilution prior to administration, whereas saline placebo does not).

10.4.4 Demographics – Phase 2/3

Demographic characteristics for Phase 2/3 paediatric participants 5 to <12 years of age were similar in tozinameran and placebo groups in the safety population. In total, most participants were White (78.9%), with 6.5% Black or African American participants and 6.0% Asian participants, 7.0% multiracial participants, and other racial groups <1%. There were 21.1% Hispanic/Latino participants. The median age was 8.0 years and 52.1% of participants were male.

Obese children (based on age- and sex-specific indices) made up 11.5% (tozinameran group) to 12.3% (placebo group) of this age group in the safety population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease (which include obesity) were present in similar proportions of participants in the tozinameran group (20.6%) and placebo group (20.3%). The most common comorbidities reported in participants at study baseline were:

- Asthma (7.8% in tozinameran and 8.3% in placebo)
- Neurologic disorders (1.3% in tozinameran and 0.4% in placebo)
- Congenital heart disease (1.0% in tozinameran and 0.7% in placebo)

One participant, who was in the tozinameran group, had an immunocompromised condition reported at baseline (acute lymphocytic leukaemia). In the safety population, similar

proportions of participants in the tozinameran group (8.8%) and placebo group (8.7%) had baseline SARS-CoV-2 positive status.

10.4.5 Reactogenicity

Reactogenicity (local reactions and systemic events) was assessed via e-diary in all Phase 2/3 paediatric participants 5 to <12 years of age for 7 days after each dose. Participants with e-diary data included N=1511 in the tozinameran group and N=749 in the placebo group post- Dose 1, and N=1501 in the tozinameran group and N=741 in the placebo group post-Dose 2.

10.4.5.1 Local Reactions

In the tozinameran group, pain at the injection site was most frequently reported in paediatric participants 5 to <12 years of age, and frequency was similar after Dose 1 and after Dose 2 of tozinameran (74.1% vs 71.0%). In the placebo group, pain at the injection site after Doses 1 and 2 was less frequently reported compared to the tozinameran group and was similar after each dose (31.3% vs 29.5%).

In the tozinameran group, frequencies of redness and swelling were similar after Doses 1 and 2. Frequencies of redness showed a modest increase from after Dose 1 compared to after Dose 2 of tozinameran (14.7% vs 18.5%). Frequencies of swelling also showed a modest increase after Dose 1 compared with Dose 2 of tozinameran (10.5% vs 15.3%). In the placebo group, redness was less frequently reported compared to the tozinameran group and was similar after each dose (5.7% vs 5.4%), and swelling was infrequent (2.7%) after both Dose 1 and Dose 2.

After the first and second dose, most local reactions were mild or moderate in severity. Severe local reactions were reported infrequently (≤0.3%) across the tozinameran and placebo groups after either dose. No Grade 4 local reactions were reported in either group

Across groups, median onset for all local reactions after receiving tozinameran was 1 to 2 days after Dose 1 or Dose 2, and all events resolved with a median duration of 1 to 2 days.

Overall, the pattern of local reactions reported in children 5 to <12 years of age after each dose was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001 with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site (still within tolerable limits). Further details are provided in the risk discussion

Subgroups of Phase 2/3 paediatric participants 5 to <12 years of age had similar reactogenicity, with regard to local reactions, across the tozinameran and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino), and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the overall patterns of local reactions across these subgroups.

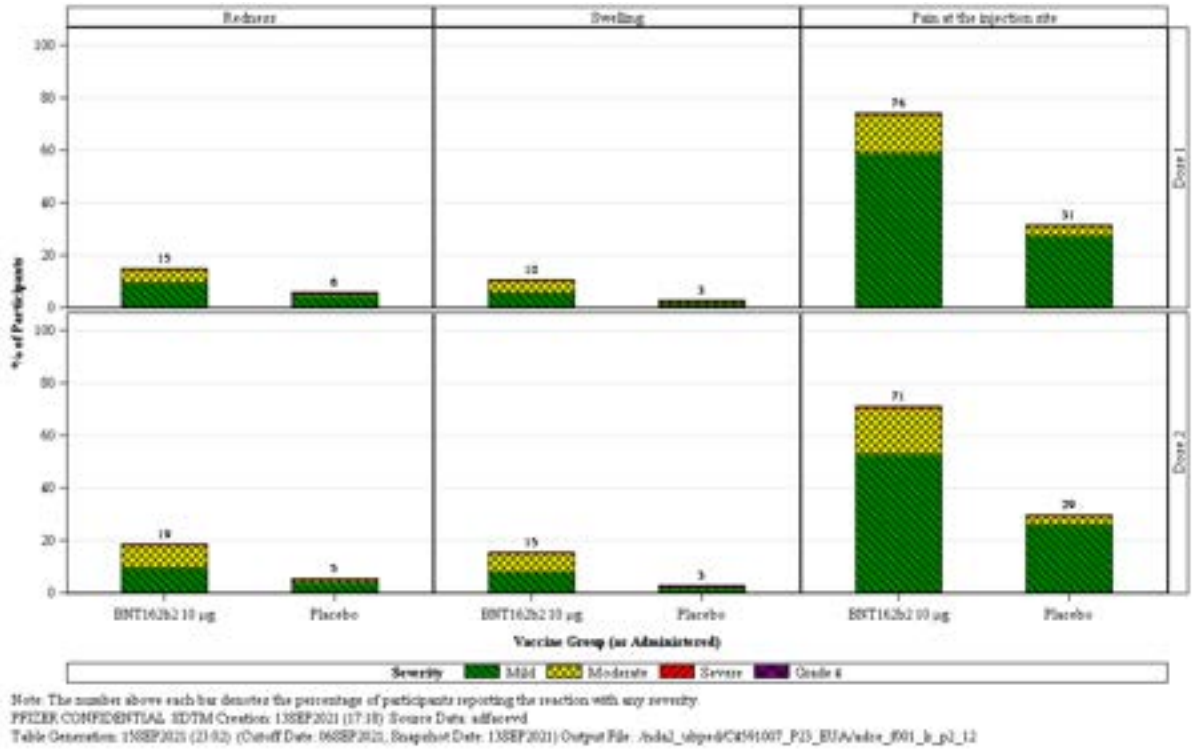


Figure 18 Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population

10.4.5.2 Systemic events

In the population of Phase 2/3 paediatric participants 5 to <12 years of age, systemic events showed increased frequencies and severity for Dose 2 compared to Dose 1 for most events, with the exceptions of vomiting and diarrhoea which were reported infrequently and at similar incidences after each dose and across both groups. Systemic events in the tozinameran group, in decreasing order of frequency after Dose 1 versus after Dose 2, were:

- fatigue: 33.6% vs 39.4%
- headache: 22.4% vs 28.0%
- muscle pain: 9.1% vs 11.7%
- chills: 4.6% vs 9.8%
- joint pain: 3.3% vs 5.2%
- fever: 2.5% vs 6.5%
- diarrhoea: 5.9% vs 5.3%
- vomiting: 2.2% vs 1.9%

Most systemic events were reported less frequently in the placebo group compared to the tozinameran group.

In the tozinameran group the use of antipyretic/pain medication was modestly increased from after Dose 1 compared to after Dose 2 (14.4% and 19.7%). Use of antipyretic/pain medication was less frequent in the placebo group than in the tozinameran group and was similar after both Dose 1 and Dose 2 (8.3% and 8.1%).

After the first and second dose, most systemic events were mild or moderate in severity. Severe systemic events were infrequent, reported at low incidences (≤0.7%) across

tozinameran and placebo groups after either dose. In the tozinameran group, highest frequencies of severe systemic events reported after Dose 1 and Dose 2 were fatigue (0.3% and 0.7%) and fever (0.2% and 0.5%).

One participant, who was in the tozinameran group, had a fever >40 °C. This participant reported a fever of 40.0 °C at 2 days after Dose 2 which returned to normal body temperature (36.7 °C) the next day; this participant had no concurrent AEs (including infections, or injuries, or other illnesses) reported at this time or during the study.

Across groups, median onset for all systemic events after receiving tozinameran was 1 to 4 days after Dose 1 or Dose 2 (most had a median of 2 days post-dose), and all events resolved with a median duration of 1 day.

Overall, the pattern of systemic events reported in children 5 to <12 years of age after each dose was generally comparable to, or less than, that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001. Further details are provided in the risk discussion

Subgroups of Phase 2/3 paediatric participants 5 to <12 years of age had similar reactogenicity, with regard to systemic events, across the tozinameran and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino), and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the overall patterns of systemic events across these subgroups.

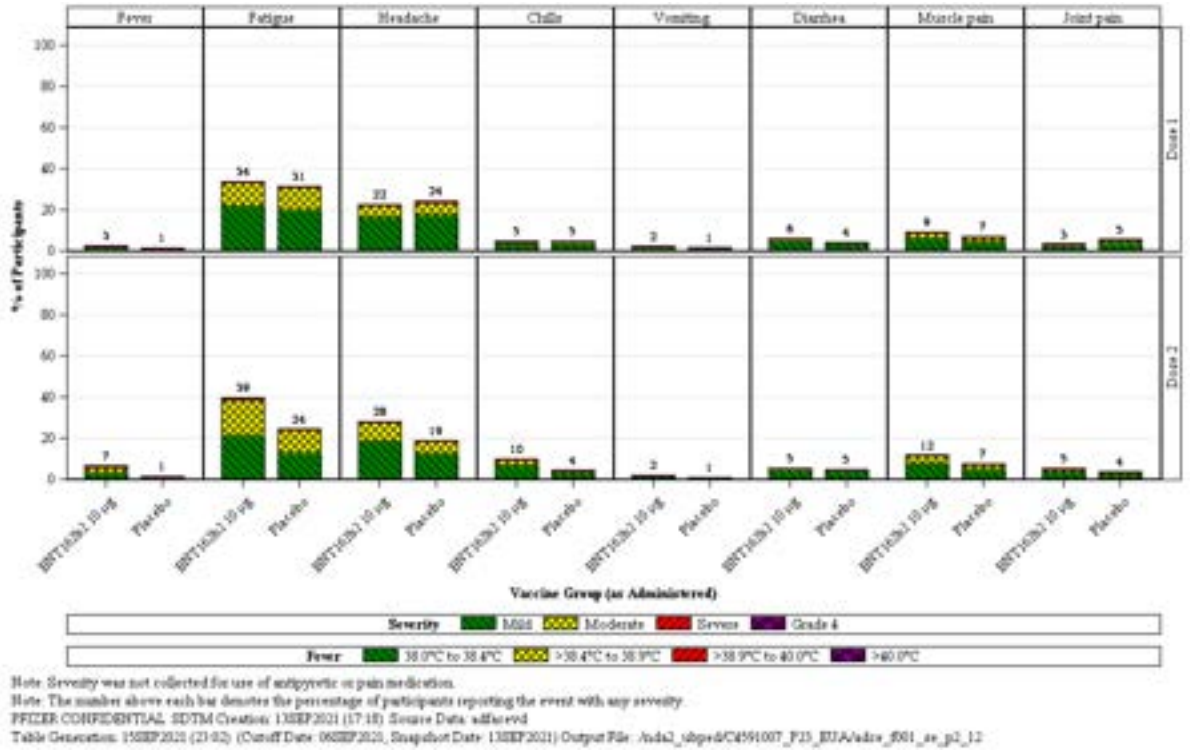


Figure 19 Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 –5 to <12 Years of Age – Safety Population

10.4.6 Adverse events

10.4.6.1 Adverse Events from Dose 1 to 1 Month After Dose 2

An overview of AEs from Dose 1 to 1 month after Dose 2 is shown below. The proportions of participants with any AE were similar in the tozinameran (10.9%) and placebo (9.2%) groups.

Any related AEs, any severe AEs, and any SAEs were reported across the tozinameran and placebo groups by ≤3.0%, 0.1%, and 0.1% (reported in the placebo group only), respectively. One participant in the placebo group had SAEs (pancreatitis and abdominal pain) that were considered by the investigator as not related to study intervention. No withdrawals due to AEs were reported. No study participants died.

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
Any adverse event	166 (10.9)	69 (9.2)
Related[c]	46 (3.0)	16 (2.1)
Severe	2 (0.1)	1 (0.1)
Life-threatening	0	0
Any serious adverse event	0	1 (0.1)
Related[c]	0	0
Severe	0	1 (0.1)
Life-threatening	0	0
Any nonserious adverse event	166 (10.9)	68 (9.1)
Related[c]	46 (3.0)	16 (2.1)
Severe	2 (0.1)	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Serious	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

Figure 20 Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Phase 2/3 – 5 to <12 Years of Age – Safety Population

Subgroups of Phase 2/3 paediatric participants 5 to <12 years of age had similar AE profiles from Dose 1 to 1 month after Dose 2, overall and categorically (i.e., related or severe events) across the tozinameran and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. No life-threatening AEs or any AEs leading to withdrawal were reported in the study. There were no meaningful differences in the overall patterns of AEs by category across these subgroups.

10.4.6.2 Adverse Events from Dose 1 to Data Cut-off Date

From Dose 1 to the data cut-off date (06 September 2021), which represents at least 2 months of follow-up after Dose 2, the proportions of Phase 2/3 paediatric participants 5 to <12 years of age with any event was similar in the tozinameran (11.6%) and placebo (9.6%) groups.

Few additional AEs were reported between 1 month after Dose 2 to the data cut-off date. Any related AEs, any severe AEs, and any SAEs were reported across the tozinameran and placebo groups by ≤3.0%, ≤0.2%, and 0.1%, respectively, up to the data cut-off date. From 1 month after Dose 2 up to the data cut-off date, 1 SAE (limb fracture) was reported in a participant in the tozinameran group that was considered by the investigator as not related to study intervention. No withdrawals due to AEs were reported. As of the data cut-off date, no study participants died.

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
Any adverse event	176 (11.6)	72 (9.6)
Related[c]	46 (3.0)	16 (2.1)
Severe	3 (0.2)	1 (0.1)
Life-threatening	0	0
Any serious adverse event	1 (0.1)	1 (0.1)
Related[c]	0	0
Severe	1 (0.1)	1 (0.1)
Life-threatening	0	0
Any nonserious adverse event	176 (11.6)	71 (9.5)
Related[c]	46 (3.0)	16 (2.1)
Severe	3 (0.2)	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Serious	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

Figure 21 Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 Through Cut-off Date (06SEP2021) – Phase 2/3 – 5 to <12 Years of Age – Safety Population

10.4.6.3 Related Adverse Events

From Dose 1 to 1 month after Dose 2, AEs assessed as related by the investigator were reported at a slightly higher frequency in the tozinameran group (3.0%) than in the placebo group (2.1%). Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 1.1% of participants in the tozinameran group compared with 0.9% of participants in the placebo group. Other notable related events reported from Dose 1 to 1 month after Dose 2 are summarized below.

- Non-serious, non-severe, related events of lymphadenopathy were reported in 0.7% of participants in the tozinameran group and none in the placebo group. All cases were considered mild.
- Non-serious related events of rash, urticaria, and other skin and subcutaneous tissue disorders were reported in 0.4% participants in the tozinameran group and 0.5% of participants in the placebo group.
- One non-serious, non-severe event of angina pectoris considered by the investigator as related to study intervention was reported by a participant in the tozinameran group. This event lasted 1 minute in duration, with onset at 2 days after Dose 2, and resolved with no sequalae or further investigation deemed warranted by the investigator.
- One related non-serious, Grade 3 event of tic was reported in a participant in the tozinameran group (later determined by neurology consultation to be unrelated).
- One non-serious, immediate (post-Dose 1) event of Grade 1 periorbital oedema considered by the investigator as related to study intervention was reported in a participant in the placebo group. This same participant reported other non-serious, Grade 1 AEs of hypersensitivity, erythema, and urticaria considered by the investigator as related to study intervention; all of these events occurred on the same day the participant received the first dose of placebo, all were reported as resolved the same day, and the participant later received the second dose of placebo without any AEs reported post-Dose 2.

10.4.6.4 Immediate Adverse Events

After Dose 1, immediate AEs (reported within 30 minutes of the first vaccination) were low in frequency (≤0.4%) in the tozinameran and placebo groups. Immediate AEs reported after Dose 1 in the tozinameran versus placebo groups were predominantly injection site pain, reported in 3 participants (0.2%) in the tozinameran group and 2 participants (0.3%) in the placebo group. No other immediate AEs post-Dose 1 were reported in the tozinameran group. Immediate AEs post-Dose 1 reported in the placebo group (n=1 each) were fatigue, hypersensitivity, erythema, urticaria, and periorbital oedema.

After Dose 2, immediate AEs (reported within 30 minutes of the second vaccination) were low in frequency (0.3%) in the tozinameran and placebo groups. Immediate AEs reported after Dose 2 in the tozinameran versus placebo groups were predominantly injection site pain, reported in 1 participant (0.1%) in the tozinameran group and 2 participants (0.3%) in the placebo group. Other immediate AEs reported post-Dose 2 in the tozinameran group (n=1 each) were injection site erythema, erythema, and nausea.

No allergic AEs were reported after either dose of tozinameran within 30 minutes after vaccination.

10.4.6.5 Severe or Life-Threatening Events

From Dose 1 to 1 month after Dose 2, severe AEs were low in frequency (0.1%) in both the tozinameran and placebo groups. Severe events reported included Grade 3 events of abdominal pain and pancreatitis (noted as occurring ‘post-injury’) both reported in 1 participant in the placebo group that were reported as SAEs considered not related to study intervention.

A non-serious Grade 3 AE of tic considered by the investigator as related to study intervention (later determined by neurology consultation to be unrelated) was reported in 1 participant in the tozinameran group. A Grade 3 rash (bilateral pleomorphic light eruption on arms) was reported by a participant in the tozinameran group, considered by the investigator as not related to study intervention and noted as possibly due to a reaction to sunscreen, and this same participant had an unrelated Grade 2 AE of leg (flank, hip, thigh) folliculitis after Dose 2 due to 'exposure in hot tub' at 24 days post-Dose 2 that resolved after 7 days of onset.

No life-threatening (i.e., Grade 4) AEs were reported from Dose 1 to 1 month after Dose 2.

10.4.6.6 Subgroup Analyses

Subgroups of Phase 2/3 paediatric participants 5 to <12 years of age had similar AE profiles from Dose 1 to 1 month after Dose 2 with regard to most frequently reported events by SOC and PT across the tozinameran and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Subgroups of race (Black or African American), ethnicity (Hispanic/Latino) and baseline SARS-CoV-2 status (positive) included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the AEs profiles across these subgroups.

10.5 Paediatric (5 to <12 Years of Age) Interim Safety Expansion Data in Phase 2/3 Study C4591007

Additional supportive safety data is provided for an additional, newly recruited N~2250 Phase 2/3 paediatric participants 5 to <12 years of age from Study C4591007 who began enrolment in August 2021. These safety expansion group participants were randomized 2:1 to receive tozinameran 10 µg or placebo. Results are presented up to the data cut-off of 08 October 2021, which represents at least 1 week of follow-up after Dose 2 for nearly all (98.5%) participants and at least 2 weeks of follow-up after Dose 2 for most (>70%) participants.

10.5.1 Expansion group safety population

The additional safety expansion group safety population for Phase 2/3 paediatric participants 5 to <12 years of age reflected the 2:1 randomization in the tozinameran (N=1591) and placebo (N=788) groups (Table 1). The only exclusions from the safety population were due to 15 participants (0.6%) not receiving study vaccine. No safety expansion group participants 5 to <12 years of age included in the safety population were HIV+

	Vaccine Group (as Administered)		
	BNT162b2 10 µg n[a]	Placebo n[a]	Total n[a] (%)
Randomized[b]			2394
Vaccinated	1591	788	2379 (99.4)
Safety population	1591	788	2379 (99.4)
HIV-positive	0	0	0
Excluded from safety population			15 (0.6)
Reason for exclusion			
Participant did not receive study vaccine			15 (0.6)

Abbreviation: HIV = human immunodeficiency virus.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 14OCT2021 (00:06) Source Data: adsl Table Generation: 14OCT2021 (13:47) (Cutoff Date: 08OCT2021, Snapshot Date: 13OCT2021) Output File: ./nda2 ubped/C4591007 P23 SAF EXP 5 11/adsl s008 saf pop p2 12

Figure 22 Safety Population – Safety Expansion Group – Phase 2/3 – 5 to <12 Years of Age

10.5.2 Duration of Follow-Up

At the time of the data cut-off date (08 October 2021), the median duration of follow-up for the Phase 2/3 paediatric safety expansion group of children 5 to <12 years of age was 2.4 weeks after Dose 2. Most participants (71.2%) had at least 2 weeks of follow-up after Dose 2. Nearly all participants (98.5%) had at least 1 week of follow-up after Dose 2.

10.5.3 Disposition

In total, 1598 participants were randomized to receive tozinameran 10 µg and 796 participants were randomized to placebo, reflecting the 2:1 randomization ratio. Most participants randomized to either tozinameran or placebo (≥98.7%) received Dose 1 and Dose 2. At the time of the data cut-off date (08 October 2021), most participants had at least 2 weeks of follow-up after Dose 2 but had not yet reached the 1-month post-Dose 2 visit.

One participant (0.1%) in the tozinameran group discontinued from the vaccination period due to AEs of pyrexia and neutropenia ('worsening from baseline'). This participant had a relevant medical history of transient benign neutropenia; this participant is continuing in the study for safety follow-up. Two participants (0.1%) in the tozinameran group and 1 participant (0.1%) in the placebo group withdrew from the study before the 1-month post-Dose 2 visit. Neither of these withdrawals was reported as due to an AE.

10.5.4 Protocol Deviations

Important protocol deviations were reported in 8 participants (0.5%) in the tozinameran group and 4 participants (0.5%) in the placebo group. All protocol deviations in the tozinameran group were related to investigational product; most (7 [0.4%]) were due to the participant being vaccinated despite meeting temporary delay criteria (i.e., anticipation of receiving nonstudy vaccine). Two (0.1%) participants in the tozinameran group did not sign informed consent or provide verbal consent; these participants did not receive study intervention and were excluded from analyses.

10.5.5 Demographics

Demographic characteristics for the Phase 2/3 safety expansion group of children 5 to <12 years of age were similar in tozinameran and placebo groups. Most participants were White (76.1%) with 5.6% Black or African American participants, 10.1% Asian participants, 7.6% multiracial participants, and other racial groups <1%. There were 13.2% Hispanic/Latino participants. The median age was 8.0 years and 50.7% of participants were male.

Obese children (based on age- and sex-specific indices) made up 11.2% (tozinameran group) and 11.0% (placebo group) of this age group in the safety population. Comorbidities present at baseline that increase the risk of severe COVID-19 disease (which include obesity) were present in similar proportions of participants in the tozinameran (19.7%) and placebo (20.2%) groups. The most common comorbidities reported in participants at study baseline were:

- asthma (8.4% in tozinameran and 9.0% in placebo)
- neurologic disorders (1.1% in tozinameran and 1.1% in placebo)
- congenital heart disease (0.6% in tozinameran and 0.4% in placebo)

One participant in the tozinameran group had a potentially immunocompromising condition reported at baseline: transient neutropenia of unknown aetiology, considered as benign and managed by a haematologist. This participant had an episode of neutropenia (‘worsening from baseline’) reported as an AE and was withdrawn from the study; see details in Section 2.3.2.5.

In the safety population, similar proportions of participants in the tozinameran group (10.2%) and placebo group (10.4%) had baseline SARS-CoV-2 positive status

10.5.6 Expansion Group Safety Summary

Phase 2/3 data from approximately 2250 children 5 to <12 years of age in a safety expansion group of Study C4591007, the majority of whom had follow-up of at least 2 weeks after Dose 2, support the conclusions from the initial enrolled group of N~ 2250 children, that tozinameran given as a two-dose primary series at 10 µg was safe and well-tolerated.

As of the data cut-off date (08 October 2021), the AE profile in this safety expansion group did not suggest any new safety concerns for tozinameran 10 µg vaccination in children 5 to <12 years of age. Further follow-up of the initial enrolment group, whose 2-month post-Dose 2 safety data were previously submitted in the EUA, now up to approximately 3 months after Dose 2 as of the present cut-off date, has shown no meaningful change to the AE profile for this age group. In the safety expansion group, few SAEs were reported in the tozinameran group: 3 participants (0.2%) had unrelated SAEs of arthritis infective of the knee, epiphyseal fracture, and foreign body ingestion. No deaths were reported. One withdrawal due to AEs was reported in the tozinameran group, due to non-serious events of pyrexia and neutropenia (‘worsening from baseline’) in a participant with pre-existing transient benign neutropenia, who is under the care of a haematologist and reported as doing well. Based on the additional follow-up for the initial enrolment group since the time of the EUA submission to approximately 3 months after Dose 2, only a limited number of non-serious, unrelated, mild to moderate AEs have been reported.

Analysis of all reported AEs in the safety expansion group and initial enrolment group did not reveal any new safety concerns or meaningfully change the observed safety profile.

At the present time, based on safety review from a total N~4500 participants (including over 3000 vaccine recipients) in the 5 to <12 years of age group in Study C4591007 (including initial enrolment and expansion groups), there have been very few AEs of clinical interest reported.

- No cases of myocarditis/pericarditis have been reported; none were reported in the safety expansion group through at least 2 weeks post-Dose 2, and none were reported in the initially enrolled group through at least 3 months post-Dose 2.
- Lymphadenopathy is an identified reaction to tozinameran in study participants ≥12 years of age and is also observed in children 5 to <12 years of age, with all events reported as mild.
- Rashes have been identified as a vaccine reaction and were more frequent in the tozinameran group than the placebo group, noting that very few were considered as related to vaccination and these were characterized as mild and self-limited.

The safety and tolerability profile of tozinameran 10 µg administered in children 5 to <12 years of age now represents a total of N~4500 participants (over 3000 active and 1500 placebo), with follow-up to at least 2 weeks after Dose 2 for the majority of participants in the safety expansion group, and a longer median follow-up to at least 3 months after Dose 2 for the initial enrolment group. These data collectively show no new safety concerns, including few AESIs and no reported cases of myocarditis/pericarditis, and support the safe and tolerable administration of tozinameran 10 µg to children 5 to <12 years of age.

10.6 Safety Conclusions

Phase 1 dose-finding safety data (in conjunction with Phase 1 immunogenicity data) led to the selection of tozinameran at the 10-µg dose level for children 5 to <12 years of age.

Phase 2/3 data from approximately 2250 children 5 to <12 years of age with a follow-up time of at least 2 months after Dose 2 showed tozinameran at 10 µg was safe and well-tolerated.

Reactogenicity in children 5 to <12 years of age was mostly mild to moderate and short-lived, with median onset of 1 to 4 days after dosing (most within a median of 2 days post-dose), and resolution within 1 to 2 days after onset. Local reactions presented predominantly as injection site pain with no effect of dose number, which was similar to what was previously reported in Study C4591001 participants ≥12 years of age; however mild to moderate redness and swelling occurred at higher frequencies in children than previously reported in C4591001. Systemic events most commonly included fatigue, headache, and muscle pain, and generally increased in frequency and/or severity with increasing dose number; these were typically milder and less frequent than previously reported in Study C4591001.

The observed AE profile in this study did not suggest any new safety concerns for tozinameran vaccination in children 5 to <12 years of age. Most reported AEs occurred from Dose 1 to 1 month after Dose 2 and reflected reactogenicity events occurring postvaccination with tozinameran, or other unrelated infections or injuries that are expected

to be observed in a paediatric general population with similar frequencies in the tozinameran and placebo groups.

A total of 3 unrelated SAEs were reported in 2 participants (1 participant in the tozinameran group had an unrelated SAE of limb fracture, and 1 participant in the placebo group had 2 unrelated SAEs of pancreatitis and abdominal pain noted as occurring 'post-injury'), and no deaths or withdrawals due to AEs were reported as of the data cut-off date (06 September 2021), which represents at least 2 months of follow-up after Dose 2.

As of the data cut-off date, there were very few AEs of clinical interest reported in children 5 to <12 years of age, and no cases of myocarditis/pericarditis were reported. Lymphadenopathy has been identified as related to tozinameran in study participants ≥12 years of age and is also observed in children 5 to <12 years of age, with all events reported as mild. Rashes were more frequent in the tozinameran group than the placebo group, but very few (n=4) were considered as related to vaccination and these were characterized as mild and self-limited.

Overall, the safety and tolerability profile of tozinameran 10 µg when administered as a two-dose primary series 3 weeks apart to approximately 1500 children 5 to <12 years of age, who had at least 2 months of follow-up since receiving their second dose, reflects age-appropriate events that are consistent with a paediatric general population and the known reactogenicity profile of tozinameran. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

10.7 Evaluator's comments

The phase II/III component of the study consisted of two cohorts of equal size approximately 2250 each. A second cohort was added at the request of FDA with the intention of increasing the size of safety database in children 5-11 years of age. The total size of the safety database consisted of approximately 3100 children in the vaccine group. Immunogenicity was assessed in a subset of 322 participants in this study.

An additional cohort of 2379 additional participants, in conjunction with the original cohort permitted evaluation of a total of approximately of 3000 vaccine recipients to define rare events for at least two weeks for most vaccine recipients, and for two to three months for over 1500 vaccine recipients.

Cohort and 1 and 2 varied by the duration of follow up. The data from an additional 2369 participants in cohort 2 were submitted during the EUA review process with the FDA. Enrolment began in cohort 1 by June 7, 2021, the data cut of was September 6, 2021 and this cohort included approximately 1500 vaccine recipients and 750 placebo recipients of whom 95% combined had at least 2 months of safety follow up after completing a two dose primary series.

Safety data from this cohort included solicited adverse events, unsolicited adverse events, serious adverse events, and adverse events of special interest. For cohort 2 – safety data from this cohort included the safety monitoring as in cohort 1 but due to the shorter follow up time focussed on SAE and AE of clinical interest. The first participant enrolled for Cohort 2 was Aug 26, 2021 and the data cut off was October 8, 2021. The cohort size was

approximately the same as cohort 1 but the median duration of follow up here was 2.4 weeks post dose 2 at the time of data cut off

Reactogenicity data was captured for seven days. Non serious adverse events were captured for a month and serious adverse events were captured of six months. To enhance possible detection of myocarditis observed in adolescents and young adults - should it occur, specific instructions were provided to investigators to be vigilant of symptoms and signs of myocarditis, and to perform workup in the event of suspected myocarditis.

The mean age of vaccination was 8 years of age. 11 percent had comorbidities including obesity.

In regard to local reactions, there was some increase in mild to moderate redness and swelling both after dose 1 and 2 in the 5–12-year age groups compared to the 16–25-year age group. Pain at the injection site was comparable between the two age groups. Local reactions met a satisfactory safety profile.

Regarding systemic events by maximum severity within 7 days after dose 2 in 5 to <12 compared to 16-25, reactions were typically higher in vaccine recipients. The incidence of fever was lower and mostly mild to moderate in individuals 5 to <12 years old compared to the older age group. This is also true for chills. Likewise, across the other systemic event parameters the responses were comparable or less to those seen in 16–25-year-olds, again representing a satisfactory systemic reaction profile for 5 to <12-year-old children.

Unsolicited adverse events in both groups were comparable of any adverse events or related adverse events occurred. There were very few serious adverse events and no related serious adverse events and no deaths. One female participant was withdrawn from the study due to a fever of 40c on day two after dose 1 accompanied by neutropenia. The fever resolved in one day – this child carried a pre-existing diagnosis of benign neutropenia followed by a haematologist and she recovered uneventfully.

Adverse events occurring at an incidence of greater than 1 percent by system organ class showed comparable rates between vaccine recipients and placebo recipients, irrespective of the category specified. Lymphadenopathy was observed in 0.9 percent of vaccine recipients in this enrolment group.

All SAEs were considered unrelated: three events were related to trauma and one was related to ingestion of a foreign body. In the expansion safety group, one participant reported infective arthritis of undiscerned aetiology 15 days after dose 1, this resolved 21 days later.

There were no adverse events of special interest (anaphylaxis, myocarditis, bell's palsy, appendicitis) observed. Angioedema and hypersensitivity were uncommonly seen and observed in both placebo and vaccine recipients and were short lived. A reported case of Henoch Schoenlein Purpura that occurred 21 days following dose 1 was considered unrelated and follow up is ongoing.

11 BENEFIT/RISK ANALYSIS

This section will be completed following a request of information from the sponsor.

12 Request for information: APPID 115492, Cominaty COVID-19 Vaccine TT50-10853-1

12.1 Medsafe RFI 1:

As described in the foreign regulatory status segment of the gazette, The Cominaty COVID-19 vaccine has been approved for emergency use application in the United States of America on the 29/10/21. The sponsor is requested to provide any Post-authorization Summary Monthly Safety Reports (SMSRs) available following the approval and administration of this vaccine in the 5–12-year age group. Additional safety data from C4591007 following the data cut-off date of 08/10/21 if available is also requested.

12.1.1 Sponsor response:

The next planned SMSR will cover the period 29 October 2021 to 15 December 2021, due on 10 January 2022 and will include review of children aged 5 to 11 years old.
There is no additional safety data for C4591007 following the data cutoff date of 08/10/21 currently available.

Evaluators comments:
This additional safety data will be evaluated as part of ongoing pharmacovigilance following provisional approval. The sponsor's response is acceptable.

12.2 Medsafe RFI 2:

As described in the clinical overview: community transmission of SARS-CoV2 in most of the US and many regions of the world is high. This is the case despite an ongoing global vaccination campaign, in part due to the now-predominant circulation of the highly transmissible B.1.617.2 (Delta) SARS-CoV-2 variant. The sponsor states that "fully vaccinated individuals remain highly protected from serious illness owing to the high efficacy of available vaccines including tozinameran but unvaccinated individuals continue to serve as a large reservoir for community transmission"

The sponsor is requested to provide data, if available, that provides evidence of reduced infectivity amongst the vaccine recipient cohort 5-12 years of age and would support the approval of the extension of indication in this age group to reduce community transmission. If such data is not available, data supporting reduction in community transmission in the 16–25-year age group in study C4591001 would also be appropriate as this age group provides the basis for the immunobridging end point in study C4591007.

12.2.1 Sponsor response

No transmission data is available in the 5 to <12-year-old age group from C4591007. An analysis is being performed in participants 16 years an older in the C4591001 study, and this data will be available early 2022.

Evaluator's comments:
Study C4591007 and C4591001 did not evaluate transmission rates of SARS-CoV2 in Comirnaty (tozinameran) recipients compared with placebo group. As the severity of

COVID-19 disease in children appears to be substantially lower compared to adults, evidence showing vaccination reduces disease transmission and therefore community

transmission would increase the favourability of the benefit risk assessment of Comirnaty (tozinameran) in children 5-<12. The ongoing evaluation of such data in the analysis being performed in participants 16 years and older in C4591001 is acceptable.

12.3 Medsafe RFI 3

The safety data reports one participant (0.1%) in the tozinameran group discontinued from the vaccination period due to AEs of pyrexia and neutropenia ('worsening from baseline'). This participant had a relevant medical history of transient benign neutropenia. The sponsor is requested to provide a further safety update for this participant.

12.3.1 Sponsor Response

The participant is a [redacted]-year-old [redacted] with a pertinent medical history of gingivitis (since December 2020) and benign transient neutropenia (since March 2021) with a baseline absolute neutrophil count of 480, who received Dose 1 on 30 August 2021.

The participant experienced pyrexia on 31 Aug 2021, 1 day after receiving Dose 1. The participant received Tylenol, and the event resolved the same day.

On 01 September 2021, 2 days after receiving Dose 1, the participant had a planned hematology appointment in follow-up to the recent benign neutropenia diagnosis in March 2021. Routine laboratory tests were completed and the complete blood count (CBC) showed white blood cells (WBC) 2.26, hemoglobin/hematocrit (H/H) 11.2/33, platelets 267, and absolute neutrophil count (ANC) 20. No other symptoms/infections were reported at that time.

On 21 September 2021, the participant, who was doing well, was seen by the investigator for Visit 2, at which time a follow up CBC was completed which showed WBC 2.78, H/H 12.1/37.6, platelets 299, and the ANC improved to 70. The participant did not receive treatment other than routine mouth washing.

The participant was discontinued from the study intervention on 21 September 2021 (i.e., did not receive Dose 2) because of the pyrexia and neutropenia and remains in the study to be evaluated for safety, immunogenicity, and/or efficacy.

Two follow-up CBCs have been performed since discontinuation of study intervention:

• 4 October 2021, which showed WBC 3.90, H/H 11.7/35.5, platelets 252, and ANC of 280

• 20 October 2021, which showed WBC 4.11, H/H 12.1/36.9, platelets 361, and ANC improved to 1240.

No further safety data is available at this time.

Evaluator's comments:
The supplementary information for the case above is clinically acceptable.

12.4 Medsafe RFI 4

In the safety narrative provided within the gazette, One [redacted] participant [redacted] years of age in the tozinameran group had an AE of mild Henoch-Schoenlein purpura with onset of 21 days after Dose 1, considered by the investigator as not related to study intervention, and reported as ongoing at the time of the data cut-off date. This event

was preceded by other AEs also considered by the investigator as unrelated to study intervention: mild headache with onset at 10 days after Dose 1 and resolved in 2 days, and mild joint swelling of the right ankle with onset at 16 days after Dose 1 and resolved in 3 days. This participant had no reported medical history and received no prohibited concomitant treatments or nonstudy vaccines.

After experiencing the AEs of headache and joint swelling within 10 days and 16 days, respectively, of Dose 1, at approximately 3 weeks after receiving Dose 1, the participant was running and bumped on her knee. She was evaluated by her primary care physician, who then diagnosed Henoch-Schoenlein purpura. The participant was treated with steroids and pain medication. Due to the initiation of steroids, the study Visit 2 appointment was delayed (at the time of the data cut-off date, Dose 2 was reported as not administered).

The sponsor is requested to provide additional information for this case: in particular any further safety data and whether dose 2 was subsequently administered following the data cut-off date.

12.4.1 Sponsor response

The participant is a [redacted]-year-old [redacted] with no past medical history, who received Dose 1 on 03 September 2021.

On post vaccination Day 16 (18 September 2021), the participant had onset of AE of ankle swelling that resolved 2 days later (20 September 2021). This was parent reported and no medical attention was received. Etiology was reported as unknown.

On post vaccination Day 19 (22 September 2021), the participant had abdominal pain.

On post vaccination Day 20 (23 September 2021), the participant bumped her knee and was evaluated by her primary care physician (PCP). The PCP diagnosed the HSP, with etiology reported as unknown. At that visit, the participant had mild abdominal pain and mild rash of palpable purpura at abdominal wall, stomach, and back. The abdominal pain resolved later that day.

On post vaccination Day 21 (24 September 2021), the participant was evaluated by the Investigator/Principal Investigator and on the exam found was to have light rash on the abdomen and back. There was no palpable purpura on the Principle Investigator’s assessment. Vitals reported included temperature of 98.7 °F, blood pressure of 100/69 mm

HG, heart rate of 90 beats per minute, and respiratory rate of 21 breaths per minute. No laboratory studies, including biopsy or urinalysis, were performed by the PCP. Treatment plan included prescription of steroids and pain meds to be used as needed. The parent did not administer the medications to the child since they did not believe it was needed. There were no other infections or non-study vaccinations reported from time of vaccination to diagnosis of HSP. Re-evaluation by PCP or referral to specialist did not occur.

The HSP resolved on 07 October 2021, 14 days after initial diagnosis with no treatment administered.

The participant received Dose 2 on 28 October 2021. No AEs were reported following Dose 2.

Evaluator's comments:
The sponsor's response is clinically satisfactory.

12.5 Medsafe RFI 5

The proposed data sheet in section 4.2 states the "Doses of COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] (30 micrograms/dose) and COMIRNATY COVID-19 VACCINE 0.5 mg/mL concentrated suspension for injection (30 micrograms/dose) are considered interchangeable." Section 6.6 of the proposed data sheet states: "If the vial has a purple plastic cap, refer to the Datasheet handling instructions for COMIRNATY (COVID-19 mRNA vaccine) Concentrate for injection 0.5 mg/mL TT50-10853."

These statements are clinically unclear and infers that the original PBS/sucrose COMINATY presentation (with a purple vial cap colour) may be used in the 5-<12 years of age group.

The sponsor is requested to amend the proposed data sheet such that the appropriate vial is clearly documented for the respective age groups. A suggested amendment of the data sheet could be to either remove this sentence or to amend as follows:

"Doses of COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] (30 micrograms/dose) and COMIRNATY COVID-19 VACCINE 0.5 mg/mL concentrated suspension for injection (30 micrograms/dose) are considered interchangeable however only the COVID-19 VACCINE [Tris/Sucrose Presentation] in the 10micrograms/0.2ml dose strength (orange cap colour) is recommended in the 5-<12 year age group"

Evaluator's comments:
Ongoing revisions of the data sheet are currently taking place and being reviewed as of 7/12/21

13 BENEFIT/RISK ANALYSIS FOLLOWING RFI

Children between the ages of 5 to 11 in New Zealand are potentially at risk of infection with the globally endemic severe acute respiratory syndrome coronavirus 2 and the associated COVID-19. While the disease-burden of COVID-19 is concentrated in the elderly, there is morbidity and mortality in children.

This application is supported by the ongoing research from Study C4591007. In addition, there is general support for the efficacy and safety of the Comirnaty vaccine through the study programme for individuals ≥12 years of age, and through the accumulating post-marketing experience.

The observed AE profile in this study did not suggest any new safety concerns for tozinameran vaccination in children 5 to <12 years of age. Overall, the safety and tolerability profile of tozinameran 10 µg reflects age-appropriate events that are consistent with a paediatric general population and the known reactogenicity profile of tozinameran. Subgroup analyses of safety endpoints suggested no meaningful differences in safety profile based on participant demographics or baseline SARS-CoV-2 status.

In addition, assessment of the use of tozinameran 10 µg, by both the FDA and EMA concurs with the Medsafe assessment that the clinical trials showed the most common side effects in this age group mirrored those in people aged 12 and above, and mainly consisted of

localised reactions such as injection site pain and swelling, or systemic reactions such as fever, and muscle pain. Benefit risk assessments from both agencies also revealed that the risks of COVID-19 infection outweigh the risk of vaccination in this age group. The FDA highlighted that in the US children 5 to <12 years of age represent 39% of cases of COVID-19 infection in individuals younger than 18 years of age.

In light of the risk of myocarditis, where the observed risk is highest in males 12 through 17 years of age, the FDA conducted a benefit-risk assessment that used modelling to predict how many symptomatic COVID-19 cases, hospitalisations, ICU admissions, and deaths in children would be prevented by vaccination versus the number of potential myocarditis cases requiring hospitalisation and/or ICU admissions that the vaccine might cause. The FDA's model predicted that overall, the benefits of the vaccine would outweigh the risks in children 5 to <12 years of age for the purposes of granting Emergency Use Authorisaion.

Current international data suggests that AEFIs in children 5 to <12 years of age are consistent with those observed in older age groups, with the majority of reports being that of expected localised and systemic reactions or symptoms associated with anxiety post-vaccination.

The data assessed, as described in the report above, demonstrates that for children at risk of COVID-19, the vaccine provides a high level of immunogenicity against this disease and is generally well tolerated. Clinical efficacy was also demonstrated. As such, Medsafe considers that the benefit risk balance of Comirnaty 10 µg vaccine when used to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 5 to <12 years of age is likely to be positive in the context of a provisional consent. However, Medsafe recommends that this application be referred to the Medicines Assessment Advisory Committee (MAAC) for consideration. Due to the timeframes in which Comirnaty 10 µg has been developed, additional clinical data is not yet available, including from the ongoing pivotal trial. Due to these data limits and the public interest in a COVID-19 vaccine for use in a paediatric population, Medsafe considers it would be beneficial for the MAAC to review Pfizer's application and to provide a recommendation before a final decision on provisional consent is made. It is also recommended that as part of their consideration, the MAAC provide advice regarding the proposed conditions outlined below.

Furthermore, Pfizer has provided an updated data sheet incorporating requested revisions. The revised data sheet is considered acceptable from a clinical point of view, pending assessment by the Medsafe quality evaluator as described in a separate report.

14 Recommendation

It is recommended that the application received 12 November 2021 (ID 115492) as it relates to Comirnaty 10 µg be referred to the MAAC for consideration and final recommendation regarding provisional consent for use according to the following indication:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

It is also recommended that the MAAC consider the following conditions to be imposed on a provisional consent:

- Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
- Provide the six months analysis data from Study C4591007. Due date: 28 February 2021.
- Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
- Provide the final Clinical Study Reports for Study C4591007 within five working days of these being produced.
- Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
- Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
- Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

EVALUATION OF A NEW MEDICINE APPLICATION

Product Details	
Type of application:	Higher Risk Medicine - Vaccine *This is an Additional dosage form - Grade 2 application for a new formulation, strength and dose form. The indication is also being extended to children aged 5 to 11 years.*
Proposed trade name:	**COMIRNATY** COVID-19 mRNA vaccine The company has been asked to include the following identifiers in the product name to ensure sufficient differentiation between the different presentations (refer RFI1 Q.2): - COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose) - COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose) The identifiers relevant to the parent vaccine once all three presentations are on the market will include: - COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose)
Dose form:	Suspension for injection (30 micrograms/0.3 mL dose presentation) Concentrate for suspension for injection (10 micrograms/0.2 mL dose presentation when diluted)
Drug substance and strength:	Tozinameran (BNT162b2[mRNA]), 0.1 mg/mL The new strength is presented as: - 0.225 mg/2.25 mL (delivers 30 micrograms/0.3 mL dose) (TT50-10853/1) - 0.13 mg/1.3 mL (delivers 10 micrograms/0.2 mL dose once diluted) (TT50-10853/1a)
Classification:	Prescription
ATC code:	J07BX03
Proposed indications and /or label claims	Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.

Initial Evaluation Completed: November 2021
Final Report Completed: December 2021

	The use of this vaccine should be in accordance with official recommendations. *The company has been asked to amend the indication to reflect the indicated age ranges for each presentation of Comirnaty, since the 10 micrograms/0.2 mL dose presentation is restricted for use to individuals aged 5 to 11 years, and the 30 micrograms/0.3 mL presentation is restricted for use in individuals aged over 12 years. Refer RFI1 Q.6.*
Administration & dosage:	*Administration:* Intramuscular injection The 10 micrograms/0.2 mL dose presentation contains 1.3 mL of vaccine concentrate per vial, and requires dilution with 1.3 mL 0.9% saline (not supplied with product) prior to use. The 30 micrograms/0.3 mL dose presentation contains 2.25 mL of vaccine per vial and does not require dilution prior to administration. *Dosage:* Adults and children 12 years of age and older: Two doses (0.3 mL each) of COMIRNATY (grey cap, do not dilute) given at least 21 days apart. A booster dose may be administered at least 6 months after the primary course in individuals 18 years of age and older. Children aged 5 to 11 years: Two doses (0.2 mL each) of COMIRNATY (orange cap, must dilute), given at least 21 days apart. Children under the age of 5 years: Safety and efficacy have not been established in children under 5 years of age.
Packaging & closure:	COMIRNATY (grey cap, do not dilute) (*30 micrograms/0.3 mL dose)* 2 mL clear vial (Type I glass), closed with a synthetic bromobutyl rubber stopper, aluminium overseal and grey flip-off plastic cap. The vials are packaged in a cardboard carton. COMIRNATY (orange cap, must dilute) (*10 micrograms/0.2 mL dose)* 2 mL clear vial (Type I glass), closed with a synthetic bromobutyl rubber stopper, aluminium overseal and orange flip-off plastic cap. The vials are packaged in a cardboard carton.
Pack size:	10 multidose vials/carton Equivalent to 60 doses of 30 micrograms/0.3 mL (6 doses per vial) or 100 doses of 10 micrograms/0.2 mL (10 doses per vial) 195 multidose vials/carton Equivalent to 1170 doses of 30 micrograms/0.3 mL (6 doses per vial) or 1950 doses of 10 micrograms/0.2 mL (10 doses per vial)

Storage conditions:	Unopened vials 6 months from the date of manufacture, stored at -90°C to -60°C, protect from light. There is a statement in Section 6.3 of the data sheet that the vaccine vials may be received frozen at -90 to -60°C, or at -25 to -15°C. Frozen vaccine can be stored either at -90 to -60°C, or 2 to 8°C upon receipt. If the vaccine is received at 2 to 8°C it should be stored at 2 to 8°C (do not refreeze). Thawed vials (unopened) Once removed from the freezer, the unopened thawed vials can be stored for a single period of up to 10 weeks at 2 to 8°C (refrigerate, do not freeze), within the 6 month shelf-life. Vaccine may be stored at temperatures between 8 and 30°C for up to 24 hours, including any time within these temperatures following first puncture. Thawed vials can be handled in room light conditions. Once thawed, the vaccine should not be refrozen. Opened vials *COMIRNATY (grey cap, do not dilute)* Chemical and physical in-use stability has been demonstrated for 12 hours at 2 to 30°C. There is a statement in the data sheet that from a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user. Diluted vials *COMIRNATY (orange cap, must dilute)* Chemical and physical in-use stability has been demonstrated for 12 hours at 2 to 30°C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. The data sheet notes that from a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
NZ sponsor:	Pfizer New Zealand Limited, Level 10, 11 Britomart Place, Auckland CBD, AUCKLAND 1010
Manufacturers & packers:	Manufacture of drug substance: BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, GERMANY *Responsible for manufacture of drug substance (in vitro transcription, DNase I and Proteinase K digestion), release and stability testing (identity, purity, process related impurities)* Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, GERMANY *Responsible for manufacture of drug substance (ultrafiltration/diafiltration, dispensing), release and stability testing (composition, strength, safety)*

	Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC, One Burtt Road, Andover, Massachusetts 01810, USA *Responsible for manufacture of drug substance, release and stability testing (composition, strength, identity, purity, process related impurities, safety), and storage of cell banks* BioNTech Manufacturing Marburg GmbH, Emil-von-Behring-Strasse 76, Marburg 35041, GERMANY *Responsible for manufacture of drug substance (in vitro transcription, DNase I and Proteinase K digestion ultrafiltration/diafiltration, dispensing), release and stability testing (composition, strength, safety)* BioNTech Innovative Manufacturing Services GmbH, Vollmersbachstrasse 66, Idar-Oberstein 55743, GERMANY *Responsible for release and stability testing only (product-related impurities, purity). Not recorded on TPDR.* Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA *Responsible for release and stability testing of the drug substance (composition, strength, identity, purity, process-related impurities). The site also performs cell bank manufacture and storage, and manufacture and testing of the starting material (linear DNA template). Not recorded on TPDR.* Labor LS SE & Co KG, Mangelsfeld 4, 97708 Bad Bocklet-Grossenbrach, GERMANY *Alternative site for bioburden testing of the drug substance.* <u>Manufacture, packaging (primary and secondary) and testing of drug product:</u> Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, 2870, BELGIUM *Responsible for LNP production and bulk drug product formulation, fill and finish, packaging (primary and secondary), release and stability testing (appearance, visible particulates, subvisible particulates, pH, osmolality, LNP Size, LNP polydispersity, RNA encapsulation, RNA content, ALC-0315 content, ALC-0159 content, DSPC content, cholesterol content, container content, lipid identities, RNA integrity, endotoxin, sterility, dye incursion). Although not applicable to the New Zealand application, this site also performs batch release by a qualified person in the European Economic Area (EEA) of commercial lots utilising drug substance from Wyeth (Pfizer), Andover, MA, USA.* <u>Finished product testing:</u> Pfizer Ireland Pharmaceuticals, Grange Castle, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND *Responsible for release and stability testing (identity of encoded RNA sequence, cell-based flow cytometry, subvisible particulates)* <u>EU site of batch release:</u> BioNTech Manufacturing GmbH, Kupferbergterrasse 17 – 19, 55116 Mainz, Germany

	Responsible for batch release by qualified person in European Economic Area (EEA). Not recorded on TPDR, as the New Zealand site of batch release performs this activity for product released to the New Zealand market. New Zealand site of batch release: Pfizer New Zealand Limited, Level 10, 11 Britomart Place, Auckland CBD, Auckland 1010
Parent product:	Comirnaty, 0.5 mg/mL concentrated suspension for injection (delivers 30 micrograms/0.3 mL dose), TT50-10853 The parent product (PBS/sucrose formulation) was granted provisional consent on 3/02/2021. Provisional consent was renewed for two years on 28/10/2021, to 3/11/2023.
Overseas approvals:	New indication (5 to 11 years) Pending approval in the EU (submitted 15/10/2021) and Australia (submitted 29/10/2021). Authorised for emergency use in the USA on 29/10/2021. Not yet submitted in Canada, Singapore, Switzerland, or the UK. New formulation (Tris/sucrose) CHMP positive opinion for granting a marketing authorisation for the 30 µg/0.3 mL Tris/sucrose formulation and dose form (dispersion for injection) was granted on 14/10/2021. The 10 µg/0.2 mL formulation is under review by the EMA (submitted 15/10/2021) and Australia (submitted 29/10/2021). Not yet submitted in Canada, Singapore, Switzerland, or the UK. *The company has confirmed that the data submitted in support of this NMA for the new indication and new formulation is identical to that submitted in the EU, USA and Australia, with the exception of country specific Module 1 information.*
Overseas evaluation reports provided:	EMA/CHMP assessment report (EMA/CHMP/576432/2021) for the 30 micrograms/0.3 mL dose (0.1 mg/mL) Tris/sucrose formulation and dose form (dispersion for injection). ***RFI1 Q.1. Please provide the questions from the EMA and TGA (and company responses) for the introduction of the Tris/sucrose formulations of Comirnaty. Please also provide the EMA/CHMP assessment report for the 10 microgram/dose presentation of the Tris/sucrose formulation, when available.*** *EAI1 Q.1. The TGA questions and associated company responses were provided. The EMA assessment reports, questions and associated company responses are not yet available. The company will be asked to provide the EMA reports when available.* ***RFI2 Q.1 Please commit to provide the EMA assessment reports for the 10 micrograms/ dose presentation of the Tris/sucrose***

		formulation of Comirnaty, when available. Please also confirm the specific obligations imposed by the EMA/CHMP on the conditional marketing authorisations of both the 10 micrograms/dose and 30 micrograms/dose Tris/sucrose presentations of Comirnaty.
	EAI2 Q.1.	*The EMA assessment report for the 10 micrograms/dose presentation was provided. The company confirmed the only new obligation imposed by the EMA/CHMP in relation to the Tris/sucrose formulation was to submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study C4591007, which has a due date of July 2024.* ***Point resolved****.*

CONTENTS

Administrative Data

Background

Pfizer New Zealand Limited has submitted this NMA to introduce a new strength and dose form of Comirnaty, an mRNA vaccine indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The company is also proposing extension of the indicated age range to include children aged 5 to 11 years.

Comirnaty was granted provisional consent for distribution in New Zealand on 3 February 2021, with 58 conditions of consent. Provisional consent was renewed on 28 October 2021 for two years to 3 November 2023, with 8 conditions of consent. All quality conditions imposed with the original approval were suitably addressed and resolved by the company prior to the renewal. The outstanding conditions relate to product distribution and clinical.

Comirnaty is currently formulated using phosphate-buffered saline (PBS) buffer (referred to as the 'PBS/sucrose' formulation) at a strength of 0.5 mg/mL. The approved drug product is presented as a 0.45 mL concentrated suspension of mRNA (encoding the SARS CoV-2 spike glycoprotein) in lipid nanoparticles that must be diluted before use. Following dilution with 1.8 mL sterile 0.9% sodium chloride, each multidose vial is able to deliver 6 doses of 30 µg RNA (BNT162b2 [mRNA]/Tozinameran) per 0.3 mL injection volume.

To provide a vaccine with an improved stability profile and greater ease of use at administration sites, Pfizer/BioNTech have developed a new drug product formulation using tromethamine (Tris) buffer instead of PBS (referred to as the 'Tris/sucrose' formulation). The new formulation has a lower strength (0.1 mg/mL) and is presented as two dose forms that differ in fill volume and the requirement for dilution prior to administration:

- *30 micrograms/0.3 mL dose*: The 30 µg RNA dose is presented as a suspension for injection. Each multidose vial contains a 2.25 mL fill volume and is administered without dilution, delivering 6 doses of 30 µg RNA per 0.3 mL injection volume. This presentation is proposed for use in individuals aged 12 years of age and older and will eventually replace the current approved vaccine.
- *10 micrograms/0.2 mL dose*: The 10 µg RNA dose is presented as a concentrate for suspension for injection. Each multidose vial contains a 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration. Once diluted, the vial is able to deliver 10 doses of 10 µg RNA per 0.2 mL injection volume. This presentation is proposed for use in individuals aged 5 to 11 years.

The key differences in the three presentations of Comirnaty are summarised in the below table.

Table 1: Original (0.5 mg/mL PBS/sucrose) and proposed (0.1 mg/mL Tris/sucrose) formulations

	Original PBS/Sucrose (current indication)	Tris/Sucrose (for current indication)	Tris/Sucrose (for new indication)
Vial cap colour	Purple	Grey	Orange
Age range	Over 12 Years	Over 12 Years	5 to <12 Years
Pharmaceutical form	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
Fill Volume	0.45 mL	2.25 mL	1.3 mL
Volume/dose	0.3 mL	0.3 mL	0.2 mL
µg RNA/dose	30 µg	30 µg	10 µg
Dilution required	Yes (1.8 mL saline)	No	Yes (1.3 mL saline)
Doses/vial	6	6	10
Strength (RNA) in vial	500 µg/mL	100 µg/mL	100 µg/mL
Pack size	195	10, 195	10, 195

The sponsor notes in the cover letter that the existing PBS/sucrose formulation would require only 0.1 mL to administer the 10 µg dose in individuals aged 5 to 11 years, which is difficult to measure accurately with standard syringes. Vaccination of this patient population is better supported by the 1.3 mL presentation of the new Tris/sucrose formulation, which provides an easier to measure 0.2 mL dose.

This submission is supported by one pivotal clinical trial, Study C4591007. Commencing with a Phase 1 dose-finding study, Phase 2/3 of Study C4591007 evaluated both the safety and immunogenicity of Comirnaty as a vaccine against COVID-19. The study included 4 different age groups; however, only the 5 to 11 years age group is analysed in the submitted application. The doses examined in Phase 1 were 10 µg, 20 µg and 30 µg, and the 10 µg dose was selected for the Phase 2/3 part of the study. Of note, the paediatric clinical trial was performed using the currently approved PBS/sucrose formulation, not the proposed Tris/sucrose formulation. The company's justification for the absence of clinical trial data for the Tris/sucrose formulation is addressed in Module 5 of this report.

Product name

The proposed proprietary name for the Tris/sucrose product is COMIRNATY (presented in capital letters on the labels and in the data sheet). This is the same name as registered for the parent PBS/sucrose 0.5 mg/mL vaccine. For ease of readability, the evaluator has used 'Comirnaty' in this report.

To differentiate the two presentations of the 0.1 mg/mL strength, the data sheet refers to the vaccine as **'***Comirnaty Ready To Use Multidose (Do Not Dilute)'* for the suspension for injection presentation administered at 30 µg/0.3 mL dose to 12 years of age and older, and *'Comirnaty Dilute to Use Multidose (For Age 5 to < 12 Years)'* for the concentrate for suspension for injection administered at 10 µg/0.2 mL dose to 5 to 11 years, following dilution. Since the proposed names are not reflected in the associated labelling (some versions of the labels do not state the trade name as Comirnaty, and others do not state the indicated age ranges; discussed further below), the company will be asked to include additional identifiers in references to the product to minimise the potential for administration errors.

The labels proposed for distribution of the vaccine in New Zealand are the same as those produced for the EU and US markets, so it would seem prudent to align the product identifiers in the data sheet and on the TPDRs for the 0.1 mg/mL presentations of Comirnaty with those approved by the EMA and FDA.

The product names in the EU are detailed below (taken from the SPC; the 30 µg/dose is approved, the 10 µg/dose is under evaluation). For each product, reference is made to the vial cap colour for dose verification.

- Comirnaty 30 micrograms/dose concentrate for dispersion for injection
  (dose verification: purple cap)
- Comirnaty 30 micrograms/dose dispersion for injection
  (dose verification: grey cap)
- Comirnaty 10 micrograms/dose concentrate for dispersion for injection
  Children 5 to 11 years
  (dose verification: orange cap)

The FDA authorised identifiers in the US product fact sheets are as follows:

- 12 years of age and older, purple cap (must dilute) (this is the original parent vaccine)
- 12 years of age and older, grey cap (no dilution) (there is a note on the FDA website that this formulation is not yet available in the USA)
- 5 – 11 years of age, orange cap (must dilute/dilute before use).

On the basis of the product names/identifiers used internationally, and the labelling proposed for distribution of the product in New Zealand, Medsafe considers that the quantity of mRNA/dose should be included in all references to the product name (as per section 1 of the data sheet), as this is the prominent identifier on the proposed labelling. To distinguish the proposed formulation from the current formulation (since both are likely to be in the New Zealand market at the same time), the company is asked to reference the vial cap colour, the type of formulation (original and new), and the indicated age ranges. To minimise confusion and avoid the use of symbols, the paediatric age range should be '5 to 11 years' as approved by the EMA, rather than '5 to < 12 years'. The following are the suggested identifiers for use in the data sheet, CMI, and all communications with New Zealand healthcare professionals:

- COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose)
- COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)
- COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose)

RFI1 Q.2.	***To minimise the potential for administration errors due to confusion over the different formulations and presentations of Comirnaty (since the same trade name is proposed and all are likely to be in the market at the same time) the company is asked to include the following identifiers in the product name in the data sheet, CMI and all communications with New Zealand healthcare professionals:*** ***COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose)*** ***COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)*** ***COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose).*** ***The identifiers have been added to the therapeutic product database reports (TPDRs).***
EAI1 Q.2.	*The sponsor accepted the proposed identifiers and has used them in the updated data sheets. Further revisions to the data sheets are required to ensure the identifiers are fully incorporated into Section 1, and to ensure the readability of the data sheet with the identifiers. This is discussed in EAI1 Q.6 of this report.* ***Point resolved.***

Labelling

The company submitted full-scale colour artworks of the vial and carton labels. Additional labels were provided in email correspondence received 22/11/2021. Multiple versions are proposed, as the company is seeking approval to use the labels produced for the EU and US markets for product distributed in New Zealand.

A labelling exemption is sought for areas of the labels that are non-compliant with New Zealand Medicines Regulations 1984 (discussed further below). The company has provided a commitment to move to labelling compliant with Medsafe requirements once manufacture is no longer constrained by pandemic conditions. On the basis of the critical need for this

product, and since a labelling exemption has been granted for the parent vaccine labels, the request for a labelling exemption for the labels proposed with this NMA will be approved by Medsafe. The company will be asked to describe the international labelling (and areas of non-compliance that require clarification) in a Dear Healthcare Professional Letter (DHPL) that accompanies release of the new presentations of Comirnaty. This is addressed in RFI1 Q.4.

Since the labels have different areas of non-compliance, each is described separately below. The following points common to the proposed labelling are noted:

- the dose form descriptions on the EU approved labels are *dispersion for injection* and *concentrate for dispersion for injection*, whereas in the data sheet 'dispersion' is replaced with 'suspension' to reflect the New Zealand specific terminology
- for the most part, the EU labelling enables the different strengths to be distinguished easily and unambiguously through the use of colour coding that aligns with the vial cap colour (orange for 10 micrograms/dose, grey for 30 micrograms/dose), and prominent references to the administered dose, exceptions are discussed below
- the vial and carton labels approved by the FDA for Emergency Use Authorisation (EUA) in the US refer to the trade name of the product as 'Pfizer-BioNTech COVID-19 Vaccine' ('Comirnaty' is used on the EU labels)
- the indicated age range for the 10 microgram/0.2 mL dose presentation is '5 years to <12 years' on the US labels, and '5 to 11 years' on the EU labels
- neither the FDA nor the EMA approved vial and carton labels state the name and strength of the drug substance
- the US labels refer to an in-use period of 6 hours; however, the proposed in-use period for product distributed in New Zealand is 12 hours (as stated in the data sheet)
    - The company notes in correspondence received 22/11/2021, that this discrepancy is a consequence of the fact that the EUA labels (and some of the Comirnaty branded labels) were created earlier than others, when the existing data only supported an in-use storage time of 6 hours.

Where applicable, the company is asked to address these issues in a DHPL (refer RFI1 Q.4).

Vial labels

<u>30 micrograms/0.3 mL dose</u>

30 mcg PAA173908 (Launch RTU EU) (41 mm x 16 mm)

The evaluator has concerns with this label as it does not state the batch number or expiry date, which is not acceptable for both post-market monitoring and safety reasons. Furthermore, the only strength identifier on the label is '6 doses', which could be confused with the parent vaccine since the dose form is described only as 'injection'. The evaluator acknowledges that the proposed label has a grey border to distinguish it from the purple border of the current approved label for the parent vaccine vial, and states '6 doses' and 'do

not dilute' rather than '6 doses after dilution' as on the parent label; however, these differences are subtle and should be brought to the attention of administrators as part of the DHPL. The company will be asked to confirm that the label is printed with the expiry/LOT details and clarify the purpose of the green box.

RFI1 Q.3.	***Please confirm the EU vial labels for both the 30 microgram/dose and 10 microgram/dose presentations are printed with the expiry date and batch details. Please also clarify the purpose of the green box on the EU vial labels. For those labels where the green box is obscuring text (eg PAA181046, PAA173907), please confirm exactly what text is under the graphic.***
EAI1 Q.3.	*The company confirmed that the batch and expiry details are printed on the packaging lines on the EU vial labels as variable text in one of the varnish areas. The other varnish area is a space for healthcare professionals to write the 'discard time' on the labels, based on the allowable storage instructions. Although not confirmed directly, the green boxes on all the labels are assumed to represent the varnish areas, as replacement labels (PAA181047, PAA181046, PAA181915, PAA173907) have been provided with the varnish areas (green boxes) removed, enabling all printed text on the artwork to be visible. The updated labels are copied next to their respective originals below.* ***Point resolved****.*

30 mcg PAA181915 (EMA approved artwork for PPQ batches) (41 mm x 16 mm); with and without the varnish overlay (refer EAI1 Q.3)

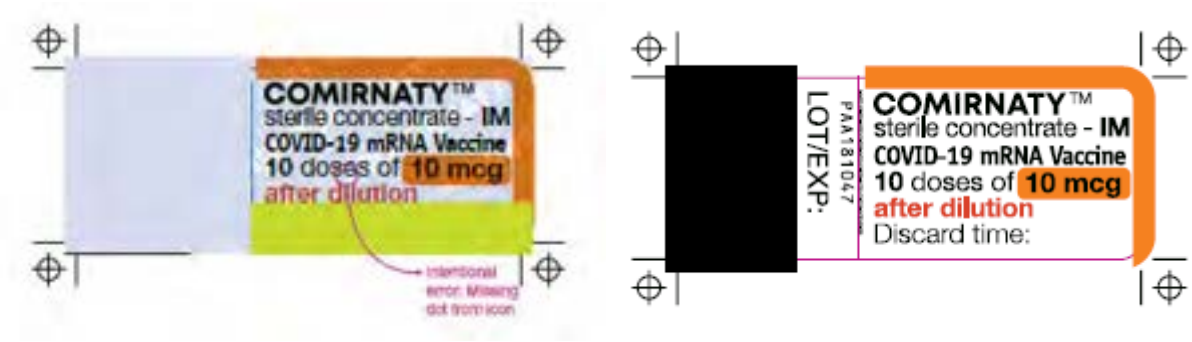
The information on this label is the same as on PAA173908. This version is more recent and has been updated to include the text 'Do not dilute' in bold font.

30 mcg PAA181046 (Launch RTU 10X EU) (16 mm x 41 mm); with and without the varnish overlay (refer EAI1 Q.3)

The only difference between this label and 30 mcg PAA173908 is the inclusion of the dosage '30 mcg' in a grey box, which is considered an improvement in terms of identification.

10 micrograms/0.2 mL dose

10 mcg PAA181047 (Launch RTU 10X EU) (41 mm x 16 mm); with and without the varnish overlay (refer EAI1 Q.3)



The absence of batch/expiry details is addressed in RFI1 Q.3. Although the vial does not state the name and strength of the drug substance, the following information is considered to sufficiently identify the product and distinguish the label from those for the other presentations of Comirnaty: i) '10 doses of 10 mcg' with the dose quantity presented in bold font in an orange box, ii) the instruction 'after dilution' and iii) reference to the dose form as 'sterile concentrate'.

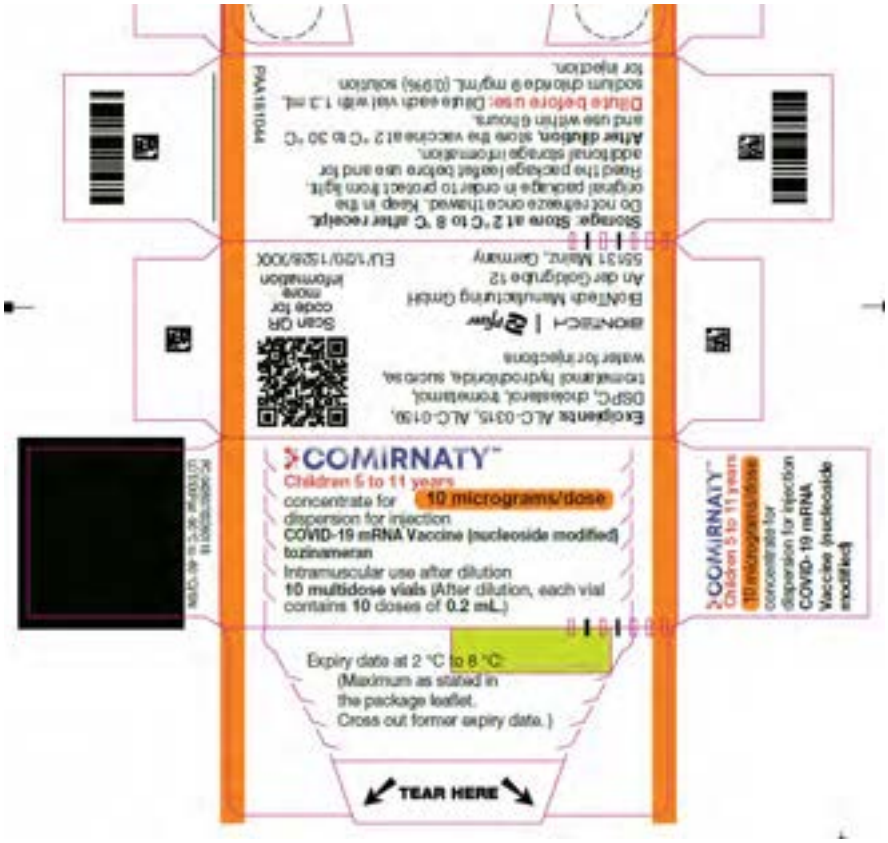
10 mcg PAA177913 (US EUA) (41 mm x 16 mm)

The US vial label for the 10 micrograms/dose presentation includes the same colour coding as the EU labels, with clear dosage information (10 doses of 0.2 mL). The instruction to dilute prior to use is suitably prominent. The in use storage period on the label for the diluted product is 6 hours at room temperature, when 12 hours is proposed for product marketed in New Zealand. This must be addressed in the DHPL and will form part of the labelling exemption.

Carton labels

10 micrograms/0.2 mL dose

10 mcg PAA181044 (Launch RTU EU) (37 x 39 x 89 mm) and *10-mcg-PAA181045 (Launch RTU EU) (37 x 47 x 89 mm)*



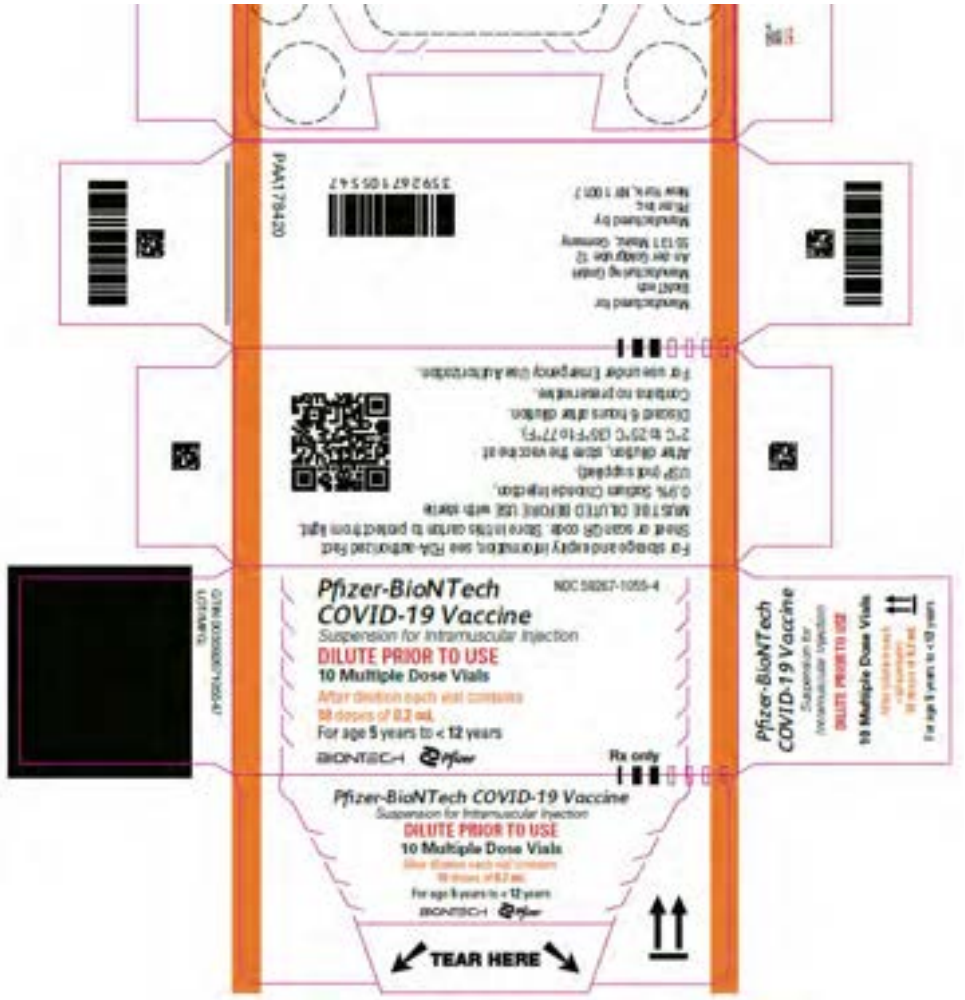
Two EU labels have been provided for the 10 pack size of the 10 micrograms/dose presentation: *PAA181044* (shown above) and *PAA181045* (same content as PAA181044 but slightly different dimensions). The sponsor states in the cover letter (and has signed the labelling declaration in the NMA form to this effect) that the artwork mock-ups for the 195 pack will be the same as for the 10 pack size of the 10 µg and 30 µg presentations, with minor changes consistent with the different pack size.

The proposed labels mostly comply with regulation 13 of the New Zealand Medicines Regulations 1984 for the labelling of medicines, with the exception of the absence of the strength of the drug substance and the absence of a classification statement. A labelling exemption is currently granted to the parent labels for the absence of this information. The risk to patient safety as a consequence of the absence of the strength of the drug substance is mitigated in part by the statement ‘each vial contains 10 doses of 0.2 mL’ on the PDP of the carton label, and the prominence of the dosage ‘10 micrograms/dose’ in an orange coloured box on two panels of the label. The label also includes ‘concentrate’ in the dose form description and mentions a requirement to dilute the vial before use at several locations across the label. The expiry date on the carton label has been updated to include the storage temperature ‘at -90°C to -60°C’ next to ‘EXP’ to ensure the correct handling of the product. An additional space has been added for the healthcare professional to write the expiry date at 2 – 8°C, with reference to the enclosed package leaflet for the current approved shelf-life at this temperature (currently 10 weeks is proposed). Section 6.3 of the data sheet also notes a requirement to write the updated expiry date on the carton label after moving the product to 2 – 8°C storage.

The storage conditions on the carton label state that the product should be stored at 2 – 8°C after receipt. This only partially aligns with the storage conditions in the data sheet, which note that the vaccine can be stored at either -90°C to -60°C or 2 – 8°C upon receipt. The labels also state that after dilution, the vaccine can be stored at 2 to 30°C for up to 6 hours. As noted above, the proposed shelf-life of the diluted product has now been extended to 12 hours at room temperature (as stated in section 6.3 of the data sheet). To minimise the risk for confusion, the sponsor will be asked to define the approved storage conditions for the unopened, opened/diluted product in the DHPL, with any discrepancies between the information in the data sheet and on the labels clearly identified.

In alignment with the approved carton labels for the parent vaccine, the proposed label includes a QR code that takes the user to a splash page 'www.comirnatyglobal.com'. From here, the individual accessing the website can select 'I am a healthcare professional' or 'I am not a healthcare professional' and the specific country in which they are located, e.g. New Zealand. The evaluator could not access the healthcare professional specific information (as a professional registration is required), but the non-healthcare professional in New Zealand is taken to the CMI published on the Medsafe website. On the basis that other countries have more than one product information document, it seems reasonable to assume the company will have appropriate strategies in place to enable a user in New Zealand to access the appropriate CMI/data sheet for the different presentations/formulations of Comirnaty.

10 mcg PAA178420 (Launch paediatrics, US) (37 x 39 x 89 mm) and *10 mcg PAA178418 (Launch paediatrics, US) (37 x 39 x 89 mm)*

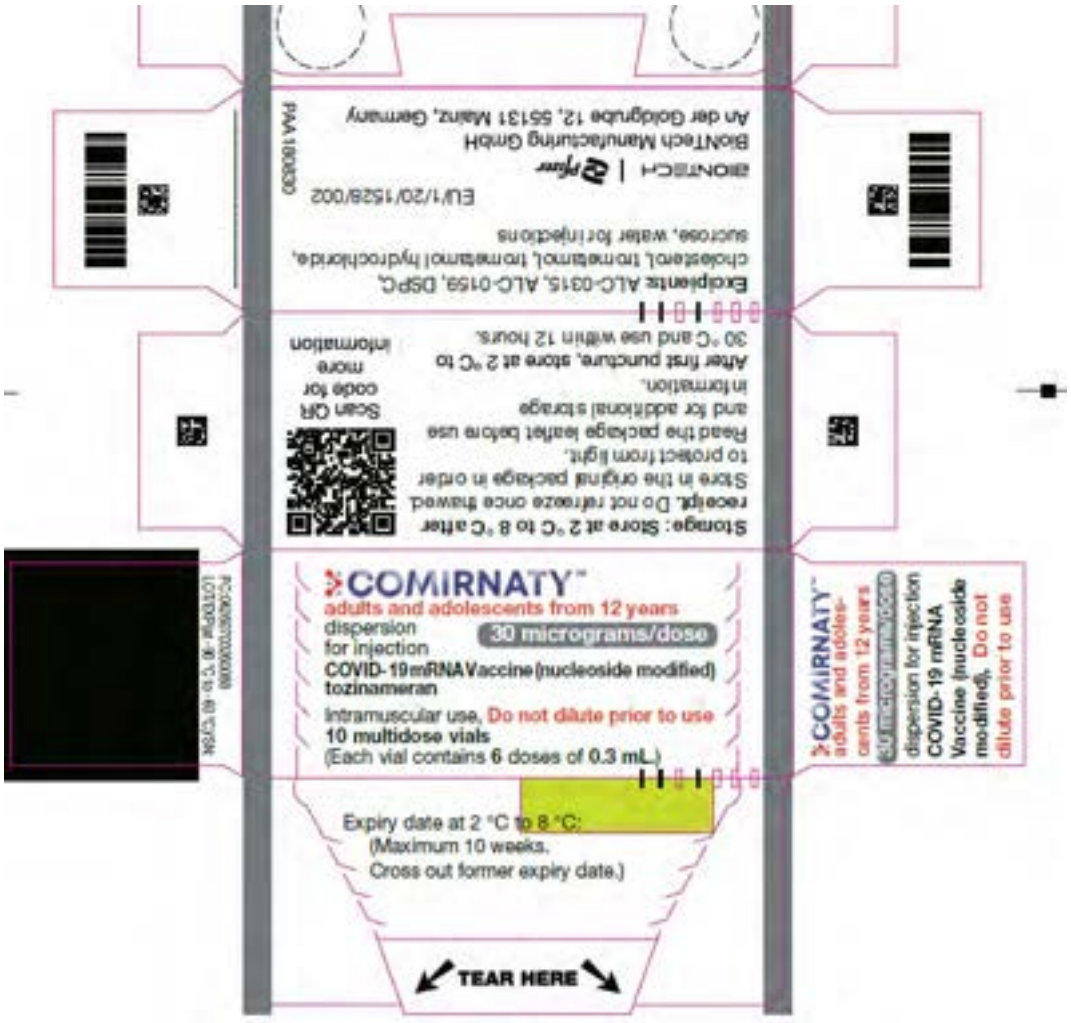


The content on the two sets of FDA EUA labels is the same except PAA178418 has the statement ‘Made in Germany’ on it. The following points are noted:

- the age range (5 years to < 12 years versus 5 to 11 years) and product name (Pfizer-BioNTech COVID-19 vaccine versus Comirnaty) on the FDA EUA labels differ from those on the EU labels
- the FDA EUA labels include the classification statement (‘Rx only) but do not state the drug substance name or strength
- the dose form description on the carton label is ‘suspension for intramuscular injection’ and does not mention that the product is a vaccine concentrate
    - this is not considered a significant safety concern, as the label clearly describes a requirement for dilution with 0.9% Sodium Chloride Injection, USP’ (not supplied) before use
- the labels states the storage conditions for the diluted product, 2 to 25°C for up to 6 hours (a 12 hour shelf-life for the diluted product is proposed)
- the storage and expiry information on the label directs the user to see the ‘FDA-authorized Fact Sheet (the package insert) or to scan the QR code
    - The QR code links to the URL https://www.cvdvaccine.com, which contains global information about the vaccine, with links to country specific information as described above for the EU labels.

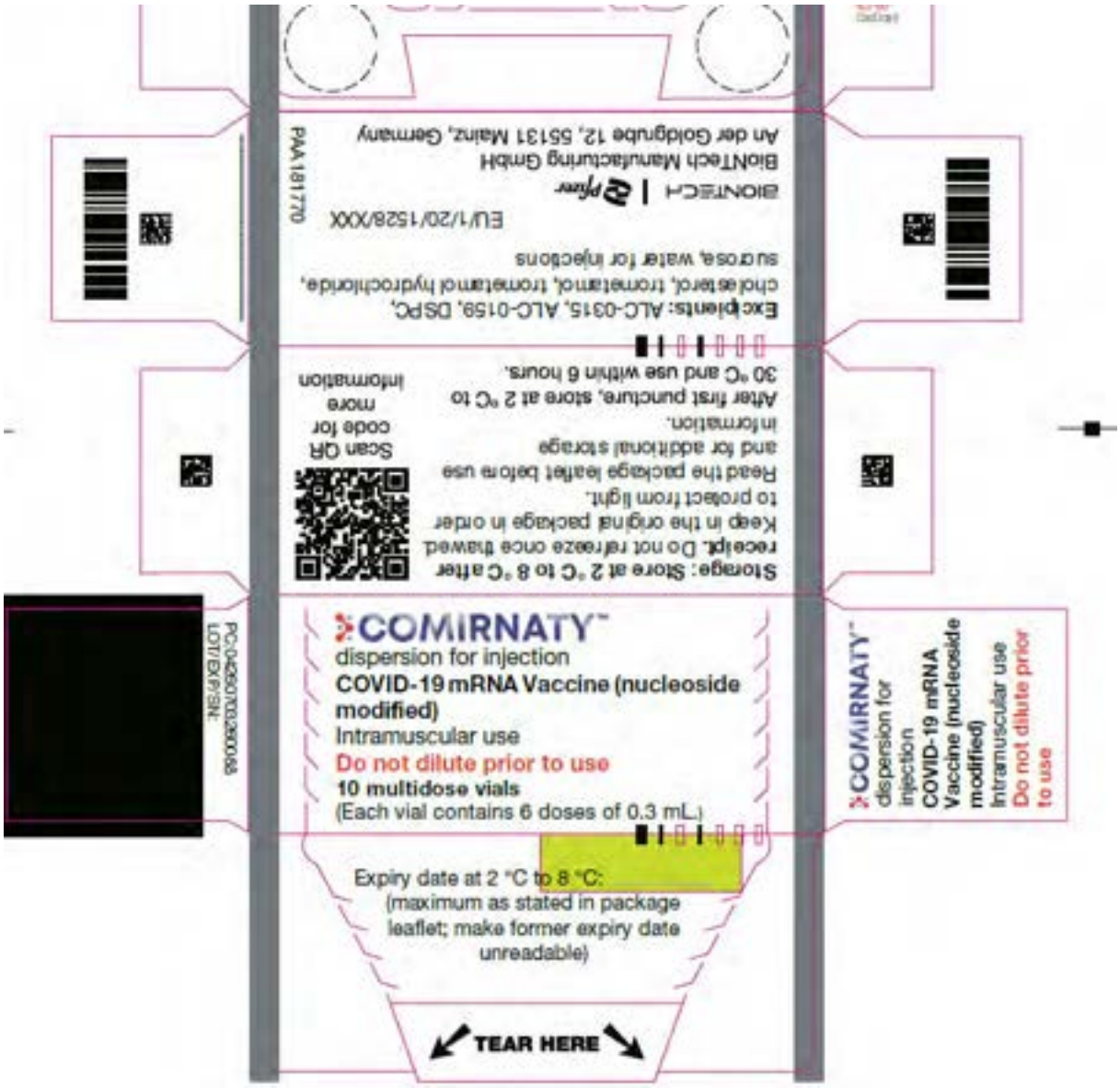
30 micrograms/0.3 mL dose

30 mcg PAA180830 (Launch RTU EU; shown below) (37 x 39 x 89 mm) and *30 mcg PAA181041 (Launch RTU EU) (37 x 47 x 89 mm)*



Two versions of the above EU label have been provided for the 10 pack size of the 30 micrograms/dose presentation that differ only in dimensions. The content and layout of the information on the label is as described for the 10 micrograms/dose carton label. The following features distinguish the two presentations: the dose form description (dispersion for injection rather than concentrate), indicated age range information, use of grey colour coding, reference to 30 micrograms/dose in a prominent grey box and 6 doses of 0.3 mL on the PDP, and the instruction 'do not dilute prior to use' in bold font on two panels of the label. It is also noted that the refrigerated shelf-life is stated as a maximum of 10 weeks on these labels (the 10 µg/dose labels direct the user to the package insert for the refrigerated shelf-life) and the in-use shelf-life for the opened product is stated as 12 hours at 2 to 30°C. While the 10 weeks shelf-life aligns with the data sheet, the storage temperature range does not (the data sheet refers to 8 to 30°C). This is addressed in RFI1 Q.6.

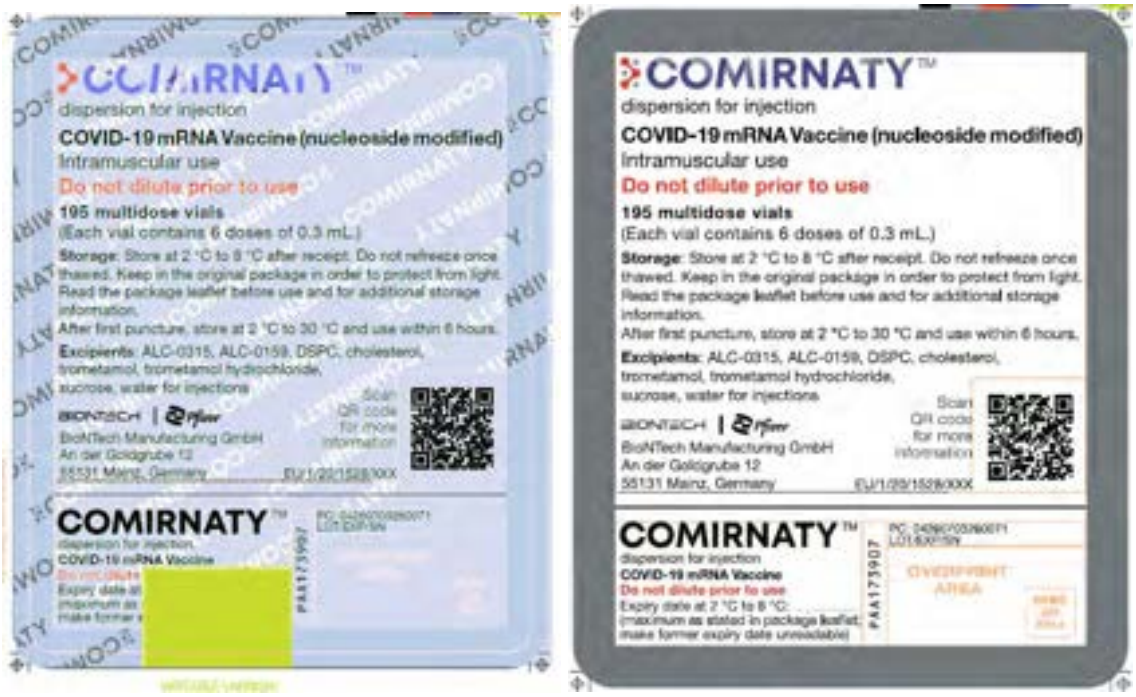
30 mcg PAA181770 (EMA approved for PPQ batches; shown below) (37 x 39 x 89 mm) and *30 mcg PAA181911 (EMA approved for PPQ batches) (37 x 47 x 89 mm)*



Two versions of the above EU label (approved by the EMA for distribution of the PPQ batches) have been provided for the 10 pack size of the 30 micrograms/dose presentation. The two versions differ only in dimensions so only one representative label is shown. The labels contain less identifying information than the carton labels described above for the 30 micrograms/dose presentation. The following points are noted: the carton labels do not state the indicated age range, the absence of prominent reference to the strength as 30 micrograms/dose, the refrigerated shelf-life is not stated (reference is made to the package insert for this information), the in use shelf-life of the opened product is described as 6 hours (not the 12 hours proposed). Although not ideal, Medsafe accepts that the use of grey colour coding, and the prominent references to the dose form and 'Do not dilute prior to use' are sufficient to identify the product. Nevertheless, the noted discrepancies (eg 6 hour in-use shelf-life) must be addressed in a DHPL.

Tray label

30 mcg PAA173907 (Launch RTU EU) (105 x 130 mm)



The company has provided the above label for the 30 microgram/dose presentation, which they refer to as a 'tray label' for the 195 pack size (the left hand version shows the varnish overlay; refer EAI1 Q.3). It is assumed this is an earlier version of the 195 pack size label (the artwork is dated Apr 2021 as compared to Sep 2021 for most of the other artwork), as the company has stated the 195 pack size will be marketed in labels based on the 10 pack size. The style and layout of the information on the label aligns with the current approved carton label for the parent product. The only points of difference that distinguish it as the new strength are the dose form 'dispersion for injection' rather than 'concentrate for dispersion for injection', reference to 'do not dilute prior to use', rather than the parent carton label that instructs the product to be diluted, and the excipient details. There does not appear to be any use of the grey colour coding used for the other labels for this strength/presentation. The label also instructs that the product is stored at 2 to 8°C after receipt (not the frozen or refrigerated temperatures described in the data sheet), and describes an in use shelf-life of 6 hours for the opened product (not the 12 hours proposed). These issues must be addressed in the DHPL. The QR code links to the same EU website as described earlier in this report.

Labelling exemption

The following areas of non-compliance require a labelling exemption:

- the absence of the name and strength of the active ingredient on the vial labels, and absence of strength on the carton labels (some carton labels also do not include the drug substance name)
- the EU (carton) and US (vial and carton) labels refer to an in use period of 6 hours at room temperature for the diluted 10 micrograms/dose product; however, 12 hours is proposed for product marketed in New Zealand.
- the absence of a classification statement on the EU labels
- the storage conditions for the unopened and opened/diluted products are incomplete and do not align with the information in the data sheet (with regards to the storage temperature on receipt and the in use shelf-life for the diluted/opened products).

On the basis that i) the proposed vaccine has been developed in response to the current global COVID-19 pandemic, and ii) will be supported by a comprehensive information programme for New Zealand healthcare professionals, the company's request for a labelling exemption for the noted areas of non-compliance will be granted. The labelling exemption will be valid for the duration of the s23 approval granted at gazettal of this NMA, or until approval of New Zealand specific labelling, whichever occurs first.

Dear Healthcare Professional Letter (DHPL)

The company will be asked to provide a DHPL for review, that addresses the below points.

RFI1 Q.4.	***Since the 0.1 mg/mL strengths of the Tris/sucrose formulation of Comirnaty will be supplied in international labelling that does not comply fully with New Zealand medicines regulations, the company must provide a 'Dear Healthcare Professional Letter' to accompany release of the products. Information included in the letter should address (but is not limited to) the following:*** ***i) An overview of the new formulation, strength, dose forms and indicated age ranges, with reference to the vial cap colour for dose verification.*** ***ii) A clear description of the proposed shelf-lives and storage conditions for the unopened, opened/diluted products (for example, some labels state that the product should be stored at 2 – 8°C upon receipt but the data sheet states the product can be stored at either -90°C to -60°C or 2 – 8°C upon receipt).*** ***iii) A description of the international labelling that will be used for distribution of the vaccine in New Zealand. The inclusion of colour photograph(s)/artwork(s) of the labels in the letter is encouraged. If more than one version of the labels for each strength/presentation will be used concurrently, differences between the labels should be identified. Of particular note are the vial label for the 30 microgram/dose presentation identified as PAA173908, and the tray label identified as PAA173907, which will need to be clearly described to distinguish them from the current approved labels for the parent (PBS/sucrose) vaccine.*** ***iv) Differences in dose form description (eg dispersion versus suspension), product name (Comirnaty versus Pfizer-BioNTech COVID-19 vaccine) and in use shelf-life (eg 6 hours versus the proposed 12 hours) on the applicable international labels should also be identified.*** ***Please provide (or commit to do so prior to launch of the vaccine to the New Zealand market), a draft DHPL that addresses the above concerns.***
EAI1 Q.4.	*The company agreed to prepare a Dear Healthcare Professional letter that addresses the concerns raised. A draft will be provided to Medsafe prior to finalisation of the letter.* ***This will be noted as a condition of approval of this NMA. Point resolved.***

Data sheet and package insert

A draft data sheet and signed declaration have been submitted. Medsafe's assessment of the clinical information in the data sheet is documented in a separate report.

The company has prepared a separate data sheet for the Tris/sucrose formulation of Comirnaty, which is based on the data sheet for the parent PBS/sucrose vaccine. The

sponsor states in the cover letter that a separate data sheet for the Tris/sucrose presentations will facilitate a smooth transition for the introduction of supply of the new Tris/Sucrose formulation and eventual depletion of stock of the PBS/Sucrose formulation that supports the existing 12 years of age and older indication. At the request of Medsafe, an updated data sheet was provided on 22/11/2021 to incorporate changes made to the data sheet during Medsafe's approval of the booster shot. The updated data sheet also includes revisions requested by the TGA.

Unlike the EMA SPC and FDA approved fact sheets, which are individual documents for each presentation of the vaccine, the proposed data sheet includes information on both the 30 micrograms/0.3 mL dose and 10 micrograms/0.2 mL dose presentations within the same document. The different presentations are referred to as '*Comirnaty Ready to Use Multidose (Do Not Dilute)'* and *'Comirnaty Dilute to Use Multidose (For Age 5 to < 12 Years)'* respectively. While acceptable in principle, the two presentations of the Tris/sucrose product have different dose forms and therefore different requirements regarding dilution, and are indicated for use in different age ranges. Since both presentations of the Tris/sucrose formulation have the same trade name, and the names used in the data sheet do not align with the prominent identifying details on the product labels, Medsafe considers that there is the potential risk for administration errors with having the information for the two presentations in the one data sheet. As per section 2.4 of Part 10 of the GRTPNZ, separate data sheets for different dose forms of the same medicine should be provided where this promotes the safe use of the medicine.

RFI1 Q.5.	***To ensure the safe use of the medicine and minimise the risk for administration errors, the company is asked to prepare separate data sheets for the 10 micrograms/dose and 30 micrograms/dose presentations of the new formulation of Comirnaty. The individual data sheets should use the naming terminology suggested in RFI1 Q.2, incorporate the changes requested in RFI1 Q.6 and be based on the respective EU SPC documents.***
EAI1 Q.5.	*The sponsor accepted this request. Individual data sheets have been prepared for the 10 micrograms/dose and 30 micrograms/dose presentations of the new formulation of Comirnaty, using the identifiers described in RFI1 Q.2. The acceptability of the data sheets is discussed in EAI1 Q.6. To ensure sufficient differentiation between the 0.5 mg/mL strength of Comirnaty and the new presentations of the 0.1 mg/mL strength, the company will be asked to incorporate the proposed identifiers for the parent product 'COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose)' in the next data sheet update for this strength/presentation.*
RFI2 Q.2	***To ensure sufficient differentiation between the 0.5 mg/mL strength of Comirnaty and the new presentations of the 0.1 mg/mL strength, please commit to update Section 1 of the data sheet for the parent vaccine to incorporate the identifiers COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose).***
EAI2 Q.2.	*The sponsor committed to updating section 1 of the data sheet for the parent product with additional identifiers, at the next available opportunity for a data sheet update.* ***This will be noted as a post-approval commitment. Point resolved.***

The content in the proposed data sheet mostly complies with New Zealand Medicines Regulations. Several changes are required to improve readability and ensure patient safety.

RFI1 Q.6.	***Please make the following changes to the proposed data sheet:***
	i) Replace references to the indicated age range of the 10 micrograms/dose

presentation from '5 to < 12 years' with '5 to 11 years'.

ii) Section 1: Include 'dose' in the bracketed information so it reads '(30 micrograms/0.3 mL dose)' …'(10 micrograms/0.2 mL dose)'.

iii) Section 2: Remove the table, and align the information in this section with that in the respective SPC document.

iv) Section 2: Include the statement 'Do not dilute prior to use.' next to 'This is a multidose vial' in the first paragraph under the table.

v) Section 4.1: Since the 10 micrograms/0.2 mL dose presentation is restricted for use to individuals aged 5 to 11 years, and the 30 micrograms/0.3 mL presentation is restricted for use in individuals aged over 12 years, please amend the indication to reflect the indicated age ranges of each presentation of Comirnaty.

vi) Section 4.2: Add the statement from the EU SPC 'Comirnaty for children 5 to 11 years of age cannot be used for individuals 12 years of age and older'.

vii) Section 4.2 The proposed data sheet states 'Doses of COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] (30 micrograms/dose) and COMIRNATY COVID-19 VACCINE 0.5 mg/mL concentrated suspension for injection (30 micrograms/dose) are considered interchangeable'. Section 6.6 of the proposed data sheet states: 'If the vial has a purple plastic cap, refer to the Data sheet handling instructions for COMIRNATY (COVID-19 mRNA vaccine) Concentrate for injection 0.5 mg/mL TT50-10853.' These statements are clinically unclear and infers that the original PBS/sucrose COMINARTY presentation (with a purple vial cap colour) may be used in the 5-11 years of age group. The sponsor is asked to amend the proposed data sheet such that the appropriate vial is clearly documented for the respective age groups. A suggested amendment of the data sheet could be to either remove this sentence or to amend as follows: 'Doses of COMIRNATY (grey cap, do not dilute) new formulation (30 micrograms/dose) and COMIRNATY (purple cap, must dilute, original formulation (30 micrograms/dose) are considered interchangeable however only COMIRNATY (orange cap, must dilute) new formulation (10 micrograms/dose is recommended in the 5-11 year age group.'

viii) Section 4.2: Amend the statement 'primary course of 2 doses (0.3 mL) at least 21 days apart', to read '… of 2 doses (0.3 mL each) at least …'.

ix) Section 6.3: Include subheadings under the main heading 'Unopened vial' and separate out the storage information for the frozen vials and thawed vials, as per the storage information in the EU SPC.

x) Section 6.3: Please move the statement 'It the vaccine is received at 2°C to 8°C it should be stored at 2°C to 8°C' to be positioned under the heading 'Thawed vial' as per the EU SPC, so that it is separate from the storage information for the frozen vaccine.

xi) Section 6.3: Revise the storage condition for the opened vial of the 30 micrograms/0.3 mL dose presentation from '8 to 30°C' to '2 to 30°C' to align with the temperature range on the product labelling and in the EU SPC.

xii) Section 6.4: To improve clarity, please remove the information in this section that is already stated in section 6.3 (as this section includes a statement to refer to section 6.3 for storage conditions after thawing and dilution).

xiii) Section 6.5: State the fill volume (contents of container) for each presentation, as per the EU SPC.

xiv) Section 6.5: Include the statement 'Not all pack sizes may be marketed' if applicable.

xv) Section 6.6: Remove references to the TT50 file in the graphics.

xvi) Section 6.6: In the graphics for both presentations, section 'Handling prior to use', include the statement 'within the 6 month shelf-life' next to 'Unopened vials can be stored for up to 10 weeks at 2°C to 8°C'.

xvii) Section 6.6: In the graphic for COMIRNATY Dilute to use multidose (For Age 5 to <12 Years), section 'Mixing prior to dilution, replace the reference to 'dispersion' with 'suspension'.

Both tracked changes and clean versions of the data sheets should be provided with the response.

EAI1 Q.6. *The requested changes have been made. The separate data sheets are considered to better support the safe use of the product; however, the below additional editorial changes are required.*

RFI2 Q.3 ***The data sheets provided in the response to RFI1 Q.6 are acknowledged. Please make the following additional changes:***

a) Both data sheets: Please include 'new formulation' and the indicated age range in the product name in Section 1 to be consistent with the naming nomenclature used in the headings throughout the data sheet. When not used as a heading, Medsafe considers it is appropriate to use only the product name (or the name and one identifier) when referencing the product to improve readability, since each product now has its own data sheet. For example, in section 6.3, the shelf-life is headed with the full name, so all subsequent references to the product in this section could be limited to 'COMIRNATY (orange cap, must dilute)' or simply 'the vaccine' where appropriate (as used currently in places). Please revise references to the product in the body of the data sheet accordingly.

b) Section 3 of the 30 micrograms/0.3 mL dose data sheet: Remove '(sterile concentrate)' from description of the pharmaceutical form.

c) Section 4.1 of the 10 micrograms/0.2 mL dose data sheet: Please change the indication wording from 'in individuals 5 to 11 years of age' to 'children aged 5 to 11 years'.

d) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Separate the heading 'Dose' onto a new line and replace references to 'Individuals 5 to 11 years of age' with 'Children 5 to 11 years of age'. Please also consider including the explanatory statement '(ie 5 to less than 12 years of age)' as appears in section 4.2 of the current SPC document.

e) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Remove the statement regarding the interchangeability of the COMIRNATY (grey cap, do not dilute) and COMIRNATY (purple cap, must dilute) presentations, as this is not relevant to the data sheet for the 5 to 11 year old vaccine.

f) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Add a heading 'Paediatric population' and include the statement 'The safety and efficacy of Comirnaty in children aged less than 5 years have not been established.'

g) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Include 'after dilution' in the statement 'COMIRNATY should be administered intramuscularly, after dilution'.

h) Section 4.2 of the 30 micrograms/0.3 mL dose data sheet: Move the heading 'Dose' to a separate line.

i) Section 4.2 of the 30 micrograms/0.3 mL dose data sheet: Please include the heading 'Paediatric population' with the accompanying text 'There is a paediatric formulation available for children 5 to 11 years of age. For details, please refer to the data sheet for COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose).'

j) Section 6.3 of both data sheets: Since the company is not proposing a shelf-life for storage at -20°C outside of Pfizer/BioNTech control, the statement '… may be received frozen at -90°C to -60°C or at -25°C to -15°C' should be amended to remove reference to 'at -25°C to -15°C' to minimise the potential for confusion to healthcare professionals (who could interpret this to mean the product can be stored at -20°C). It is noted that this change has been made to the current EU SPC for the 10 micrograms/dose presentation.

k) Section 6.3 of both data sheets. Medsafe notes that the shelf-life information in the current EU SPC for the unopened vials has been amended from 'Vaccine may be stored at temperatures between 8 to 30°C for up to 24 hours, including any time within these temperatures following dilution' (as stated in the current data sheets) to 'Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8°C and 30°C', which is clearer and aligns with the storage information in the FDA fact sheets. Please make the same change to the New Zealand data sheets.

l) Section 6.3 of both data sheets: For ease of reference, please also include the thawing times in this section, in addition to appearing in the graphics, as per the EU SPC. For example for the 10 micrograms/0.2 mL presentation 'When stored frozen at -90°C to -60°C, 10-vial packs of the vaccine can be thawed at 2°C to 8°C for 4 hours or individual vials can be thawed at room temperature (up to 30°C) for 30 minutes.'

Both tracked changes and clean versions of the data sheet should be provided with the response.

EAI2 Q.3. The sponsor has made the requested changes except for RFI2 Q.3(f), which was to add the statement 'the safety and efficacy of Comirnaty in children aged less than 5 years have not been established' in section 4.2 (dosage and administration), since there is a statement to this effect in section 4.4 (warnings

and precautions). The company does not consider duplication of this wording in section 4.2 to be helpful, when the statement does not apply to dose or administration. Instead they consider section 4.4 is the appropriate location for advice to prescribers regarding safety and efficacy for a patient population that is not indicated in the label. The evaluator notes that the New Zealand Data Sheet Explanatory Guide recommends the inclusion of this information in both sections of the data sheet and that the requested statement is included in section 4.2 of the EU SPC for the 10 micrograms/dose presentation. Nevertheless, this will not be pursued on the basis that section 4.2 of the proposed data sheet clearly defines the indicated age range of the patient population in the heading 'Children 5 to 11 years of age', and since there is a warning about not administering the product to children under 5 years of age in section 4.4.

With regards to point RFI2 Q.3(a), it was the intention of the evaluator that the company retain the use of full identifiers in the headings, but only use the product name or limited identifiers when referencing the product in the body of the document to improve readability. However, in the revised document, it appears the company has chosen to use only limited identifiers in both the headings and the body of the document. Although not ideal, the revised data sheet is easier to read, and the identifiers used by the company, namely cap colour, the need for dilution and where appropriate, the indicated age range, are considered the critical features necessary to ensure appropriate identification and correct administration of the product. Since the full identifiers are stated in section 1 of the data sheet, and a separate data sheet has been prepared for each presentation, this will not be pursued further.

The following additional changes were identified during final quality review of the data sheet and will be communicated to the sponsor as part of the outcome of evaluation email:
1) Section 2 of the 30 micrograms/0.3 mL dose data sheet: Please write the statement 'Do not dilute prior to use' in bold font.
2) Section 2 of the 10 micrograms/0.2 mL dose data sheet: Please write the statement 'must be diluted' in bold font.
3) Section 4.2 of both data sheets: Please replace the statement 'COMIRNATY for children 5 to 11 years of age cannot be used for individuals 12 years of age and older' with 'COMIRNATY (orange cap, must dilute) should be used only for children 5 to 11 years of age'.
4) Section 6.6 of the 10 micrograms/0.2 mL dose data sheet. Please use orange colour in the graphics as per the FDA approved fact sheets. Please also consider using purple colour in the graphics of the parent PBS/sucrose vaccine data sheet when this is updated as per the commitment made to RFI2 Q.2.
5) Section 9 of both data sheets: The approval date should reflect the date of gazettal of the Tris/sucrose formulations of the drug product.
6) Section 10 of both data sheets: This will need to be updated accordingly, following the above revisions.
***Point resolved**.*

The sponsor has indicated on the NMA form that the product will be supplied with a package insert and both the EU and US labels refer to an enclosed package leaflet. Copies of these documents should be provided.

RFI1 Q.7. Please provide copies of the EU and US package inserts that are referred to from the respective international product labels, or confirm that the package insert for product marketed in New Zealand will be the New Zealand data sheet, if applicable.

EAI1 Q.7. The company confirmed that the package inserts will be the international product label leaflets, the EU SmPC and US PI, and will align with the approved labelling of those markets. Copies of the leaflets were provided for reference. As with the parent vaccine, the data sheet will be included with product distributed to the vaccination sites in New Zealand. ***Point resolved****.*

Consumer Medicine Information has been provided for the Tris/sucrose formulation of Comirnaty, which is based on the CMI for the parent PBS/sucrose vaccine. The information in the CMI aligns with that in the proposed data sheet. The company will be asked to prepare separate CMI for each presentation of the new formulation.

RFI1 Q.8. Please prepare individual CMI documents for each strength and presentation of Comirnaty. The naming terminology used in the CMI should reflect that described in RFI1 Q.2.

EAI1 Q.8. Individual CMI documents have been provided for each presentation of the new formulation of Comirnaty that incorporate the naming terminology described in RFI1 Q.2; however, both are entitled 'COMIRNATY COVID-19 VACCINE'. The company will be asked to include an identifier such as the indicated age range and cap colour (at a minimum) in the headers, to clearly differentiate the two CMI documents.

RFI2 Q.4 The CMI documents provided in response to RFI1 Q.8 are acknowledged; however, both are entitled COMIRNATY COVID-19 VACCINE. Please include an identifier such as the indicated age range and cap colour (at a minimum) in the headers, to clearly differentiate the two CMI documents.

EAI2 Q.4. The two CMI documents have been amended to include the indicated age ranges in the headers. The absence of additional identifiers will be accepted on the basis that the documents are intended for consumers, not healthcare professionals (so reference to cap colour and dilution are not relevant to this audience). ***Point resolved****.*

The sponsor has signed the CMI commitment in the NMA form that following consent to distribute, an electronic copy of the CMI will be submitted to Medsafe and will comply with the requirements published on the Medsafe website.

NZMT listing certificates were provided for each presentation and pack size with the exception of the 195 pack size for the 10 microgram/0.2 mL vials. This should be provided.

RFI1 Q.9. Please provide the New Zealand Medicines Terminology Listing Certificate for the 195 vial pack size of the 10 microgram/0.2 mL presentation of Comirnaty.

EAI1 Q.9. The requested document was provided. ***Point resolved****.*

GMP status of manufacturers and packers

The applicant has provided the following evidence of GMP compliance for the drug substance and drug product manufacturing, testing and packaging sites.

Table 2: Proposed manufacturing sites and GMP status

Manufacturing step	Site address		Certificate number/type	Expires
API manufacturers	The sponsor refers to the approved details for the parent product, Comirnaty TT50-10853			
Drug product manufacture, packaging and testing	Pfizer Manufacturing Belgium, Rijksweg 12, Puurs, 2870, Belgium	TGA	MI-2020-CL-10925-1 Authorises the site for sterile finished product manufacture of injections, release for supply and testing (endotoxin, sterility, biological)	**31/12/2021**
Finished product testing	Pfizer Ireland Pharmaceuticals, Grange Castle, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND	TGA	~~MI-2020-CL-12300-1~~ The GMP certificate authorises the site for testing API, not the finished product. This is addressed in the below RFI.	~~9/05/2022~~
			MI-2019-CL-04765-1 Authorises the site for testing of sterile dosage forms (microbial, biological, chemical and physical)	**9/05/2022**

The GMP certificates held on file at Medsafe for the API manufacturing sites are current with the exception of Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, Germany, which expired on 31/03/2021. Updated evidence of cGMP for this site is requested below. The sponsor will also be asked to provide updated evidence of cGMP for Pfizer Puurs, since the GMP certificate for this site will expire on 31/12/2021.

RFI1 Q.10. Please provide evidence of cGMP for the API manufacturing site Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, Germany, as the current GMP certificate held on file at Medsafe for the site expired on 31/03/2021.

EAI1 Q.10. TGA GMP clearance MI-2021-CL-05908-1 was provided, which has an expiry date of 26/08/2024. The clearance authorises the site for the active material manufacture of BNT162b2(mRNA), testing (endotoxin, chemical/physical and biological), packaging and storage of the API. This is acceptable. ***Point resolved****.*

RFI1 Q.11. The GMP certificate provided for Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, Ireland, authorises the site for API testing. Please provide evidence of cGMP that authorises the site for testing the finished product.

EAI1 Q.11. TGA GMP clearance MI-2019-CL-04765-1 was provided (expiry date 9/05/2022). The clearance is specific to the product and authorises the site for testing of sterile dosage forms (microbial, biological, chemical and physical). This is acceptable; Table 2 has been updated accordingly. ***Point resolved****.*

RFI1 Q.12. The GMP certificate provided for Pfizer Manufacturing Belgium NV , Rijksweg 12, Puurs B-2870, Belgium, will expire on 31/12/2021. Please provide a commitment to send Medsafe updated evidence of cGMP for this site, once it is available.

EAI1 Q.12. The company committed to providing the updated evidence of cGMP for this site once it becomes available. ***This will be noted as a post-approval commitment of this NMA. Point resolved****.*

Module 3.2.S. Drug Substance

The drug substance used to manufacture the Tris/sucrose formulation of Comirnaty is identical to that used for the currently approved PBS/sucrose finished product. The same drug substance manufacturing and testing sites are used for both products. Consequently, Module 3.2.S has not been provided with this submission and full reference is made to the approved details for the parent product.

The only change to the drug substance information that is being introduced with this NMA is the change in name from BNT162b2 [mRNA] to the INN ‘Tozinameran’. This change is also considered applicable to the parent product. The data sheet has been updated accordingly.

Module 3.2.P. Drug Product

3.2.P.1. Description and composition of the drug product

The Tris/sucrose drug product is a preservative-free, sterile suspension (referred to in the dossier as ‘dispersion’) of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer. The Tris/sucrose drug product is formulated as 0.1 mg/mL RNA in 10 mM Tris buffer, 300 mM sucrose, pH 7.4, and is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminium seal with flip-off plastic cap. The drug product is administered by intramuscular injection.

There are two presentations of the 0.1 mg/mL Tris/sucrose drug product, which are differentiated in the dossier by the dose of RNA that is administered (30 µg and 10 µg RNA per dose), and in the data sheet by the plastic cap colour (grey and orange). The two presentations are identical with respect to drug product formulation but differ in fill volume and the requirement for dilution prior to administration:

i. The ‘30 µg RNA per 0.3 mL dose’ presentation of 0.1 mg/mL Comirnaty has a fill volume of 2.25 mL per vial, and does not require dilution prior to administration. Each vial is able to deliver 6 doses of 0.3 mL. The vial cap colour of this presentation is grey.

ii. The ‘10 µg RNA per 0.2 mL dose’ presentation of 0.1 mg/mL Comirnaty has a fill volume of 1.3 mL per vial, and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration. Following dilution, each vial is able to deliver 10 doses of 0.2 mL. The vial cap colour of this presentation is orange.

The dossier also refers to a 3 µg dose presentation, which is planned for a future NMA once clinical data supporting a new paediatric indication for this dosage is available. Single-dose vial formats are also planned (this submission is for the multi-dose vials only).

The composition of the drug product, including quality standards, function, and concentration is shown in Table 3 for the 30 µg RNA per 0.3 mL dose presentation, and Table 4 for the 10 µg RNA per 0.2 mL dose presentation. The formulation details as recorded in Medsafe’s database are also included in the attached Therapeutic Product Database Reports (TPDRs).

With the exception of the novel lipids ALC-0315 and ALC-0159, the structural lipid DSPC, and the buffer component Tris HCl, which are controlled to in house specifications, the excipients in the drug product comply with compendial requirements.

Table 3: Formulation details of 0.1 mg/mL Comirnaty, 30 µg RNA per 0.3 mL dose

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per 2.25 mL vial[a]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	1.43	3.22 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.41 mg	0.05 mg
DSPC	In-house specification	Structural lipid	0.31	0.70 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	1.40 mg	0.19 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	231.8 mg	31 mg
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20	0.45 mg	0.06 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32	2.97 mg	0.4 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

a. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
b. Also known as Trometamol
c. Also known as Tromethamine HCl and Trometamol HCl
d. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered ingredients (excipients).

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)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

Table 4: Formulation details of 0.1 mg/mL Comirnaty, 10 µg RNA per 0.2 mL dose

Name of Ingredients	Reference to Standard	Function	Concentration Prior to Dilution (mg/mL)	Amount per vial after dilution[a,b]	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.1	130 µg	10 µg
ALC-0315	In-house specification	Functional lipid	1.43	1.86 mg	0.14 mg
ALC-0159	In-house specification	Functional lipid	0.18	0.23 mg	0.02 mg
DSPC	In-house specification	Structural lipid	0.31	0.40 mg	0.03 mg
Cholesterol	Ph. Eur.	Structural lipid	0.62	0.81 mg	0.06 mg
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103	133.9 mg	10.3 mg
Tromethamine (Tris base)[c]	USP-NF, Ph. Eur.	Buffer component	0.20	0.26 mg	0.02 mg
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[d]	In-house specification	Buffer component	1.32	1.71 mg	0.13 mg
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[e]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

a. Vials filled at 1.3 mL drug product and diluted to 2.6 mL with 0.9% sodium chloride (NaCl) prior to administration. NaCl at 11.7 mg/vial and 0.9 mg/dose after dilution.
b. Values are rounded to maintain the same level of precision as the label claim, with trailing decimals not shown, where applicable.
c. Also known as Trometamol
d. Also known as Tromethamine HCl and Trometamol HCl
e. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered ingredients (excipients).

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)

No overages are applied to the formulation of the drug product.

3.2.P.2. Pharmaceutical development

The pharmaceutical development of the Tris/sucrose drug product focused on development of a formulation that demonstrated comparable quality to the current registered PBS/sucrose vaccine, but with enhanced stability and ease of use (ie the ready-to-use preparation). Additional development was performed to support the Tris/sucrose formulation, specifically the use of Tris buffer instead of PBS, and corresponding changes to the diafiltration and concentration steps. The development activities utilised the principles described in ICH Q8, risk assessments, development studies and prior experience with similar RNA-lipid nanoparticle vaccines, as discussed below.

3.2.P.2.1. Components of the drug product

3.2.P.2.1.1. Drug substance

The tozinameran (BNT162b2) drug substance used to manufacture the Tris/sucrose drug product is the same as that used for the current PBS/sucrose drug product. There are no obvious compatibility issues between the drug substance and the excipients present in the drug product formulation.

3.2.P.2.1.2. Excipients

The four lipid excipients (ALC-0315, ALC-0159, DSPC, cholesterol) and the sucrose cryoprotectant used in the manufacture of the Tris/sucrose drug product are the same as those used for the current PBS/sucrose drug product. Two new excipients, Tris base (trometamol/tromethamine) and Tris HCl (trometamol HCl/tromethamine HCl) are used in the Tris/sucrose formulation to achieve the desired product pH. Both buffer components are present in several parenteral medicinal products (including vaccines) approved in New Zealand. The evaluator also notes (from the EMA approved SPC) that the Spikevax COVID-19 mRNA vaccine (Moderna) contains trometamol and trometamol hydrochloride. There is a statement in the dossier that the Tris buffer is listed in the in the FDAs inactive ingredient database and is therefore considered safe for use in the Tris/sucrose formulation of the Comirnaty vaccine.

There are no ingredients of animal origin in the drug product.

3.2.P.2.2. Drug product

3.2.P.2.2.1. Formulation and test method development

The Tris/sucrose formulation is based on the current PBS/sucrose formulation with the following differences:

- the formulation buffer has changed from phosphate buffered saline (PBS) to tromethamine (Tris) buffer
- sodium chloride, dibasic sodium phosphate, monobasic potassium phosphate and potassium chloride have been removed from the formulation; however the same target pH is maintained
- the RNA concentration is lower
- the drug product does not require dilution for administration of the 30 µg dose (the parent vaccine is administered at the same dose (ie 30 µg/0.3 mL) but requires dilution prior to administration).

There are no changes to the drug substance or the lipids used to produce the lipid nanoparticles (LNPs) that are formulated to produce the bulk drug product.

Formulation development

The Tris/sucrose formulation was developed to provide a drug product with an enhanced stability profile compared to the current PBS/sucrose drug product, which requires storage at ultralow temperatures (-90°C to -60°C) and has limited stability at higher temperatures.

Multiple studies directed toward the target product profile were performed to identify alternate presentations and formulations of the vaccine. These studies (not described) were stated to include alternate cryoprotectants and buffers, most of which did not demonstrate a significant benefit when compared to the current phosphate-based sucrose formulation. However, a potential benefit of a Tris buffer and sucrose combination was observed, as detailed below.

Drug product samples formulated with either a phosphate based buffer or a Tris-based buffer with RNA concentrations of 0.2 mg/mL and 0.05 mg/mL to bracket the target concentration (0.1 mg/mL), were stored at accelerated temperatures of 2 – 8°C, 25°C, and 35°C for up to 7 days, with critical quality attributes tested on days 0, 1, 4 and 7. Lipid nanoparticle (LNP) size remained stable in the Tris-based formulation at both RNA concentrations tested, in contrast to the increase in LNP size observed for the phosphate-based formulation. Small improvements in RNA integrity at higher temperatures and lower late-migrating species (LMS) were observed in the Tris formulation relative to the phosphate-based formulation. Albeit limited, the results of the study indicated that a Tris-based formulation would provide better stability at higher temperatures than a phosphate-based formulation. Additional studies were performed to assess if increasing the sucrose quantity in the Tris formulation would further improve stability but did not demonstrate any benefit. On the basis of the development studies, the company chose a formulation comprising 0.1 mg/mL RNA, 300 mM sucrose (same quantity as for the PBS/sucrose formulation) and 10 mM Tris buffer, pH 7.4 (same pH as parent vaccine). The evaluator notes that while the sucrose concentration of the Tris/sucrose formulation is the same as for the PBS/sucrose formulation, the quantity of sucrose administered will be different, based on the different dilution requirements of the proposed presentations prior to administration.

Development stability studies through 6 months storage

Several studies were performed to assess the stability of the Tris/sucrose formulation. The key findings of these studies are shown below:

Study 1

A single Tris/sucrose drug product lot (0.1 mg/mL RNA, 7.5 mM Tris, 300 mM sucrose) manufactured at laboratory scale was placed on stability at -80°C and -20°C for 24 weeks, and 2 – 8°C and 25°C for up to 12 weeks. Results for LNP size, polydispersity, RNA integrity, LMS, encapsulation efficiency, and RNA content were compared to the specifications for the PBS/sucrose drug product and to clinical ranges (based on release results for 10 lots of the PBS/sucrose drug product designated for clinical trial testing). The key findings of this study are summarised as follows:

- results at -80°C demonstrate stability for 24 weeks with all results meeting acceptance criteria and falling within clinical ranges
- at -20°C, all results remained within acceptance criteria; however, trends for increasing LNP size (starting at 4 weeks) and decreasing RNA encapsulation (starting at 8 weeks) were observed, with results for these parameters falling outside the clinical ranges at 12 weeks and 24 weeks respectively
- at 2 – 8°C results were within specifications and clinical ranges for 4 weeks, though RNA integrity shows a slight downward trend and LMS a slight upward trend
- at 25°C all results remained within acceptance criteria for up to 2 weeks; however, RNA integrity decreased below the clinical range after 1 week of storage.

Overall, this study supports storage of the Tris/sucrose drug product at -80°C for up to 24 weeks, at -20°C for up to 8 weeks, at 2 – 8°C for up to 4 weeks, and at 25°C for up to 1 week.

Study 2

A second lab-scale development study was performed to evaluate longer allowable storage at 2 – 8°C (the study was performed out to 24 weeks), using a drug product batch with a higher Tris concentration (10 mM). As observed during the first study, the Tris/sucrose drug product lot was stable for up to 24 weeks when stored at -80°C, and for up to 12 weeks when stored at -20°C (results for LNP size and encapsulation efficiency fell outside the clinical ranges at 24 weeks but were still within drug product specification acceptance criteria). At 2 – 8°C, the drug product was stable through 12 weeks storage (results were still within drug product acceptance criteria at 24 weeks but outside the clinical ranges). At 24 weeks storage, LNP size and LMS increased and encapsulation decreased. At 25°C, RNA integrity decreased at 2 and 4 weeks, and LMS increased after 4 weeks. Overall, this study supports storage of the Tris/sucrose drug product at -80°C for up to 24 weeks, at -20°C for up to 12 weeks, at 2 – 8°C for up to 12 weeks, and 25°C for up to 1 week.

Study 3

A third stability study was performed on a development batch of the drug product with the proposed formulation, filled at 0.5 mL (single dose vial; not proposed with this NMA) and 2.25 mL (multidose vial). The two volumes bracket the 1.3 mL fill vial. As observed in the first two studies, the Tris/sucrose drug product was stable for up to 24 weeks at -80°C; for up to 12 weeks at -20°C, with trends towards increasing LNP size and LMS, and decreasing RNA integrity; 12 weeks storage at 2 – 8 °C, with some increases in LNP size and LMS and decreasing RNA integrity; and 1 week at 25°C, based on decreasing RNA integrity and increasing LMS. This third study additionally demonstrated that Tris/sucrose drug product was stable for 24 weeks at -50°C, but less than 4 days at 35°C based on decreasing RNA integrity and increasing LMS. No differences were observed in the results obtained for the two fill volumes.

The stability of the Tris/sucrose drug product to short-term temperature excursions was demonstrated in a study where samples were removed from storage at -80°C or -50°C and stored at -10°C or -5°C for 7 days. At the end of the 7 day excursions, the samples were tested for critical quality attributes, with all results falling within acceptance criteria. The proposed freeze/thaw allowances are intended to be used during drug product manufacture where applicable. The data sheet instructs the end user that the product should not be refrozen once thawed.

In vitro expression and mouse immunogenicity testing

In vitro expression (IVE) was evaluated in side-by-side testing of three primary Tris/sucrose drug product lots (EX0490, EW4564, EW4565) against four PBS/sucrose lots (EL9267, EL3249, EL1404, EK4175). While all batches were well above the release acceptance criterion of ≥ 30%, it is noted that the range of IVE results were lower for the Tris/sucrose batches compared to the PBS/sucrose batches (76 – 79% versus 85 – 94% respectively). This will not be pursued as the PPQ Tris/sucrose lots manufactured at Pfizer Puurs demonstrated higher IVE levels, that were within the historical ranges for the PBS/sucrose drug product lots (discussed later in this report).

The Tris/sucrose batches also demonstrated comparable immunogenicity in mice compared to the PBS/sucrose batches.

Excess volume in vials

Assessments of hold up and delivered volumes were determined for both Tris/sucrose presentations to demonstrate the stated number of doses could be delivered (30 µg/dose: 6 x 0.3 mL doses and 10 µg/dose: 10 x 0.2 mL doses). The results demonstrate that the

proposed number of doses can be achieved but only when using low dead-volume syringes (hold up of no more than 0.035 mL per syringe/needle assembly). The average non-extractable hold-up volume in the vial was 0.07 mL. It is unclear what vials were used in the study (as two are proposed); however there is a statement in the dossier that 'considering standard variability of component dimensions of the 2 mL borosilicate and aluminosilicate vials, no non-extractable volume difference is expected.'

3.2.P.2.2.2. Overages

There are no manufacturing overages in the formulation. The following overfills are included to ensure the stated number of doses can be removed from the vials:

- *30 µg/0.3 mL dose presentation* – target fill volume of 2.25 mL, to enable delivery of 6 doses of 0.3 mL (1.8 mL), leaving 0.45 mL excess (overfill) volume
- *10 µg/0.2 mL dose presentation* – target fill volume of 1.3 mL, which is diluted with 1.3 mL 0.9% saline to give a total volume of 2.6 mL, to enable delivery of 10 doses of 0.2 mL (2.0 mL), leaving 0.6 mL excess volume.

The overfills are suitably justified.

3.2.P.2.2.3. Physicochemical and biological properties

The quality attributes of the Tris/sucrose drug product are similar to those of the parent PBS/sucrose drug product. The following physicochemical properties are noted: density: 1.04 g/mL at 20°C; viscosity: 1.42 cP measured at 20°C; osmolality: 352 to 363 mOsm/kg.

The stability and freeze/thaw data generated for development Tris/sucrose drug product lots demonstrated an enhanced stability profile supportive of increased storage times at 2 – 8°C and freeze/thaw stability that would simplify transport and administration of the drug product. The stability of the Tris/sucrose drug product is discussed in section 3.2.P.8 of this report.

The PBS/sucrose and Tris/sucrose formulations both express S1 antigen at significant levels when tested side-by-side for *in vitro* expression (discussed above), and both are immunogenic in mice.

3.2.P.2.3. Manufacturing process development

Development history and lot genealogy and usage

Based on the formulation studies described above, three primary (stability) Tris/sucrose drug product lots were manufactured during product development. The scale of the primary stability lots was 7% of the planned commercial scale manufacture of 160 g of RNA. Lot EX0490 was filled at 0.48 mL as a single-dose vial; however, only multidose vials are proposed in this NMA. Details of the primary drug product lots and the lots manufactured during process validation at full commercial scale (160 g RNA, 1600 L) are shown in Table 5.

Table 5: Tris/sucrose primary stability and process performance qualification lots

DP Lot Number	Drug Product Presentation	Site of Manufacture	Date of Manufacture	Bulk Batch Size (grams RNA)[a]	Fill Batch Size (Number of vials)
Primary Stability					
EX0490	Vial (30 µg dose SDV)	Pfizer, Puurs	18-Feb-2021	12[a]	27085[b]
EW4564	Vial (30 µg dose MDV)	Pfizer, Puurs	25-Feb-2021	12[a]	32796[c]
EW4565	Vial (30 µg dose MDV)	Pfizer, Puurs	04-Mar-2021	12[a]	37821[d]
Process Performance Qualification					
FC8273	Vial (30 µg dose MDV)	Pfizer, Puurs	04-May-2021	160	671,970
FE4594	Vial (30 µg dose MDV)	Pfizer, Puurs	01-Jun-2021	160	680,745
FJ5683[e]	Vial (30 µg dose MDV)	Pfizer, Puurs	06-Aug-2021	160	318,785
FJ5682[e]					324,064
FK5127[f]	Vial (10 µg dose MDV)	Pfizer, Puurs	19-Aug-2021	160	1,088,432
FK5128[f]	Vial (3 µg dose MDV)				114,930

a. Amount of RNA removed from commercial batch LNP pool for Tris/Sucrose bulk drug product formulation. (See 3.2.P.2.3 Development History – Tris/Sucrose)
b. From 1.3 grams RNA from bulk drug product
c. From 7.38 grams RNA from bulk drug product
d. From 8.51 grams RNA from bulk drug product
e. Lots FJ5683 and FJ5682 were manufactured from the same Bulk batch FJ5026 which was split for filling
f. Lots FK5127 and FK5128 were manufactured from the same Bulk batch FK1099 which was split for filling
Abbreviations: SDV = Single dose vial; MDV = Multi-dose vial

Manufacturing process development and characterisation

The PBS/sucrose and Tris/sucrose formulations have identical unit operations for drug substance thaw, dilution of drug substance, preparation of the organic phase and lipid nanoparticle formation and stabilisation. The process parameters for these steps are therefore maintained for the Tris/sucrose formulation with no additional process development or characterisation studies performed for these operations. Additionally, the drug substance light exposure and stability of lipids solubilised in ethanol studies similarly support both the PBS/sucrose and Tris/sucrose operations. Process development and characterisation studies were performed for the unique steps for the Tris/Sucrose formulation as detailed in Table 6 and summarised below.

Table 6: Comparison between the Tris/sucrose and PBS/sucrose drug product manufacturing processes

Process Step	PBS/Sucrose	Tris/Sucrose 2.25 mL/vial (30 µg)	Tris/Sucrose 1.3 mL/vial (10 µg) & 0.4 mL/vial (3 µg)
Raw materials & Excipients	No changes to DS manufacturing, lipids or lipid suppliers.		
Batch Size	70-160g mRNA		
LNP Formation	Identical		
Buffer Exchange, Concentration and Filtration	Citrate Buffer (DF1): ≥ 2x Diavolumes PBS (DF2): ≥ 8x Diavolumes Preconcentration step	Tris buffer (DF1): ≥ 2x Diavolumes Tris buffer (DF2): ≥ 8x Diavolumes Preconcentration step	Tris buffer (DF1): ≥ 2x Diavolumes Tris buffer (DF2): ≥ 8x Diavolumes Preconcentration step
Concentration Adjustment and Addition of Cryoprotectant	Dilution to target DP concentration of 0.5 mg/mL with 1.2 M Sucrose in WFI solution and PBS/sucrose buffer.	Dilution to target DP concentration of 0.1 mg/mL with 1.2 M Sucrose, 10 mM Tris Solution.	Dilution to target DP concentration of 0.1 mg/mL with 1.2 M Sucrose, 10 mM Tris Solution.
Aseptic Filling	Fill target: 0.45 mL	Fill target: 2.25 mL	Fill target: 0.4 mL Fill target: 1.3 mL
TIR/TOR Hold Time[a]	≤214h including ≤46h TOR	≤336h including ≤72h TOR	≤336h including ≤72h TOR

a. Cumulative time in vessels or glass vials at 2-8°C from the start of concentration adjustment and cryoprotectant addition until the start of freezing, including time held in stainless steel vessels, sterile filtration, filling, inspection, and secondary packaging, with ≤72 hours of this time allowed up to 25 °C
Abbreviations: DF: Diafiltration

The unique steps in the manufacturing process of the Tris/sucrose drug product include:

i) the use of Tris buffer at the buffer exchange and concentration (TFF) step for the first and second diafiltration steps, instead of citrate and PBS, respectively
ii) the concentration adjustment and addition of cryoprotectant step is modified to use 1.2 M sucrose, 10 mM Tris, pH 7.5 instead of 1.2 M sucrose (in WFI)
iii) subsequent steps of sterile filtration, aseptic filling, capping/crimping, labelling and freezing for storage are essentially the same between the Tris/sucrose and PBS/sucrose finished products with minor adjustments to reflect the different filling volume freeze/thaw cycles.

The process development and characterisation studies performed to support the above changes are suitably described and justified. Of note, filter adsorption development studies demonstrated no significant loss of drug product related to filter adsorption. Laboratory-scale refiltration studies were performed to demonstrate the feasibility of refiltration of the Tris/sucrose drug product. Analytical results for RNA concentration, LNP polydispersity and LNP size demonstrated that the quality of the drug product was not adversely affected by five successive filtrations of the Tris/sucrose drug product. Additional studies were performed to confirm that there is no impact of needle shear stress through the filling needles during the filling operations.

Demonstration of comparability of Tris/sucrose drug product to PBS/sucrose drug product

Release testing of the primary drug product lots and PPQ lots (FC8273, FE4394, FJ5682; 1600 L, 2.25 mL fill) met the proposed release specifications and were within the pre-determined comparability acceptance criteria based on historical release data for 94 PBS/sucrose lots. The details of the 94 historical lots were not provided. The company will be asked to confirm that clinical batches were included in the setting of the comparability acceptance criteria.

RFI1 Q.13. Please provide further information on the 94 historical drug product batches used to set the comparability acceptance criteria. The response should confirm that batch data from clinical drug product lots was included in the assessment, and provide the batch size ranges of the drug product lots used to establish the acceptance criteria.

EAI1 Q.13. The 94 historical drug product lots are of the PBS/sucrose formulation and include BNT162b2 clinical drug product lot EE3813 (used in the paediatric clinical study C4591007) and other early clinical lots manufactured at Polymun, with fill and finish performed at either Polymun or Pfizer, Puurs. Lot ER5832 (also used in study C4591007) was not included in the 94 historical drug product lots, but data provided by the company (discussed in Module 5 of this report) demonstrates that lot ER5832 is of comparable quality to the historical PBS/Sucrose lots. Additional BNT162b2 drug product lots included in the historical lots used to establish comparability acceptance criteria were manufactured using the currently globally registered drug product supply nodes (bulk drug product manufactured at Puurs, mibe (Dermapharm), Polymun, and Kalamazoo followed by fill and finish at Puurs and Kalamazoo). Although not all sites are approved for supply of drug product to New Zealand, this does not affect the setting of comparability acceptance criteria, as all sites are under the control of Pfizer and are therefore expected to produce drug product of comparable quality. The bulk drug product batch sizes ranged from 1 L for early clinical lots to 278 L used in the PPQ campaigns for commercial-scale production. Subsequently, drug product lots manufactured at the 320 L batch size were demonstrated to be comparable to those manufactured at smaller scales. On the basis of the company's response, the lots used to set the comparability acceptance criteria can be considered suitably representative of the commercial and clinical drug product. ***Point resolved.***

The primary and PPQ Tris/sucrose drug product lots also met established acceptance criteria for heightened characterisation testing and were comparable to a PBS/sucrose reference lot

(EL8983) with respect to surface charge (zeta potential), size distribution (AF4), surface PEG characterisation (^{1}H NMR), and for purity by 5'-cap (RNase H followed by LC-UV), poly(A) tail (ddPCR) and poly(A) tail length and distribution (enzyme digestion followed by RP-HPLC-UV). The few minor differences noted (eg small differences in 5'-cap related species retention times; attributed to mobile phase mixing) are not expected to impact efficacy and safety. The results of the studies support the comparable quality of the Tris/sucrose and PBS/sucrose drug products. The analytical comparability of the two formulations is discussed further in the clinical section of this report, to justify the absence of clinical data for the Tris/sucrose formulation.

3.2.P.2.4. Container closure system

The proposed packaging is a 2 mL Type I borosilicate or aluminosilicate glass vial closed with a 13 mm bromobutyl elastomeric stopper. The 2 mL borosilicate glass vial for the Tris/sucrose drug product is comparable to the original PBS/sucrose vial but with a thicker glass wall (1.2 mm versus 0.85 mm). The thicker walled borosilicate vials were approved for use as an alternative container for the PBS/sucrose product in CMN reference date 25/10/2021, ID: 115197. As part of this CMN, the company provided data to demonstrate that the thicker walled vials are equivalent in terms of processability, container closure integrity and drug product interaction. A freezing rate analysis was also provided to demonstrate that the thicker walled vials do not impact the quality of the drug product with regards to freezing and thawing rates. The 2 mL aluminosilicate vial is not currently approved for use with the PBS/sucrose product but is introduced for the Tris/sucrose product as it is considered to provide additional material strength for the larger fill volumes.

Both types of glass vials are stated to meet USP <660>, Ph. Eur. 3.2.1 hydrolytic resistance and JP 7.01 soluble alkali test requirements for glass containers; however, it is unclear what quality the aluminosilicate glass is. Clarification is sought.

RFI1 Q.14. Please clarify the quality of the aluminosilicate glass vials in terms of their hydrolytic resistance (ie Type I, II or III). If the vials are not Type I glass, section 6.5 of the data sheet should be updated accordingly.

EAI1 Q.14. The company confirmed the aluminosilicate glass vials meet the Type I hydrolytic testing criteria in USP <660>, Ph. Eur. 3.2.1. and JP 7.01. This is acceptable for containers for parenteral products. ***Point resolved****.*

An assessment of the propensity of the borosilicate and aluminosilicate glass vials to form particulates and/or delaminate was performed. The delamination risk assessment studies evaluated container manufacture (moulded vial vs tubing, indexing vs continuous glass conversion), glass coefficient of expansion, container processing (depyrogenation method/conditions, terminal sterilisation, surface treatment with sulphates), drug product pH, drug product form (lyophilised vs aqueous), drug product formulation (use of citrates, phosphates or other buffers, ionic strength, use of sodium salts of organic acids) and the intended shelf life of the drug product. The results of the studies were not provided in the dossier, but were stated to have identified a moderate risk for glass delamination with the use of borosilicate 2 mL tubular type 1 glass vials and a low risk with the use of aluminosilicate glass vials. As the risks are moderate and low, the company does not consider that additional mitigation is required for glass delamination. Medsafe is unaware of any issues with regards to delamination of the borosilicate vials currently in use with the parent vaccine, and since the study identified that aluminosilicate vials have a reduced risk for delamination, this will not be pursued further.

The bromobutyl stoppers used for the Tris/sucrose products are the same as those used currently with the PBS/sucrose parent vaccine and meet USP <381>, Ph. Eur. 3.2.9 and JP 7.03 compendial chemical testing requirements for elastomeric closures. Controlled extraction studies were performed on the stoppers during registration of the parent vaccine using model solvents that varied in pH and solvent strength. Since the same stoppers are

used with the Tris/sucrose product, the studies have not been repeated. This will be accepted.

Leachable studies are in progress to support the Tris/sucrose commercial container closure system with representative drug product lots FC8273, FE4394, and FJ5682 filled with 2.25 mL Tris/sucrose drug product. The 2.25 mL filled vial for the 30 µg/0.3 mL dose presentation is considered worst-case compared to lower fill volumes stored in the same container closure system that also require dilution prior to use. The vials used in the studies (borosilicate or aluminosilicate) are not described (results for both should be provided). The vials are stored at -90°C to -60°C (with sample testing at T_0, T_6, T_{12}, T_{18} and T_{24} months) and 2 to 8°C (with sample testing at T_0, T_6 months). There is confirmation in the dossier that the samples are being tested using methods validated for the following potential leachables: palmitic acid, stearic acid, Irganox 1076, silicon, magnesium, bromine, sulphur, and zinc (validation data not provided). Any unexpected leachable compounds observed above 1.5 µg/day TDI will undergo a toxicological risk assessment that will take into account established permitted daily exposures (PDEs), as per ICH Q3C and M7. Since the aluminosilicate vials are new, the available leachables data should be provided.

RFI1 Q.15. Please provide the available results from the leachables studies currently in progress to support the Tris-sucrose commercial container closure system (for both the borosilicate and aluminosilicate vials). If only T_0 data is available, the company should commit to provide the results of the leachables studies post-approval.

EAI1 Q.15. Initial timepoint results were provided for Tris/sucrose drug product lots FC8273, FE4394 and FJ5682 stored in either the borosilicate or aluminosilicate vials, at 2 to 8°C or -90 to -60°C. A Safety Concern Threshold (SCT) was initially defined as 1.5 µg/day Total Daily Intake (TDI) for each compound, a level at which any unidentified or identified leachable compound presents negligible safety concern to patients. The putative hazard of each potential leachable compound was further assessed and the SCT adjusted accordingly based on the presence or absence of a mutagenic concern. Potential leachable compounds without a mutagenic concern were assigned a SCT of 5.1 µg/day TDI. The 1.5 µg/day and 5.1 µg/day SCTs are based on Product Quality Research Institute (PQRI) and the principles of ICH M7 (R1) Mutagenic Impurities (2017). On the basis of the overseas regulatory approval of this product and container closure system, this strategy will be accepted by Medsafe.

All results were below the safety concern threshold (SCT) of 5.1 µg/day total daily intake (TDI). In addition, no unidentified leachable compounds have been detected. The results for elements have all been below the listed method quantitation limit with the exception of bromine, with levels observed at 0.03 µg/day in product stored in the borosilicate vials (at both temperatures). The evaluator notes that a similar level of bromine was observed in the leachables studies performed on the parent PBS/sucrose vaccine stored in borosilicate vials (discussed in CMN ref date 25/10/2021, ID: 115197 for Comirnaty TT50-10853). Based on a comprehensive review of available safety data, the company considers the presence of bromine at 0.03 µg/day TDI, and elements at or below their method quantitation limits in the Tris/sucrose drug product pose a negligible risk to patients. The company committed to provide the results of the leachables studies post-approval, approximately 1 month post-data collection to allow time for submission preparation. On the basis of the available development data, which supports the suitability of both types of vials for use with the Tris/sucrose drug product, and the existing market history for the parent product, which supports the safety of the borosilicate vials (and by inference the presence of bromine at 0.03 µg/day TDI), this will be accepted. Although the company was not required to

*provide the leachables data as a condition of approval for the parent vaccine [redacted], **provision of the results from the ongoing leachables studies for the Tris/sucrose drug product lots will be noted as a post-approval commitment for this NMA since the aluminosilicate vials are new. Point resolved.***

Functional properties of the container closure system, specifically penetrability, fragmentation and self-sealing capacity, were performed to support the 11 punctures of the Tris/sucrose 10 µg dose vials (for dilution with 0.9% sodium chloride and administration of 10 doses of the vaccine). Test parameters were based on procedures described in USP <381> and Ph. Eur. 3.2.9, with each test performed on both 21- and 23-guage needles. Results for penetrability, fragmentation and self-sealing capacity met acceptance criteria. Prior studies supported 7 penetrations of the PBS/sucrose seals for dilution and administration of 6 doses.

Container closure integrity (CCI) verification by headspace analysis was performed at the maximum fill volume of 2.25 mL (during the NMA for the parent PBS/sucrose product the company confirmed that the maximum volumetric capacity of the 2 mL vial with the stopper in place is 3.4 mL) for both the 1.2 mm wall thickness borosilicate glass vials and for the aluminosilicate vials. The fill volume of the parent vaccine is 0.45 mL and for the 10 µg/0.2 mL dose vaccine it is 1.3 mL. The study evaluated routine freezing procedures to -80°C and shipping simulations, including vibration and drop studies. None of the vials were broken during the study and all vials maintained integrity as determined by headspace analysis by CO_2 ingress.

Development studies were performed to assess CCI during freezing and following exposures of the PBS/sucrose product to frozen storage temperatures (-70°C, -84°C and in nitrogen cooled blast freezers to temperatures as low as -97.68°C). Additional testing was undertaken to demonstrate the thicker glass wall and aluminosilicate glass vials could maintain integrity with the higher fill volumes used for the Tris/sucrose drug product. Prior to assessing the impact of aggressive freezing parameters, all vials were pre-treated in a depyrogenation tunnel for at least 3 hours at 300°C. The vials were filled with either 15% mannitol solution (worst case solution for glass breakage) or a sucrose-based solution, and submerged for 5 minutes in liquid nitrogen (-200°C). The vials were then thawed and visually inspected for breakages, cracks or crevices. The studies showed that none of the aluminosilicate vials broke during testing, regardless of the contents or fill volumes. A portion of the standard glass borosilicate vials with a 0.85 mm wall thickness were found to have breakage when filled with the worst-case mannitol solution, though none of the sucrose filled borosilicate glass vials broke during testing. In summary, both vial types demonstrated robustness to aggressive freezing parameters with challenging formulations and improved resistance to glass breakage, which is at increased risk due to the greater fill volume for the Tris/sucrose drug product compared to the PBS/sucrose drug product (1.3 mL and 2.25 mL versus 0.45 mL).

The proposed primary and secondary packaging and closure and pack sizes are appropriate for the product. There are no obvious compatibility (based on the available stability data) or safety issues that need to be resolved.

3.2.P.2.5. Microbiological attributes

The Tris/sucrose drug product is supplied as a preservative-free, multi-dose suspension for intramuscular injection. During manufacture, the formulated bulk drug product is 0.2 µm sterile filtered prior to being aseptically filled into vials. The drug product is tested for sterility and bacterial endotoxins at release according to compendial requirements. Alternatively, an in-house rapid sterility test may be utilised (as approved for testing the PBS/sucrose product).

Container closure integrity testing (dye ingress, vacuum decay and CO_2 headspace analysis) is suitably described and validated. The studies assessed both the borosilicate and aluminosilicate glass vials filled on lines FC1, FC2 and WSL10 at Pfizer Puurs and sealed with

combinations of the proposed Datwyler/West bromobutyl stoppers and seals. The results support the integrity of the container closure system at the proposed frozen storage conditions (-90 to -60°C; CO_2 headspace analysis testing was performed at -80°C).

3.2.P.2.6. Compatibility

The company has assessed the physicochemical stability and compatibility of the drug product following removal from frozen storage and first opening, dilution with 0.9% sodium chloride (the 10 µg/0.2 mL dose presentation only) and with commonly used administration components (polypropylene and polycarbonate syringes with attached 25 G needle).

The compatibility studies are summarised in the following tables:

Table 7: Compatibility studies

Table 3.2.P.2.6-2. BNT162b2 Tris/Sucrose 30 µg Dose, 0.1 mg/mL, Administration Simulation Study 1

Drug Product Lot	Concentration (mg/mL)	Study Hold Time		
		Study Conditions	Hold time Container and Contact Material	Delivery Needle Size
Development lot[a]	0.1	24 hours at 30 °C/ambient light	Glass Vial	25 gauge, 1.5 inch, stainless steel
		6 hours in syringes at 30 °C/ambient light following 24 hours at 30 °C/ambient light in vials	Polypropylene Syringe	
			Polycarbonate Syringe	

a. Development LNPs made at laboratory scale have been demonstrated to be representative of those made at full scale for commercial manufacture.

Table 3.2.P.2.6-4. BNT162b2 Tris/Sucrose 30 µg Dose, 0.1 mg/mL, Administration Simulation Study 2

Drug Product Lot	Concentration (mg/mL)	Study Hold Time		
		Study Conditions	Hold Time Container and Contact Material	Delivery Needle Size
FC8273 EW4564[a]	0.1	Vials: 0 and 24 hours at 30 °C/75% RH	Glass Vials	25 G 1½ inch
		Syringes: 24 hours at 2-8 °C, 12 hours at 30 °C/75% RH	Polycarbonate Syringes	
			Polypropylene Syringes	

a. Lot EW4564 was used for one set of samples at T0 and 12 hours at 30 °C/75% RH.
Abbreviations: RH = Relative humidity

Table 3.2.P.2.6-7. Study Design for Dosing Simulation for 10 µg Doses

DP Concentration (mg/mL)	Container/ Ancillaries	Time Point (Hours)
1.3 mL Drug Product MDV for 10 µg Dose (FF9442)		
0.050	Vial	T0
	Polypropylene syringe	T12 at 30 °C
	Polycarbonate syringe	
	Polypropylene syringe	T24 at 5 °C
	Polycarbonate syringe	
	Vial	T24 at 30 °C

Abbreviations: T = Time (hours) at temperature; PP = Polypropylene; PC = Polycarbonate; MDV = Multi-dose vial;

The samples in each study were tested for appearance, pH, RNA content and encapsulation, *in vitro* expression, RNA integrity, LNP size and polydispersity. The vials were protected from light during frozen storage; however, the studies were performed under ambient light.

With the exception of *in vitro* expression and RNA integrity, which decreased slightly with increasing storage at higher temperatures, there were no changes in the tested quality attributes. The results of the studies support the physicochemical stability of the prepared dosing solutions (10 µg/0.2 mL and 30 µg/0.3 mL) for up to 24 hours at 30°C in the thawed vials, and for up to 24 hours at 2 – 8°C and 12 hours at up to 30°C in the prepared syringes. Microbial in-use hold time studies demonstrated that the prepared dosing solutions do not increase microbial growth above 0.5 log following storage for greater than 12 hours at 20 – 25°C (out of the five compendial microorganisms tested as per USP <51>, growth was only detected above a 0.5 log increase for *Escherichia coli* at 24 hours).

Based on the results of these studies (albeit limited) the company is proposing an in-use storage period of up to 24 hours at ambient temperatures (up to 30°C) in the original vials, with no more than 12 hours storage at this temperature after initial puncture of the vial stopper (for dilution or first use). Although the microbial in use studies were performed at 20 – 25°C, the upper allowable storage temperature of 30°C will be accepted by Medsafe on the basis of the justifications provided by the company during assessment of the parent PBS/sucrose vaccine that i) the growth promoting properties of the solution will be the same regardless of natural variances in room temperature, and ii) the application of a 2x safety factor to allow for any potential organisms that could multiply faster at 30°C versus 25°C (growth was observed at 24 hours, so the proposed 12 hours reflects a 2-fold safety margin).

The studies cover the recommended storage conditions for the opened and diluted products in Section 6.3 of the data sheet, which states:

> *The unopened vials of Comirnaty Ready to Use Multidose (Do not dilute) and Comirnaty Dilute to Use Multidose (For age 5 to < 12 years) may be stored at temperatures between 8°C to 30°C for up to 24 hours, including any time at these temperatures following first puncture/dilution. Thawed vials can be handled in room light conditions.*
>
> *Chemical and physical in-use stability of the opened 'Do not dilute' vials has been demonstrated for 12 hours at 8°C to 30°C. For the 'Age 5 to <12 years' product, chemical and physical in-use stability following dilution with 0.9% sodium chloride has been demonstrated for 12 hours at 2°C to 30°C. From a microbiological point of view, unless the method of opening/dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.*

While reference to the ambient temperature range of 8°C to 30°C for up to 24 hours for the unopened vials will be accepted (as the shelf-life for storage of the unopened vials at refrigerated conditions (2 – 8°C) is up to 10 weeks), the company will be asked to amend the temperature range in the in use stability studies of the opened 30 microgram/0.3 mL dose vials to 2°C to 30°C (rather than 8°C to 30°C). The temperature range of 2°C to 30°C is more representative of the temperature range used in the compatibility studies and will align the data sheet with the EU SPC and the in use storage conditions on the proposed labelling. This is addressed in RFI1 Q.6.

There is no discussion in the dossier regarding the age of the drug product prior to use in the compatibility studies. Since the proposed shelf-life is only 6 months, this will not be pursued further but should be taken into consideration for any shelf-life extensions post-approval.

3.2.P.3. Manufacture

3.2.P.3.1. Manufacturers

See Product Details section of this report. The proposed sites are currently approved for manufacture, packaging and testing of the parent PBS/sucrose drug product.

3.2.P.3.2. Batch formula

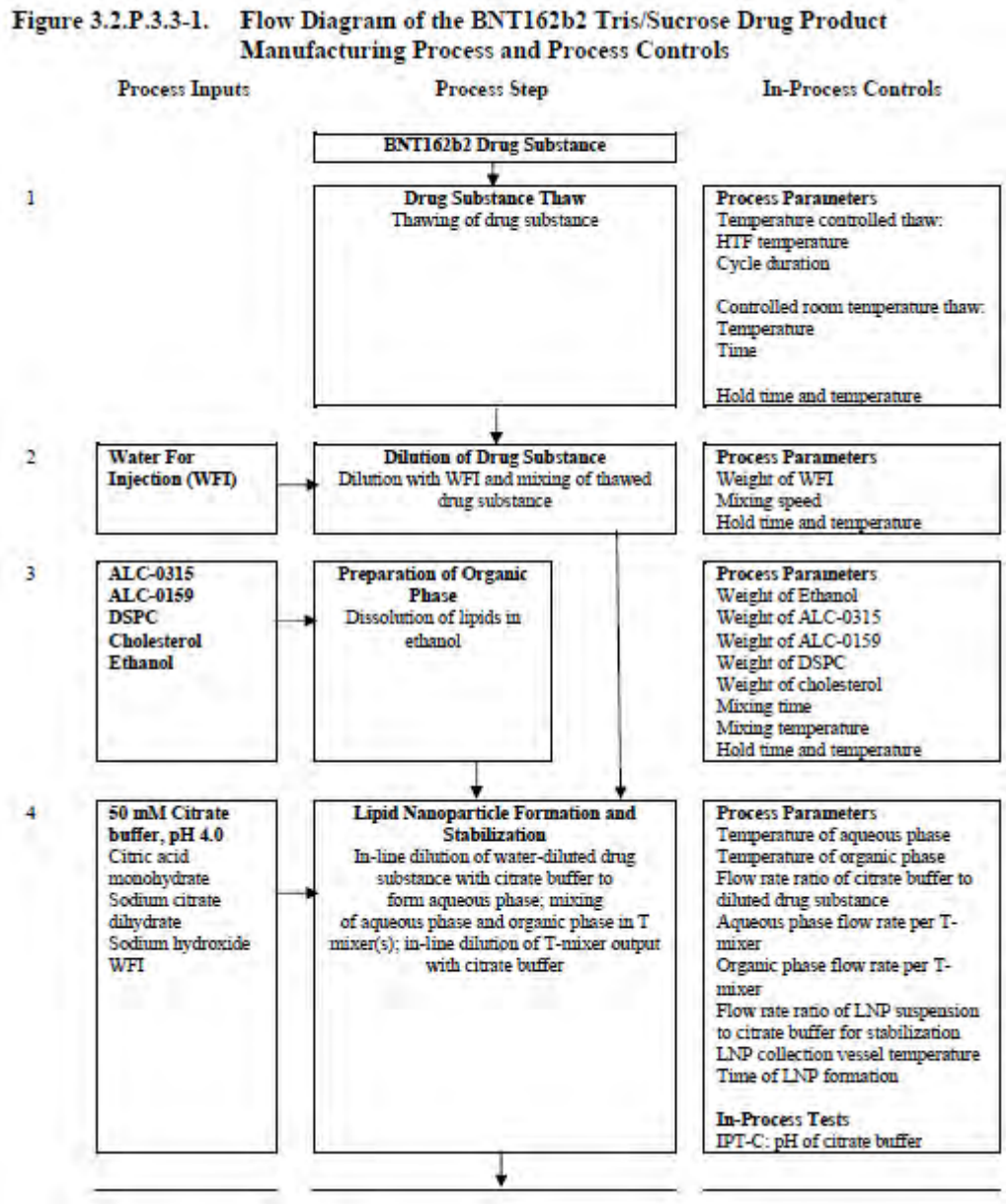
The commercial batch size is 160 g RNA, corresponding to 1,600 L of 0.1 mg/mL drug product. This batch size yields approximately 711,000 vials at 2.25 mL fill volume and approximately 1,230,000 vials at 1.3 mL fill volume.

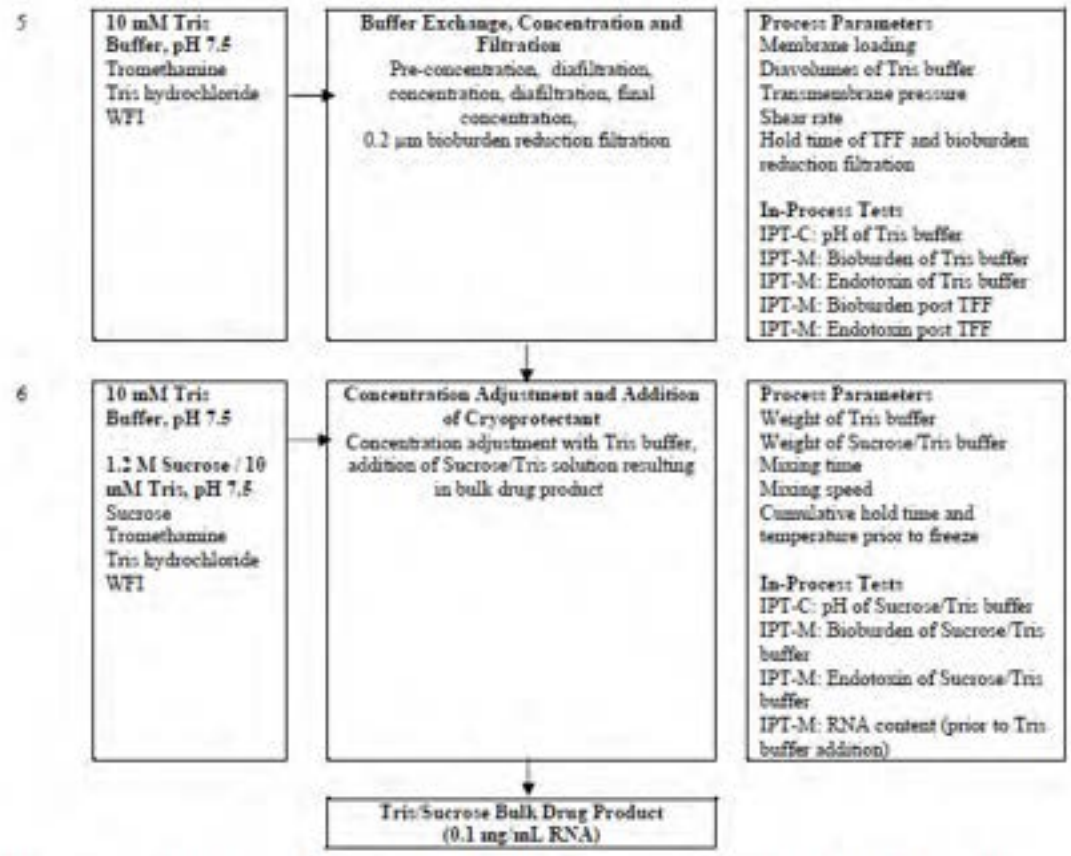
The batch and product formulae are consistent.

3.2.P.3.3. Description of manufacturing process and process controls

The finished product manufacturing process is shown in Figure 1 and includes lipid nanoparticle fabrication and bulk drug product formulation (Steps 1 – 6), followed by sterile filtration and aseptic filling (fill and finish; Steps 7 – 11).

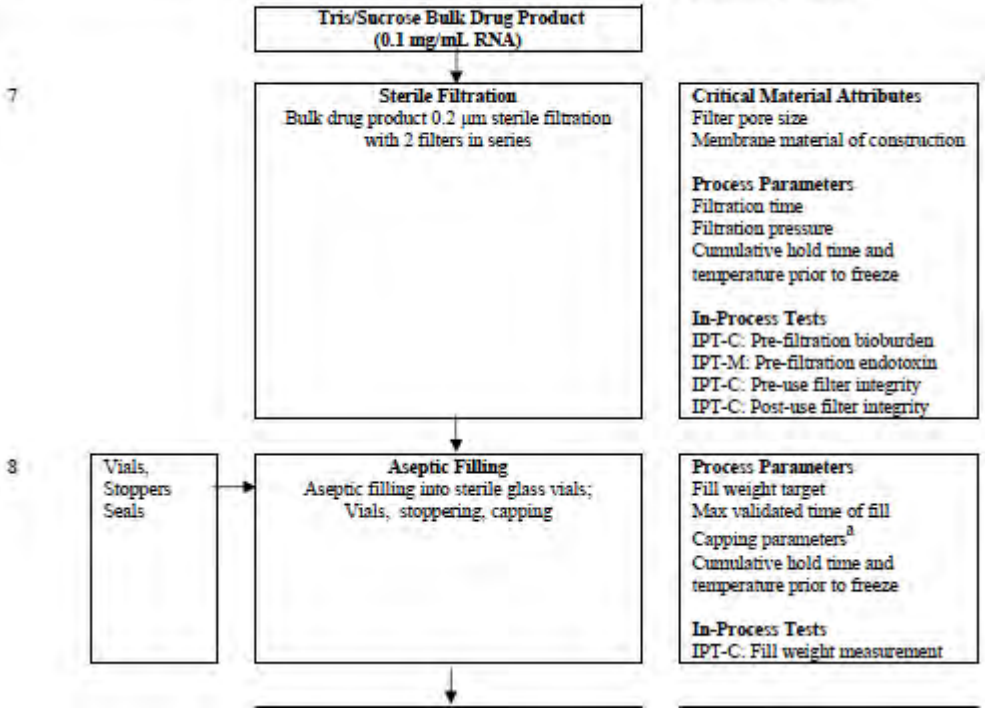
Figure 1: Flow diagram of Tris/sucrose drug product manufacturing process

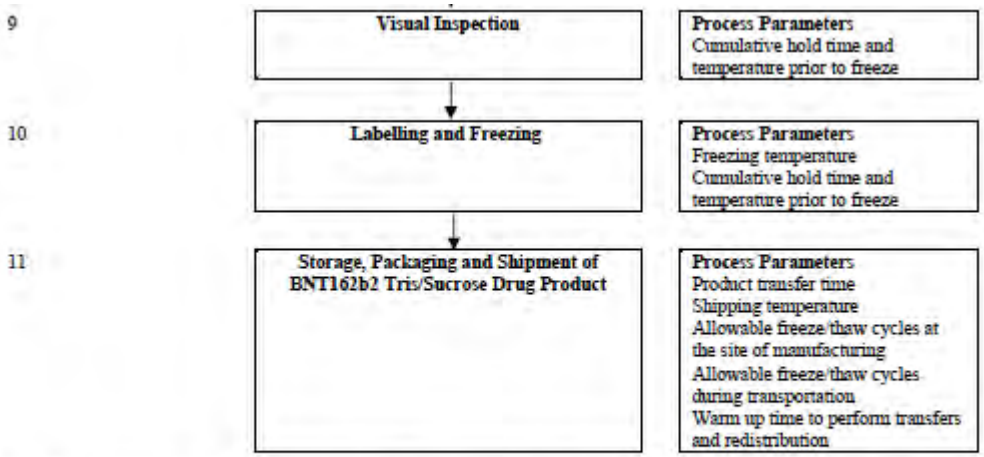




Abbreviations: IPT-C = In-process test for control; IPT-M = In-process test for monitoring; ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine

Figure 3.2.P.3.3-1. Flow Diagram of the BNT162b2 Tris/Sucrose Drug Product Fill and Finish Manufacturing Process and Process Controls





a. FC2: Crimping speed, upper spring force, lower spring force, differential force. FC1; Crimping speed, differential force. WSL10: Crimping Speed, Crimping Pressure.
Abbreviations: IPT-C = in-process test for control; IPT-M = in-process test for monitoring

The manufacturing process for the Tris/sucrose drug product is identical to that for the PBS/sucrose formulation through LNP formation and stabilisation, with subsequent process changes including buffer exchange into Tris buffer instead of PBS, concentration adjustment to 0.1 mg/mL RNA instead of 0.5 mg/mL, and fill volumes of 1.3 mL and 2.25 mL instead of 0.45 mL. It is noted that the Tris buffer used in the manufacturing process is tested for bioburden (limit: 0 CFU/mL) and endotoxins (limit: < 0.1 EU/mL) by the supplier, according to compendial requirements.

The manufacturing process for 30 µg dose differs from the process for the 10 µg dose in the following processing steps:

- Step 8 ‘Aseptic filling’ is performed on different filling lines at different fill volumes: FC1 and FC2 for the 30 µg dose at 2.25 mL fill and WSL10 for the 10 µg dose at 1.3 mL
- different flip-off cap colours are used: dark grey (30 µg) and orange (10 µg)
- Step 9 ‘Inspection’ is performed using in-line automated inspection on FC1 and FC2 for the 30 µg dose, while for the 10 µg dose the IL-11 automated inspection line is used
- Step 10 ‘Labelling and packaging’ is performed on different packaging lines: FC0 and FC1 for 195x packaging of 30 µg dose, ILPACK01 for 195x packaging of the 10 µg dose.

As approved for the parent PBS/sucrose vaccine, a single refiltration of bulk drug product through the sterile filtration step may be performed in cases where the sterilising grade filter fails to meet the post-use integrity test or if a technical issue compromises the integrity of the system. The refiltration is performed using new, identical 0.2 µm sterilising filters. An out-of-limit bioburden result will preclude a refiltration step. Refiltration of the Tris/sucrose drug product was validated during the process validation studies, and is supported by development study data.

The hold times applied during drug product manufacture are shown in the below tables and were confirmed during the process validation studies. All hold times following sterile filtration were verified and consistent with the validated media fill times, ensuring acceptable microbial control during the drug product manufacturing process. The sterile filtration processing steps are within the maximum times determined by bacterial retention filter validation. All manufacturing operations and in-process holds are conducted at 15 – 25°C, unless otherwise specified.

Table 8: Hold times in the Tris/sucrose drug product manufacturing process

Table 3.2.P.3.3-16. LNP Production and Bulk Drug Product Formulation Process Hold Times

Material or In-Process Hold Description[a]	Process Steps	Target Hold Time
Drug substance thaw	Controlled thaw equipment: Time drug substance in ethylene vinyl acetate (EVA) containers is thawed with heat transfer fluid at 25 °C target set point.	Target 6 hours
	Controlled room temperature thaw: Time drug substance in EVA containers is thawed at controlled room temperature.	≤32 hours[b]
Drug substance post thaw	Maximum time that thawed BNT162b2 drug substance can be held at 15-25 °C and 2-8 °C in the ethylene vinyl acetate (EVA) container including addition of DS to the vessel up to the point of dilution.	≤24 hours at RT + ≤48 hours at 2-8 °C[b]
Drug substance post dilution at 15-25 °C	Time from addition of WFI to drug substance until end of LNP formation step	≤12 hours[c]
Organic phase post mix at 15-25 °C	Time from end of organic phase mixing until end of LNP formation.	≤48 hours[c]
Citrate buffer at 15-25 °C	Total hold time for citrate buffer post addition of Water for Injection to be used for LNP formulation or concentration/buffer exchange step.	≤72 hours[c]
10 mM Tris buffer at 15-25 °C	Total hold time for Tris buffer post addition of WFI or start of in-line dilution to be used for buffer exchange/concentration, filtration and concentration adjustment steps.	≤96 hours
1.2 M sucrose, 10 mM Tris solution 2-25 °C	Total hold time for Sucrose/Tris solution post addition of WFI to be used for concentration adjustment step.	≤10 hours
LNP formation	Time from start of mixing aqueous and organic phases at 15-25 °C until start of TFF step including collection and hold at 2-25 °C.	≤12 hours[c]
Time of TFF and bioburden reduction filtration unit operation 2-25 °C	Time from start of TFF operation to end of bioburden reduction filtration while product is at 2-25 °C.	≤16 hours
Post bioburden reduction filtration at 2-8 °C	Time post bioburden reduction filtration until end of sterile filtration with ≤12 hours until the start of concentration adjustment and cryoprotectant addition.	≤36 hours

a. Temperature values of 15-25 °C represent room temperature
b If the controlled room temperature thaw time exceeds 32 hours, any additional time is included in the drug substance post thaw hold time.
c. Hold times based on process validation studies performed with the PBS/Sucrose formulation.
Abbreviations: RT = Room temperature; WFI = Water for Injection; LNP = lipid nanoparticle; TFF = Tangential flow filtration.

Table 3.2.P.3.3-10. Fill and Finish Process Hold Times

Material or In-Process Hold Description	Process Steps	Target Hold Time
Liquid drug product in vessels or glass vials at 2 to 25 °C.	Cumulative time in vessels or glass vials at 2-8°C from the start of concentration adjustment and cryoprotectant addition until the start of freezing, including time held in stainless steel vessels, sterile filtration, filling, inspection, and secondary packaging, with ≤72 hours of this time allowed up to 25 °C	≤336 hours[a]

a. Sterile filtration time limited based on microbial retention study; fill hold time limited based on media fill study.

The drug product has an allowable time out of freezing to perform transfers and shipping as shown in Table 9. The allowable out of storage conditions and times allowances are supported by the available drug product stability data.

Table 9: Process parameters for product handling, redistribution and storage during transport

Process Parameter	Acceptable Range
Allowable freeze/thaw cycles post initial freezing at the manufacturing site	≤1 cycle[a]
Cumulative time product can be warmed up to a maximum of -5 °C to perform transfers and redistribution during shipping	≤24 hours
Temperature range for shipping and for inventory transfer and redistribution during transport[b]	-90 to -60 °C
Allowable freeze/thaw cycles during transportation up to point of use	≤1 cycle[a]
Alternate shipping temperature range at -25 °C to -15 °C	≤ 48 hours
Alternate shipping temperature range at 2 °C to 8 °C	≤ 80 hours

a. Allows thawing at temperatures up to 25 °C. Product refrozen to -70 °C.
b. Multiple transfers are allowed, however vials must be returned to -90 to -60 °C storage between transfers.

The total time allowed out of -90 to -60°C storage throughout transport from the drug product manufacturing site to the administration site is a cumulative 152 hours, including up to 48 hours at -25 to -15°C, 24 hours at -5°C and 80 hours at 2 – 8°C.

3.2.P.3.4. Controls of critical steps and intermediates

The in-process controls in the drug product manufacturing process are shown in the below tables. The dossier also describes additional process parameters applied during manufacture, which align with those approved for the PBS/sucrose drug product.

Table 3.2.P.3.3-5. IPT-C Test for 50 mM Citrate Buffer, pH 4.0

In-process Test	Acceptance Criteria
pH	4.0 ± 0.1

Table 3.2.P.3.3-7. IPT-C Test for 10 mM and 150 mM Tris Buffer, pH 7.5

In-process Test	Acceptance Criteria
pH	7.5 ± 0.2

Table 3.2.P.3.3-11. IPT-C Tests for 1.2 M Sucrose, 10 mM Tris Solution

In-process Test	Acceptance Criteria
pH	7.5 ± 0.2

Table 3.2.P.3.3-2. IPT-C Tests for Sterile Filtration

In-process Test	Acceptance Criteria
Pre-use filter integrity[a]	Pass
Post-use filter integrity[a]	Pass
Bioburden (pre-sterile filter)	≤10 CFU/100 mL

a. As the filtration step uses redundant filters, only one of the two filters is required to pass both pre- and post-use filter integrity tests.

Table 3.2.P.3.3-5. IPT-C Test for Aseptic Filling

Dose	In-process Test	Acceptance Criteria
30 µg	Fill weight measurement[a]	2.195 – 2.476 g
10 µg	Fill weight measurement[a]	1.268 – 1.430 g

a. The fill weight dispensed in vials is controlled by a fill weight check (IPT-C). The result of the IPT-C is used to make adjustments (if needed) to the filling machine to ensure the fill weight in vials remains within the acceptance criterion for the fill weights.

Descriptions of the in process test methods were provided. A fluorescence assay is performed as an IPT-M to quantify RNA content prior to concentration adjustment and addition of cryoprotectant and has been suitably validated for use with the Tris/sucrose product. The compendial method for bioburden (USP <61>, Ph. Eur. 2.6.12 and JP 4.05) has been suitably verified.

3.2.P.3.5. Process validation and/or evaluation

Formulation at 1600 L batch scale and filling at 2.25 mL fill volumes

Validation of the manufacturing process was performed in two phases. Initially, two Process Performance Qualification (PPQ) runs were manufactured at 1600 L batch scale for filling at 2.25 mL per vial (PPQ 1 and PPQ 2), and one PPQ run (PPQ 3) at 700 L scale. PPQ3 was split into 500 L and 200 L lots for filling at 1.3 mL (PPQ 3a) and 0.4 mL (PPQ 3b) per vial respectively (refer Table 10). Due to a confirmed out of specification (OOS) result for RNA integrity at release for lot PPQ 3b (57%), a replacement PPQ lot, PPQ 4 was manufactured at 1600 L scale and split into two 800 L lots for filling at 2.25 mL per vial on FC1 and FC2. The OOS result PPQ3 was investigated; however a root cause could not be identified. Additionally, extended characterisation testing on PPQ 3b shows that this lot is comparable to PPQ 1 and 2 lots and to PBS/sucrose drug product lots, supporting the rationale that the root cause was not linked to the new formulation. Since the 0.4 mL fill volume is not relevant to this NMA, and an additional PPQ batch was manufactured for this fill volume (discussed below) this will not be pursued further. The PPQ batches encompass the three proposed filling lines for the Tris/sucrose drug product and the proposed vial types.

Table 10: Tris/sucrose drug product process validation lots

PPQ #	1	2	3a[a]	3b[b]	4a[c,d]	4b[c,d]
Drug Product Lot Number	FC8273	FE4394	FF9442	FF9438	FJ5683	FJ5682
Date of Manufacture	04 May 2021	01 June 2021	03 July 2021		06 August 2021	
Formulation Booth	FB 5/6	FB 5/6	FB 5/6		FB 3/4	
Bulk Lot Number	FC1257	FD0813	FF8096		FJ5026	
Bulk Batch Size	1600 L	1600 L	700 L		1600 L	
Filling Line	FC1	FC2	WSL10	WSL10	FC1	FC2
Filling Lot Number	FC8273	FE4394	FF9442	FF9438	FJ5695	FJ5691
Filling Batch Size	1600 L	1600 L	500 L	200 L	800 L	800 L
Fill volume	2.25 mL	2.25 mL	1.3 mL	0.4 mL	2.25 mL	2.25 mL
Vial Type	1.2 mm[e] Borosilicate	Alumino-silicate	1.2 mm[e] Borosilicate		1.2 mm[e] Borosilicate	Alumino-silicate

a. Lots FF9442 and FF9438 were manufactured from the same bulk drug product lot FF8096, split into 500 L and 200 L portions for filling at 1.3 mL and 0. 4 mL, respectively.
b. A confirmed out of specification results was obtained for FF9438, see Section 3.2.P.3.5.12 Deviations.
c. Lots FJ5682 and FJ5683 were manufactured from the same bulk drug product lot FJ5026, split into two 800 L portions for filling. was split in FJ5691 (800L) and FJ5695 (800L).
d. For PPQ 4 onwards additional item numbers have been added for packaging, to facilitate packing both 10-pack and the 195-pack.
e. Wall thickness of the glass vials.

In a separate study (discussed below) a second bulk PPQ lot was split into two filling PPQ lots (PPQ 5a and PPQ 5b) as a repeat of PPQ 3a and PPQ 3b (10 µg and 3 µg, respectively) to generate additional data.

With the exception of the OOS result for PPQ 3b, all PPQ runs met all established acceptance criteria for in-process controls, extended testing (eg for quality attributes after concentration adjustment and addition of cryoprotectant), and final drug product release. The final product testing included testing of vials from the beginning, middle and end of the filling operations and confirmed suitable homogeneity across a filling run. RNA integrity was measured at the maximum Time in refrigerator/Time out of refrigerator (TIR/TOR) (NMT 336 h) and complied with acceptance criteria. As discussed earlier in this report, the release testing and heightened characterisation testing results for the PPQ batches were within the predetermined comparability acceptance criteria based on 94 historic PBS/sucrose lots. The

process validation demonstrated that the manufacturing process at Pfizer, Puurs, when executed within the ranges established for commercial manufacture, is robust and produces Tris/sucrose drug product that meets pre-determined acceptance criteria. All PPQ lots have been enrolled in the stability programme (refer section 3.2.P.8 of this report).

Formulation at 1600 L batch scale and filling at 1.3 and 0.4 mL fill volumes

The above process validation study demonstrated that the Tris/sucrose drug product manufactured at 1600 L bulk drug product scale and filled into vials at 2.25 mL fill volume met predetermined acceptance criteria. One additional PPQ run was performed to support filling at 1.3 mL and 0.4 mL in support of 10 µg and 3 µg dosages (not proposed with this NMA) for paediatric use. The PPQ lot was manufactured at 1600 L batch scale and split into 1550 L and 50 L portions for filling at 1.3 mL and 0.4 mL respectively. The PPQ lot was filled on WSL10. The PPQ lot details are shown in the below table.

Table 11: 1.3 mL (and 0.4 mL) PPQ batch details

PPQ #	5a	5b
Drug Product Lot Number	FK5127[a]	FK5128[a]
Date of Manufacture	19 August 2021	
Formulation Booth	FB 3/4	
Bulk Lot Number	FK1099	
Bulk Batch Size	160g/1600 L	
Filling Line	WSL10	WSL10
Filling Lot Number	FK1702	FK1703
Filling Batch Size	1550 L	50 L
Fill volume	1.3 mL	0.4 mL
Vial Type	1.2 mm Borosilicate	1.2 mm Borosilicate

a. Lots FK5127 and FK5128 were manufactured from the same bulk drug product lot FK1099, split into 1550 L and 50 L portions for filling at 1.3 mL and 0. 4 mL, respectively

All results met established in-process controls and final drug product release acceptance criteria. Additional testing was performed to confirm filling homogeneity across a run. Samples tested at the beginning, middle and end of filling for LNP size, LNP polydispersity, RNA encapsulation, RNA and lipid content met acceptance criteria and demonstrated suitably consistency across samples. RNA integrity was not measured in the assessment of filling homogeneity as this attribute is highly influenced by the product hold time prior to freezing. Instead, samples for RNA integrity were tested at the maximum time in refrigerator/time out of refrigeration (TIR/TOR =336 h 12 min; TOR = 72 h 10 min) and met acceptance criteria. Deviations encountered in the study were suitably described and deemed not to impact the outcome of the validation study. The PPQ lots were enrolled in the stability program (stability data pending).

Validation of aseptic filling by media fills

The aseptic filling procedures on filling lines FC1, FC2 and WSL10 at Pfizer, Puurs have been validated by media fills. All three filling lines have previously been validated for filling the PBS/sucrose drug product. The media fill studies are summarised as follows:

- *FC1*: 11,171 to 15,894 2 mL Type I glass vials (1 mL fill) were filled in three media fill runs between 10/08/2020 and 12/03/2021 (maximum filling time 154 h 1 min); 0 contaminated units were detected
- *FC2*: 16,212 to 27,698 2 mL Schott vials (1 mL fill) were filled in three media fill runs between 17/08/2020 and 2/09/2020 (maximum filling time 161 h 24 min); 0 contaminated units were detected
- *WSL10*: 42,287 to 43,206 8 mL vials (2 mL fill) were filled in three media fill runs between 26/02/2020 to 29/04/2020 (maximum filling time 199 h 2 min); 0 contaminated units detected.

The media fills challenged the aseptic manufacturing process (minimum line speed, interventions, maximum proposed hold times). The vials filled on FC1 and FC2 are representative of the vials that will be used for commercial manufacture. The 8 mL vials filled on WSL10 are considered worst case due to the larger neck diameter (and hence greater exposure of the open vials to the environment). This will be accepted.

Validation of the process steps hold times

The hold times described in Table 8 have been suitably validated. The in process hold times unique to the Tris/sucrose drug product manufacturing process, namely the Tris buffer, pH 7.5 hold time, the 1.2 M sucrose, 10 mM Tris solution hold time, the tangential flow filtration (TFF) and bioburden reduction filtration unit operations, and the post bioburden reduction filtration were initially based on those established for comparable steps for the PBS/sucrose process and were confirmed by the results obtained from the Tris/sucrose process validation runs (included an assessment of microbiological control (bioburden and endotoxin testing)). Process validation lot FC8273 was subjected to a cumulative hold time study, which evaluated the cumulative effect of the maximum process hold times for each process step, from the start of thawing of the drug substance until the start of freezing of drug product, on the microbiological and physicochemical quality of the drug product. All in process testing results for the hold challenge batches PPQ 1, PPQ 2 and PPQ 4 met the pre-determined acceptance criteria. Lot FC8273 met release acceptance criteria.

Sterilising filter membrane validation

The sterilising grade filters used for the sterile filtration of the formulated Tris/sucrose bulk drug product use a polyethersulfone (PES) 0.2 µm filter membrane. When sterile filters supplied by Sartorius are used, two 1.2 m^2 or 2 m^2 steam-in-place cartridges are used in series during the sterile filtration of the formulated drug product into a holding vessel. The sterile filter membrane validation study assessed microbial retention, filter membrane compatibility and extractables testing. All testing was performed with the Tris/sucrose bulk drug product. The filter integrity testing was validated using Tris buffer and drug product as the wetting agents. The microbial retention studies were performed under worst-case operating conditions for batch size (1600 L), filter contact time (8 hours) and pressure (up to 2.1 bar) compared to the commercial manufacturing process. The processing conditions were simulated on a laboratory scale, with the test target values scaled down, on an area-to-area basis, as appropriate. All results met acceptance criteria. The potential leachables identified in the extractables study were shown to be well below the safety concern threshold for any compound. In summary, the studies for microbial retention, membrane compatibility, extractable substances and filter integrity demonstrate that the filter devices containing Sartopore 2 and Sartopore Platinum PES 0.2 µm membranes are appropriate for the sterile filtration of the bulk Tris/sucrose drug product.

Refiltration validation

Refiltration is not a routine step in the manufacturing process but will be performed when the sterilising grade filter fails to meet the post-use integrity test, or if a technical issue occurs that compromises the integrity of the system. The validation performed for the PBS/sucrose drug product to support an allowable single refiltration is considered directly applicable to the Tris/sucrose drug product,, since the filtration steps in the manufacturing processes are equivalent and the same filters are used. A development study with Tris/sucrose drug product, demonstrated no impact on product quality when 30 mL of Tris/sucrose drug product at 0.18 mg/mL was filtered 5 times, each filtration through a new filter. If a refiltration step is required, additional sampling for bioburden and endotoxin will be performed. In addition, the critical quality attributes potentially affected by sterile filtration (LNP size, LNP polydispersity and RNA encapsulation) will be tested. At least one refiltered drug product lot will be placed on stability. This is acceptable.

Verification of in process test methods

The in process compendial method for bioburden was suitably verified for use with the Tris/sucrose drug product.

Shipping validation

The drug product is shipped primarily at temperature conditions of -90 to -60°C; however, shipping conditions may include the use of passive thermal conveyances that maintain temperatures of -20 ± 5°C and 2 – 8°C for air and road shipments. The total time allowed out of -90 to -60°C storage throughout transport from the drug product manufacturing site to the dosing site is a cumulative 152 hours, including up to 48 hours at -20 ± 5°C, 24 hours at -5°C and 80 hours at 2 – 8°C (refer Table 9). One thaw at temperatures up to 25°C and refreeze to -90 to -60°C is allowed during transportation to the point of use. The temperature excursion allowances are based on the existing shipping validation data for the PBS/sucrose drug product, the available stability data for the Tris/sucrose drug product, and the freeze/thaw studies performed on the Tris/sucrose drug product during development. In addition, an extended simulated transport study was performed with samples of the Tris/sucrose drug product that evaluated worst-case shipping hazards and storage temperatures of -80°C, -20°C, 0°C and 10°C, over a total duration of 200 hours. The details of the transport simulation study are shown in Table 12, and was designed to replicate the entire global supply chain from the point of manufacture to points of use, including, hospitals, pharmacies, clinics or other administration facilities. The dossier notes that the total moving time for Tris/sucrose drug product for global distribution is 48 hours (ie well within the 200 hours examined in the study).

Table 12: Shipping validation study

Table 3.2.P.3.5-3. Combined Profiles for Simulation

Step #	Total duration (hours)	Step duration (hours)	Pressure (psia)	Non – Accelerated ISTA profile	Temperature (°C)	Box Numbers being Tested
1	24	24	14.2[a]	Jet Aircraft	-80	6-10
2	60	36				1,2,3,4,5,6,7,8,9,10
3	72	12		Steel Spring truck		
4	120	48			-20	
5	130	10	10.9	Jet Aircraft	0	2,3,4,5,7,8,9,10
6	140	10				
7	150	10				
8	153	3				3,4,5,8,9,10
9	156	3	9.3	Steel Spring truck		
10	160	4	14.2	Air Ride Truck		
11	170	10			10	4,5,9,10
12	176	6				
13	180	4				
14	190	10				5,10
15	200	10				

a. No pressure control needed for 14.2 psia as the lab ambient pressure is approximately 14.3 psia. The difference of 0.1 psia is within the ±0.4 psia acceptable tolerance of low pressure system.

Following the simulated temperature exposures/durations, samples were tested for stability indicating attributes, with all results meeting acceptance criteria. Of note, samples in Box 10 (exposed for 72 hours at -80°C, 48 hours at -20°C, and 80 hours at 0 – 10°C) showed a slight increase in LNP size compared to samples stored at -80°C for the duration of the study, but all results were well within acceptance criteria. This is acceptable.

The company will be asked to confirm that the New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

RFI1 Q.16. Please confirm that the New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

EAI1 Q.16. A suitable confirmation was provided. ***This will be noted as a condition of approval of this NMA. Point resolved****.*

3.2.P.4. Control of excipients

3.2.P.4.1 - 3.2.P.4.4. Specifications and test methods

The compendial excipients, cholesterol, sucrose and water for injection (WFI), and the non-compendial excipients ALC-0159 (2-[(polyethylene glycol)-2000]-N,Nditetradecylacetamide), ALC-0315 ((4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2- hexyldecanoate) and DSPC (1,2 distearoyl-sn-glycero-3-phosphocholine) used in the Tris/sucrose formulation are the same as those used in the PBS/sucrose formulation. Reference is made to the approved dossier of the parent product for information regarding the manufacture and quality control of these excipients.

One new compendial excipient, Tris (trometamol), and one new non-compendial, non-novel excipient, Tris hydrochloride (Tris HCl; trometamol hydrochloride), are used in the manufacture of the Tris/sucrose drug product. No animal derived raw materials are used in the manufacture of these excipients.

Since the Tris is compendial (controlled to the Ph. Eur., with additional testing for microbial contamination as per Ph. Eur. 2.6.12), no further information is required. The specifications for Tris hydrochloride are shown in Table 13.

Table 13: Specifications for Tris hydrochloride

Test	Analytical Methods	Acceptance Criteria
Appearance	Visual examination	Colorless crystals to white crystalline powder
Identification[a]	USP <197M>, Ph.Eur. 2.2.24	Sample spectrum is consistent with appropriate reference spectrum
Assay	Titration	NLT 99.0%
Absorbance	USP <857>	NMT 0.06 at 260 nm NMT 0.06 at 280 nm NMT 0.01 at 400 nm
Loss on Drying	USP <731>	NMT 0.5%
Melting Point	USP <741>	147 – 153 °C
pH	USP <791>	3.5 – 5.0
Microbiological Contamination	Ph. Eur. 2.6.12	TAMC NMT 100 CFU/g

a. Test performed by or on behalf of the drug product manufacturer.

The Tris HCl is tested for identification by or on behalf of the drug product manufacturer and the remaining tests may be accepted based on the supplier's certificate of analysis (CoA). Tris HCl is an acid form of the compendial excipient trometamol and the specifications established for Tris HCl are justified on the basis of their alignment with the Ph. Eur. 1053 monograph for trometamol, tromethamine (USP) and general limits applied to excipients (eg microbial limits as per Ph. Eur.). The compendial methods used to test the Tris HCl are stated to have been verified (data not provided). Summary method verification data has been provided for the in house assay method used to test and release the Tris HCl. The method was validated for precision (intermediate and repeatability), linearity, range, ruggedness, accuracy and specificity with all results meeting acceptance criteria. This is acceptable.

3.2.P.4.5. Excipients of human or animal origin

There are no excipients of human or animal origin used in the manufacture of the drug product.

3.2.P.4.6 Novel excipients

There are two novel excipients in the drug product: ALC-0159 and ALC-0315. Information regarding the manufacture and quality control of these excipients is as approved for the parent PBS/sucrose formulation of Comirnaty.

3.2.P.5. Control of drug product

3.2.P.5.1. and 3.2.P.5.6. Release and expiry specifications

The drug product is controlled according to in house and compendial specifications as shown in Table 14. With the exception of LNP size and RNA integrity, the same acceptance criteria are applied at release and expiry.

Table 14: Release and expiry specifications of the 30 micrograms/dose (grey cap) and 10 micrograms/dose (orange cap) Tris/sucrose formulations of Comirnaty

Quality Attribute	Analytical Procedure[a]	Procedure Number(s)	Acceptance Criteria
Composition and Strength			
Appearance	Appearance (Visual)	TM9173A (PGS-Puurs)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) *(Ph Eur. 2.9.20, USP <790>, JP 6.06)*	TM9173A (PGS-Puurs)	May contain white to off-white opaque, amorphous particles
Subvisible Particles	Subvisible Particulate Matter *(USP <788>, light obscuration method, Ph. Eur. 2.9.19)*	GPB29 (PGS-Puurs) SOP-13114 (PGS-GC)	Particles ≥10 µm: ≤6000 per container
			Particles ≥ 25 µm: ≤600 per container
pH	Potentiometry *(Ph. Eur. 2.2.3, USP <791>)*	TMC0007 (PGS-Puurs)	6.9 – 7.9
Osmolality	Osmometry[b, c] *(USP <785>)*	TM8209A (PGS-Puurs)	240-400 mOsmol/kg
LNP Size	Dynamic Light Scattering (DLS)	TM9332A (PGS-Puurs)	56-101 nm (release) 56-120 (stability)
LNP Polydispersity	Dynamic Light Scattering (DLS)	TM9332A (PGS-Puurs)	≤ 0.3
RNA Encapsulation	Fluorescence assay	TM9375A (PGS-Puurs)	≥ 85%
RNA content	Fluorescence assay	TM9375A (PGS-Puurs)	0.074 – 0.126 mg/mL
ALC-0315 content	HPLC-CAD	TM9215A (PGS-Puurs)	0.90 - 1.85 mg/mL
ALC-0159 content			0.11 - 0.24 mg/mL
DSPC content			0.18 - 0.41 mg/mL
Cholesterol content			0.36 - 0.78 mg/mL
Vial content (volume)	Container content[c]	TM9196A (PGS-Puurs)	Not less than 2.115 mL (for 2.25 mL/30 µg vial)
			Not less than 1.222 mL (for 1.3 mL/10 µg vial)

Quality Attribute	Analytical Procedure[a]	Procedure Number(s)	Acceptance Criteria
Identity			
Lipid identities	HPLC-CAD[c]	TM9215A (PGS-Puurs)	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR[c]	SOP-111956 (PGS-GC)	Identity confirmed
Potency			
In Vitro Expression	Cell-based flow cytometry	SOP-113198 (PGS-GC)	≥ 30% Cells Positive
Purity			
RNA Integrity	Capillary Gel Electrophoresis	TM9308A (PGS-Puurs)	≥ 58% intact RNA (release) ≥ 50% intact RNA (stability)
Adventitious Agents			
Bacterial Endotoxin	Endotoxin (LAL) *(Ph. Eur. 2.6.14, USP <85>, JP 4.01)*	LAB-38322 (PGS-Puurs)	≤ 12.5 EU/mL
Sterility	Sterility[d] *(Ph. Eur. 2.6.1, USP <71>, JP 4.06)*	LAB-38323 (PGS-Puurs)	No Growth Detected
Container Closure Integrity	Dye incursion[e]	TM8999A (PGS-Puurs)	Pass

a. All assays performed for release and stability unless otherwise noted.
b. In accordance with Ph. Eur. 2.2.35, with minor difference in instrument calibration
c. Assay not performed on stability.
d. Testing by the Rapid Sterility Test is performed in accordance with the compendia except for incubation duration and detection method.
e. Tested at release and on stability for stability batches only
Abbreviations: PGS = Pfizer Global Supply; GC = Grange Castle; LNP = Lipid nanoparticles; CAD = Charged aerosol detector; RT-PCR = Reverse transcription polymerase chain reaction; FACS = Fluorescence activated cell sorter; LAL = Limulus amebocyte lysate; EU = Endotoxin unit

The proposed release and expiry specifications for the Tris/sucrose drug product are identical to those currently approved for the PBS/sucrose drug product, with the exception of the acceptance criteria for osmolality (to reflect the different characteristics of PBS versus Tris buffer), and for the six content assays (RNA, ALC-0315, ALC-0159, DSPC, cholesterol, and vial content) as a consequence of the five-fold difference in RNA concentration and different fill volumes.

The osmolality of the BNT162b2 Tris/Sucrose drug product is performed at release according to USP <785>, and in accordance with Ph. Eur. 2.2.35. The acceptance criterion range is set on the basis of limited manufacturing history, calculations of expected osmolality from first principles given the known formulation, and to ensure the formulation is approximately isotonic in order to ensure tolerability of the injection.

The Tris/sucrose drug product acceptance criteria for RNA and lipid content are different from the current PBS/sucrose drug product, as the Tris/sucrose drug product has a target RNA content of 0.1 mg/mL as compared to 0.5 mg/mL (prior to dilution) for the PBS/sucrose drug product. The Tris/sucrose drug product acceptance criteria for RNA and individual lipid content are therefore five-fold lower than those initially established for the PBS/sucrose drug product. The acceptance criteria for RNA and lipid content in the PBS/sucrose drug product were tightened recently on the basis of the availability of significantly more batch data for this product, and to fulfil condition 13 of provisional approval. The specifications for the Tris/sucrose drug product remain based on those initially established for the PBS/sucrose drug product before tightening, as only limited batch data is available for the new formulation. This will be accepted by Medsafe; however, the company will be asked to reassess and

revise the finished product specifications acceptance limits as further data becomes available.

RFI1 Q.17. Please commit to reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available, and indicate a time-frame for when this reassessment will be completed and provided to Medsafe.

EAI1 Q.17. The company committed to reassess and revise the finished product specifications acceptance criteria for RNA and lipid content as further data becomes available. The reassessment will be completed 4Q2022 and will be provided to Medsafe. ***This will be noted as a condition of approval of this NMA. Point resolved****.*

The proposed limits for vial content are based on the dose delivery studies performed during development. The minimum vial content limits of 2.115 mL for the 30 µg vial, and 1.222 mL for the 10 µg vial, were derived as summarised in the following tables and are acceptable to Medsafe. As noted in section 3.2.P.7 of this report, the maximum volumes of the prepared products following filling and dilution (for the 10 µg vials) are within the 3.4 mL maximum volumetric capacity of the proposed vials.

Table 15: Theoretical assessment of fill volume and doses delivered for vial content limits

Table 3.2.P.5.6-11. Theoretical Assessment of Fill Volume and Doses Delivered – 2.25 mL Fill Volume

Step	Volume Requirements	Total Volume needed in Vial
Tris/Sucrose MDV 0.1 mg/mL, 2.25 mL Fill (No dilution required)		
6 doses	6 x 0.3 mL per dose	1.8 mL
Dosing syringe/needle overage	6 x 0.035 mL per syringe	0.21 mL
Non-extractable volume	0.07 mL	0.07 mL
Minimum volume required		2.08 mL
Minimum fill volume required	2.115 mL	

Table 3.2.P.5.6-13. Theoretical Assessment of Fill Volume and Doses Delivered – 1.3 mL Fill Volume

Step	Volume Requirements	Total Volume needed in Vial
Tris/Sucrose MDV 0.1 mg/mL, 1.3 mL Fill		
10 doses	10 x 0.2 mL per dose	2.0 mL
Dosing syringe/needle overage	10 x 0.035 mL per dose	0.35 mL
Non-extractable volume	0.07 mL per vial	0.07 mL
Minimum volume required		2.42 mL
Volume of saline added by health care provider	1.3 mL	-1.3 mL
Minimum fill volume required (calculated)		1.12 mL
Minimum Fill volume required (criterion)		1.222 mL

The impurity profile of the Tris/sucrose drug product is based primarily on the impurity profile of the materials used for its manufacture. Four process-related impurities resulting from the drug product manufacturing process have been identified and are identical to those for the PBS/sucrose drug product: ethanol (lipid solubilisation), citrate (dilution buffer for LNP formation), HEPES (drug substance excipient buffer) and EDTA (drug substance excipient buffer). All four impurities have been demonstrated to be removed to acceptably safe levels (the dossier includes a safety risk assessment for EDTA, HEPES and citrate under theoretical worst-case concentrations), so are not controlled for in the finished product specifications. The impurity analysis does not specifically comment on elemental impurities; however, this will not be pursued because vaccines are outside the scope of ICH Q3D and USP<232 and no risk for elemental impurities was identified for the parent PBS/sucrose drug product (it is not considered that the use of the Tris buffers would introduce an increased risk of elemental impurities).

On the basis of the above information and the justifications provided by the company, the proposed specifications for the 30 micrograms/dose and 10 micrograms/dose presentations of 0.1 mg/mL Comirnaty are acceptable to Medsafe.

3.2.P.5.2 and 3.2.P.5.3. Analytical procedures: description and validation

The analytical procedures for container closure integrity, endotoxin, osmometry, potentiometry (pH) and sterility (either the compendial method or the rapid sterility test may be used) are identical to those approved for use with the PBS/sucrose drug product so are not discussed further here. The remaining procedures have been updated for analysis of the Tris/sucrose presentation as summarised below. The majority of changes involve minor modifications to sample preparation, and in some cases sample volumes, to account for the difference in mRNA concentration between the PBS/sucrose and Tris/sucrose presentations. The changes made to the analytical procedures used to test the Tris/sucrose drug product include:

- *Appearance*: 'fluorescence' is removed as a qualifier for the light source to allow use of alternative types of light
- *Capillary Gel Electrophoresis:* minor changes to the sample and control concentrations
- *Cell-Based Flow Cytometry*: the concentration of antibody used in the assay is increased; minor changes to reagents, equipment and incubation times; change from drug product reference material to drug product sample as the drug product control (used to confirm system suitability (assay); cells are transfected in duplicate instead of quadruplicate; absolute difference of S1+ cells is now calculated instead of percent relative standard deviation (for system suitability assay acceptance criteria)
- *Container Content*: updated to state the minimal volume requirements relevant to the proposed Tris/sucrose presentations
- *Dynamic Light Scattering*: the requirement for a drug product assay control is removed as the nanosphere size standard control confirms proper instrument performance (confirmed during method validation to demonstrate precision, accuracy and linearity (standard and sample) in the measurement of drug product hydrodynamic diameter)
- *Fluorescence Assay*: minor changes to reagents and equipment
- *High Performance Lipid Chromatography-Charged Aerosol Detection (HPLC-CAD)*: representative chromatograms for the PBS/sucrose drug product are replaced with those for the Tris/sucrose drug product
- *Reverse Transcription Polymerase Chain Reaction (RT-PCR)*: the dilution of the test samples is changed to 1:10,000 instead of 1:100,000, associated with the lower RNA sample concentration
- *Subvisible Particulate Matter*: now references USP <788> instead of USP <787>.

All tests are performed at Pfizer Puurs tests with the exception of *in vitro* expression by cell-based flow cytometry, and identity of the encoded RNA sequence by RT-PCR, which are performed at Pfizer Ireland Pharmaceuticals, Grange Castle (referred to as 'Pfizer, Grange Castle'). Pfizer Ireland Pharmaceuticals also performs the compendial test for subvisible particles.

The compendial methods for appearance, osmometry, potentiometry, subvisible particles, endotoxins and sterility have been verified for testing the Tris/sucrose drug product at Pfizer, Puurs (the subvisible particles method was also verified at Pfizer, Grange Castle). The verification reports for sterility and endotoxin testing were provided, and confirm the suitability of the test methods for use with the Tris/sucrose drug product (absence of matrix interference and confirmation of verified dilution/maximum valid dilution (endotoxin method only)). The alternative rapid sterility method was validated for use with the Tris/sucrose drug product at Pfizer, Puurs. Two lots of 0.1 mg/mL Tris/sucrose drug product with a 2.25 mL fill (FE4394 and FC8273) and one lot of Tris/sucrose drug product with a 1.3 mL fill (FF9442)

were individually inoculated with a panel of seven organisms at NMT 100 CFU. The results of the study (positive results in the assay for spiked samples, negative results for controls) support the use of the rapid sterility test method with the Tris/sucrose drug product.

Method validation results from Pfizer, Puurs were provided for the non-compendial methods for container content (validated for intermediate precision using the highest and lowest fill volumes (2.25 mL and 0.4 mL respectively)) and container closure integrity (validated for precision, accuracy, bias and reproducibility, LOD and robustness; the validation included the use of vials with a 20 µm defect/hole as a positive control). The method validation support the suitability of these methods for their intended use at Pfizer, Puurs.

Based on the comparability of the PBS/sucrose and Tris/sucrose formulations, and since the critical operational parameters of the test methods validated for use with the PBS/sucrose drug product and the analyte being monitored are unchanged, the company applied an 'extension of validation' approach to the validation of the remaining non-compendial methods for use with the Tris/sucrose product. With this approach, a subset of assay characteristics were qualified to account for the minor modifications to the methods associated with the decrease in RNA concentration in the Tris/sucrose drug product, as detailed below:

- *Capillary Gel Electrophoresis (CGE)*: Performance of the CGE analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria for precision (repeatability and intermediate), linearity, specificity, and robustness (in plate stability). All results met acceptance criteria.
- *Cell-Based Flow Cytometry*: Performance of the cell-based flow cytometry analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria from the PBS/sucrose presentation for reproducibility, specificity, and detection limit. All results met acceptance criteria.
- *Dynamic Light Scattering*: Performance of the DLS analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria for precision (repeatability), linearity, specificity, and robustness (sample stability). All results met acceptance criteria.
- *Fluorescence*: Performance of the fluorescence analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria for precision (repeatability and intermediate), accuracy, specificity, linearity, range, and robustness (sample stability). All results met acceptance criteria.
- *High Performance Lipid Chromatography-Charged Aerosol Detection (HPLC-CAD)*: Performance of the HPLC-CAD analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria for precision (repeatability), specificity, linearity and robustness (in vial stability). All results met acceptance criteria.
- *Reverse Transcription Polymerase Chain Reaction (RT-PCR):* Performance of the RT-PCR analytical procedure on the Tris/sucrose presentation was verified against a set of defined acceptance criteria for specificity and for a subset of robustness studies (eg varying sample concentration, drug product extraction method, sample volume used for extraction, effect of freezing the extracted mRNA samples). All results met acceptance criteria.

The validations were performed at Pfizer Analytical Research and Development (ARD; the cell-based flow cytometry method was also co-validated at the Chesterfield, MO site (ARD-STL) and then transferred to Pfizer, Puurs (DLS, fluorescence, HPLC-CAD, CGE) and Pfizer, Grange Castle (RT-PCR, cell-based flow cytometry). The company has requested a waiver for providing evidence of method transfer to these sites on the basis that i) the only differences between the Tris/sucrose and the PBS/sucrose drug products are the buffer and RNA concentration, ii) the analytical procedures have been validated for both drug product formulations and demonstrated to be suitable for their intended use, and iii) the receiving laboratories have experience with and previously validated the analytical procedures for testing the PBS/sucrose drug product. Since the Pfizer, Puurs and Pfizer, Grange Castle

sites are already approved for the proposed testing, and on the basis of their cGMP status, this will be accepted by Medsafe.

3.2.P.5.4. Batch analyses

Batch analysis data has been provided for the batches shown in Table 16. All batches were manufactured at Pfizer, Puurs. The primary drug product lots were manufactured at 7 – 17% of the commercial scale and are representative of the commercial manufacturing process. The PPQ batches were manufacture at full commercial scale. All results met release acceptance criteria and showed suitable consistency across batches. Results for RNA integrity ranged from 64 to 72% (limit ≥ 58%), IVE from 76 to 91% (limit ≥ 30%), LNP size from 68 to 77 nm (limit 56 – 101 nm), and RNA encapsulation from 89 to 97% (limit ≥ 85%).

Table 16: Tris/sucrose drug product lots

Drug Product Lot #	Site of Manufacture	Date of Manufacture	Bulk Batch Size (grams RNA)	Purpose
EX0490	Pfizer, Puurs	18-Feb-2021	12	Primary Stability
EW4564	Pfizer, Puurs	25-Feb-2021	12	Primary Stability
EW4565	Pfizer, Puurs	04-Mar-2021	12	Primary Stability
FC8273	Pfizer, Puurs	04-May-2021	160	Process Performance Qualification - 2.25 mL Fill, 30 µg dose. Supportive Stability
FE4394	Pfizer, Puurs	01-Jun-2021	160	Process Performance Qualification - 2.25 mL Fill, 30 µg dose. Supportive Stability
FJ5682[a]	Pfizer, Puurs	06-Aug-2021	160	Process Performance Qualification - 2.25 mL Fill, 30 µg dose. Supportive Stability
FJ5683[a]	Pfizer, Puurs	06-Aug-2021		Process Performance Qualification – 2.25 mL Fill, 30 µg dose. Supportive Stability
FK5127[b]	Pfizer, Puurs	19-Aug-2021	160	Process Performance Qualification – 1.3 mL Fill, 10 µg dose. Supportive Stability
FK5128[b]				Process Performance Qualification, – 0.4 mL Fill, 3 µg dose Supportive Stability

a. Bulk drug product lot FJ5026 was split into two 80 g portions for separate filling as lots FJ5682 and FJ5683.
b. Bulk drug product lot FK1099 was split into 155 and 5 g portions for separate filling as lots FK5127 and FK5128

The company will be asked to provide batch release data/CoAs for the first three batches of vaccine intended for the New Zealand market, prior to their distribution.

RFI1 Q.18. Please commit to provide batch release data/CoAs for the first three batches of vaccine intended for the New Zealand market, prior to their distribution. Please also commit to provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.

EAI1 Q.18. A suitable commitment was provided. ***These will be noted as conditions of provisional approval of this NMA. Point resolved****.*

3.2.P.6. Reference standards or materials

The drug substance reference material detailed in Section 3.2.S.5.1 for the currently approved PBS/sucrose drug product is also used for the Tris/sucrose drug product for release and stability testing in the fluorescence assay (RNA encapsulation and RNA content). For test methods that require a drug product control, the PBS/sucrose drug product

control is utilised in the Tris/sucrose analytical procedure, as specificity studies have demonstrated that neither of the matrices interfere with method performance. A Tris/sucrose drug product control will be established in the future, as the PBS/sucrose drug product presentation is phased out.

The company also uses lipids purchased from Avanti as reference materials for release and stability testing of the drug product using the HPLC-CAD method (for measuring ALC-0315, ALC-0159, DSPC and cholesterol). The lipid reference materials are identical to those approved for use with the PBS/sucrose drug product.

As noted during the assessment of the NMA for the parent product, the introduction of any new reference standards, or changes to the procedure used to qualify the reference standards, must be notified to Medsafe via CMN.

3.2.P.7. Container closure system

The container closure components for the Tris/sucrose drug product are shown in Table 17.

Table 17: Container closure system

Component	Description
Vial	2 mL Type I borosilicate glass vial, 1.2 mm wall thickness,13 mm finish 2 mL Aluminosilicate glass vial, 13 mm finish
Vial Stopper	13 mm vial stopper composed of gray Datwyler FM457 elastomer (bromobutyl rubber) coated with silicone oil[a]
Vial Seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap

a. Silicone oil lubricant complies with USP/National Formulary (NF) requirements for Dimethicone, Ph. Eur. requirements for Dimethicone, Ph. Eur. requirements for Silicone Oil Used as a Lubricant, Yakuki 327 Silicone Oil for Medical Device Lubricant (I)

The vials are as described for the parent PBS/sucrose drug product with the following exceptions:

- the wall thickness of the 2 mL Type 1 borosilicate glass vials (supplied by Schott) is 1.2 mm rather than 0.85 mm as approved originally for the parent product (the 1.2 mm vials were introduced for the PBS/sucrose product manufactured at Pfizer Puurs in CMN ref date 25/10/2021, ID: 115197)
- a 2 mL (nominal fill volume) aluminosilicate glass vial from Corning with a wall thickness of 0.85 mm is also introduced for packing the Tris/sucrose product
    - The Corning website describes the aluminosilicate glass vials as 10 times stronger than conventional borosilicate vials.

Vials from all suppliers are considered equivalent in terms of processability, container closure integrity and drug product interaction. Both vial types met all safety considerations and demonstrated robustness to aggressive freezing parameters with improved resistance to glass breakage, which is at increased risk due to the greater fill volume for the Tris/sucrose drug product compared to the PBS/sucrose drug product (1.3 mL and 2.25 mL versus 0.45 mL respectively). The vials meet USP <660>, Ph. Eur. 3.2.1 hydrolytic resistance and JP 7.01 soluble alkali test requirements for glass containers. The vials are sterilised and depyrogenated by dry heat by the drug product manufacturer. During the NMA for the parent PBS/sucrose product the company confirmed that the maximum volumetric capacity of the 2 mL vial with the stopper in place is 3.4 mL. Since the aluminosilicate and borosilicate vials have the same dimensions, it seems reasonable to assume the maximum 3.4 mL volumetric capacity would also apply to the borosilicate vials. The maximum volume of the prepared product will be 2.6 mL (1.3 mL fill of the 10 µg vial + 1.3 mL of diluent = 2.6 mL; the 30 µg vial is filled at 2.25 mL), which is within the 3.4 mL vial capacity.

The stoppers (supplied by Datwyler) and vial seals (supplied by West and Datwyler) for use with the Tris/sucrose drug product are the same as those used with the PBS/sucrose drug

product. The different strengths/presentations are distinguished by the colour of the flip-off cap as follows:

Purple: 30 µg/0.3 mL dose presentation of the 0.5 mg/mL PBS/sucrose product
Grey: 30 µg/0.3 mL dose presentation of the 0.1 mg/mL Tris/sucrose product
Orange: 10 µg/0.2 mL dose presentation of the 0.1 mg/mL Tris/sucrose product.

The dossier includes suitable schematic drawings of the container closure components and in-house specifications for quality control testing of the components on receipt at the drug product manufacturing site. Supplier CoAs for the new container closure components introduced with this NMA (namely the aluminosilicate glass vials) could not be located and are requested to confirm the stated compendial compliance.

RFI1 Q.19. Please provide representative supplier certificates of analysis for the new aluminosilicate glass vials. These should include supplier statements regarding compendial compliance.

EAI1 Q.19. A representative supplier certificate of analysis for the Corning Valor aluminosilicate glass vials was provided, which confirms the stated compendial compliance (and Type I glass). ***Point resolved****.*

3.2.P.8. Stability

3.2.P.8.1. Stability summary and conclusion

The company is proposing an initial 6 month shelf-life for the Tris/sucrose drug product, when stored at the recommended storage condition of -90°C to -60°C. The current approved shelf-life for the parent PBS/sucrose product at this storage temperature is 9 months. The data sheet states to store the product in the original package in order to protect from light.

The company is also proposing an allowable short term storage at 5 ± 3°C for up to 10 weeks, within the 6 month shelf-life, based on the available stability data for Tris/sucrose product stored at this temperature and the thermal cycling studies.

The proposed shelf life is based on the available stability data for the PBS/sucrose drug product, the 24 weeks development stability data described in section 3.2.P.2.2, and up to three months stability data for the Tris/sucrose primary drug product lots manufactured at Pfizer, Puurs. The primary stability lots were manufactured at approximately 7 – 17% of the proposed commercial scale.

The following stability data has been provided for the Tris/sucrose drug product:

- *Long-term (-90°C to -60°C)*: T_0 for two PPQ lots (FE4394, FC8273), up to 3 months for three primary stability lots (EX0490, EW4564, EW4565; the study will continue for 24 months)
- Additional (-50 ± 5°C): one month for three primary stability lots (EX0490, EW4564, EW4565; the study is complete)
- *Additional (-20 ± 5°C)*: one month for one PPQ lot (FC8273), T_0 for one PPQ lot (FE4394), up to 3 months for three primary stability lots (EX0490, EW4564, EW4565; the study will continue for 24 months)
- *Additional (5 ± 3°C):* one month for one PPQ lot (FC8273), T_0 for one PPQ lot (FE4394), up to 3 months for three primary stability lots (EX0490, EW4564, EW4565; the study will continue for 6 – 12 months)
- *Thermal stress (25 ± 2°C/60 ± 5% RH and 30 ± 2°C/60 ± 5% RH):* one month for two primary stability lots (EX0490, EW4564; the study will continue for 1 month)

In addition, thermal cycling and photostability data has been provided to support the in use shelf-life of the drug product.

The primary stability lots (EX4090, EW4564, EW4565) were manufactured at Pfizer, Puurs at approximately 10 – 17% of the proposed commercial batch scale and are representative of the commercial manufacturing process. One lot (EX4090) was filled at 0.48 mL (to provide a single 30 µg dose in 0.3 mL injection volume) and the others at 2.25 mL volume (the volume filled for the 30 µg dose/0.3 mL presentation; considered worst case for freezing). The PPQ lots in the stability study (FC8273 (2.25 mL fill), FE4393 (2.25 mL fill), FJ5682 (2.25 mL fill), FK5127 (1.3 mL fill), FK5128 (0.4 mL fill)) were manufactured at Pfizer, Puurs at 1600 L commercial scale. The PPQ lots bracket the fill volumes and vial types proposed for commercial manufacture, though stability data is currently only available for product in the borosilicate vials filled with 2.25 mL.

On the basis of the demonstrated analytical comparability of the Tris/sucrose and PBS/sucrose products, Medsafe considers that the existing stability data for the PBS/sucrose drug product, combined with the available stability data for the Tris/sucrose drug product (from development, primary stability and PPQ lots) support the proposed 6 month shelf-life at -90°C to -60°C, and 10 weeks storage at 2 – 8°C at the point of use, within the 6 month shelf-life.

Section 3.2.P.2.2 of the dossier states that the Tris/sucrose formulation was developed to provide a drug product with an enhanced stability profile compared to the PBS/sucrose drug product, which requires storage at ultralow temperatures (-90°C to -60°C) and has limited stability at higher temperatures. While an extension in the shelf-life for the thawed product is introduced with the new formulation, the proposed storage conditions still require storage of the frozen vaccine at ultralow temperatures, even though the parent PBS/sucrose vaccine is currently approved for storage at -20°C for 2 weeks (unopened). A comparison of the PBS/sucrose and Tris/sucrose storage conditions and shelf-lives is shown below. With the exception of the bottom row of the table, all shelf-lives relate to the unopened vaccine vials.

Table 18: Comparison of storage conditions/shelf-lives for the PBS/sucrose and Tris/sucrose formulations

Storage condition	Shelf-life for PBS/sucrose formulation	Shelf-life for Tris/sucrose formulation
-90°C to -60°C *Ultra Low Temperature Freezer*	9 months	6 months
-25°C to -15°C *Freezer*	Up to 2 weeks	Not proposed
2°C to 8°C *Refrigerator*	Up to 1 month	10 weeks
2°C to 30°C	2 hours	~~24 hours~~ 12 hours *(refer RFI2 Q.3)*
	6 hours following dilution	12 hours following dilution/vial puncture

The evaluator notes that Sections 6.3 and 6.4 of the proposed data sheet state that the Tris/sucrose vaccine may be received frozen at -90°C to -60°C or at -25°C to -15°C, which implies the product can be stored at -20°C; however, the company is not proposing a shelf-life at this storage temperature. On the basis of the demonstrated comparability of the Tris/sucrose and PBS/sucrose formulations, and since the available stability data for the primary stability lots supports the storage of the Tris/sucrose formulation for up to 10 weeks

at -20 ± 5°C (within the 6-month shelf life) the company will be asked to register a storage condition at this temperature, to facilitate ease of handling and storage at the point of use.

RFI1 Q.20. Section 6.4 of the data sheet states that the vaccine may be received frozen at -90°C to -60°C or at -25°C to -15°C, which implies the product can be stored at -20°C; however, a shelf-life at this storage temperature is not proposed with this NMA. The parent PBS/sucrose vaccine is currently approved for storage at -20°C for 2 weeks (unopened). On the basis of the demonstrated comparability of the Tris/sucrose and PBS/sucrose formulations, and since the available stability data for the primary stability lots supports the storage of the Tris/sucrose formulation for up to 10 weeks at -20 ± 5°C (within the 6 month shelf life), please consider introducing an allowable storage condition at -25°C to -15°C for the unopened Tris/sucrose vials, to facilitate ease of handling and storage at the point of use.

*EAI1 Q.20. The company responded that the stability data from the cycling studies at -20 ± 5°C followed by storage at 2 – 8°C demonstrated that the vaccine is not stable to this combination of storage conditions for the full point of use storage period (defined as 10 weeks at 2 – 8°C). Specifically, drug product stored at -20 ± 5°C for 1 month followed by storage at 2 – 8°C for 2, 3 and 4 months failed acceptance criteria after 4 months (1 month at -20 ± 5°C and 3 months at 2 – 8°C) for LNP polydispersity for all three lots tested and failed in vitro expression (IVE) for one of the three lots. Storage for 2 and 3 months at -20°C followed by storage at 2 – 8°C for 2, 3 and 4 months showed increasing LNP size and polydispersity and decreasing RNA encapsulation, RNA integrity and IVE levels, including not meeting the acceptance criteria for LNP size, LNP polydispersity and IVE levels at various timepoints. Based on the available data, the company does not consider it appropriate to allow storage of unopened vials at -20 ± 5°C. The allowed 10 weeks storage at 2 – 8°C facilitates ease of handling and storage at the point of use and was therefore selected as the most appropriate storage condition. This will be accepted. Limited handling and shipment at -20 ± 5°C within Pfizer/BioNTech control is allowed and limited to ≤ 48 hours (refer Section 3.2.P.3.3 of this report). Since the company is not proposing a -20°C shelf-life outside of the company's control (ie for distributors/healthcare professionals), the company will be asked to remove reference to the product being received at -25°C to -15°C in section 6.3 of the data sheet, to minimise the potential for confusion. This is addressed in RFI2 Q.3. **Point resolved**.*

3.2.P.8.2. Post-approval stability protocol and stability commitment

The primary stability studies are ongoing and will continue to 24 months. Post-approval, a minimum of one lot of Tris/sucrose drug product will be enrolled in the commercial stability program at the long term storage condition of -90 to -60°C each year that drug product is manufactured. The post-approval commercial stability protocol is shown in Table 19.

Table 19: Post-approval commercial stability protocol for drug product stored at -90 to -60°C

Analytical Procedure/ Quality Attribute		Test Intervals (Months)[a]
Appearance (Visible)		0, 6, 12, 18, 24
Appearance (Visible Particulates)		
pH		
Subvisible Particulate Matter		
Dynamic Light Scattering (DLS)	LNP Size	
	LNP Polydispersity	
Fluorescense Assay	RNA Encapsulation	
	RNA Content	
HPLC-CAD	ALC-0315 Content	
	ALC-0159 Content	
	DSPC Content	
	Cholesterol Content	
Cell-based Flow Cytometry	In Vitro Expression	
Capillary Gel Electrophoresis	RNA Integrity	
Container Closure Integrity Test		Annually through end of shelf life
Sterility		0, End of shelf life
Endotoxin		

a. Additional test intervals may be included for the purpose of extending expiry.
LNP = Lipid Nanoparticle

The sponsor has signed the post-approval stability commitment in the NMA form to complete the ongoing stability studies and inform Medsafe of any out-of-specification results, or data indicating that batches may be out of specification before the shelf life is reached.

3.2.P.8.3. Stability data

Long-term, accelerated/additional, stressed storage conditions

The up to three months stability results for the three primary stability lots stored at -90°C to -60°C comply with acceptance criteria with no obvious trends.

For storage at accelerated/additional storage conditions (-50 ± 5°C, -20 ± 5°C, 5 ± 3°C), the 1 to 3 months stability data met acceptance criteria for all parameters tested. A small increase in LNP size over time is evident in some of the primary stability batches stored at -20 ± 5°C or 5 ± 3°C (as seen during the development stability studies). In vitro expression and RNA integrity also decreased over time in batches stored at 5 ± 3°C.

For storage at stressed conditions (to support short term temperature excursions), the 1 month stability data were out of specification for LNP polydispersity, *in vitro* expression and RNA integrity. The data indicate that the Tris/sucrose finished product has limited stability at these temperatures (the currently available results demonstrate stability through 2 weeks storage at 25 ± 2°C and 3 days storage 30 ± 2°C).

The PPQ batches were placed on stability between June and August 2021, so additional stability data should now be available. This is requested.

RFI1 Q.21. Please provide the updated stability data that should now be available for the primary stability and PPQ Tris/sucrose drug product lots in the ongoing stability studies.

EAI1 Q.21. Updated stability was stated to have been provided with the response, which the company states supports a 9 month expiry date. The evaluator could not locate the updated stability data in the response documentation, this is addressed in RFI2 Q.5. The company considers a 9 month expiry date is supported by i) up to 6 months stability data for the three primary (pilot scale) drug product lots stored at -90 to -60°C, as all results met acceptance criteria (data not provided), ii) the established 9 month shelf-life for the PBS/sucrose drug product, and iii) up to 24 weeks Tris/sucrose development stability data. The stability data from the three primary drug product lots also support storage at 2 – 8°C for 3 months, allowing for 10 weeks storage at 2 – 8°C at the point of use. From the company response it

appears they are seeking an extension in the shelf-life of the unopened drug product to 9 months, although the updated data sheet still references a 6 month shelf-life, and it appears that only 6 months has been approved in the EU and USA based on the product information documents currently available for these countries. Since only 3 months stability data has currently been provided for the primary scale batches, and release data for the PPQ batches, Medsafe will only approve a 6 month shelf-life for the unopened drug product. The company will need to submit a CMN post-approval, along with appropriate supportive data, for an extension of the shelf-life to 9 months.

RFI2 Q.5 ***The response to RFI1 Q.21 cites updated stability data included with the response; however, this could not be located by Medsafe. Please provide the updated stability data. Please note that Medsafe will only be approving a 6 month shelf life, when product is unopened and stored at -90 to -60°C. This is due to the limited stability data available for commercial scale batches with the new formulation. If the company wishes to extend the long term storage shelf life, then a CMN will be required post-approval along with appropriate supportive data.***

EAI2 Q.5. *The company noted the 6 month shelf-life for unopened product stored at -90 to -60°C, and confirmed a CMN will be submitted post-approval to extend the shelf-life. The additional stability data cited in the response to RFI1 Q.21 was not provided. Currently, only three months long-term stability data has been provided for the primary stability batches (manufactured at 7 – 17% of the commercial scale), and release testing results for the PPQ batches. The primary stability batches were placed on stability in March and April 2021, so up to 6 months long-term data should now be available. [redacted], Medsafe will also approve a 6 month shelf-life for the drug product.* ***Nevertheless, provision of the updated stability data will be noted as a condition of approval of this NMA, with a deadline of February 2022****, at which point 9 months long-term data should be available for the primary stability batches, and 6 months long-term data for the PPQ batches.* ***Point resolved****.*

Photostability

Results from photostability testing (as per ICH Q1B) of one Tris/sucrose drug product lot (EW4564) were provided. Small decreases in IVE and RNA integrity were observed for samples exposed to light as compared to those protected from light; however, all results remained within acceptance criteria. The results demonstrate that the Tris/sucrose drug product does not need to be protected from light. The data sheet states to store the product in the original package to protect from light, but notes that once thawed, the vials can be handled in room light conditions.

Thermal stress and cycling

A total of five thermal cycling studies are being performed. The first three cycling studies are evaluating storage at -20°C for 1 month, 2 months and 3 months, respectively, followed by storage at 2 – 8°C for the remainder of the study. This represents the worst case frozen condition, followed by point of use storage at 2 – 8°C.

- Thermal cycling 1: -20°C for 1 month then 2 – 8°C for 6 months (3 months data available for three primary stability lots)

- Thermal cycling 2: -20°C for 2 month then 2 – 8°C for 6 months (2 months data available for three primary stability lots)
- Thermal cycling 3: -20°C for 3 month then 2 – 8°C for 6 months (3 months data available for three primary stability lots)
- Thermal cycling 4: -90°C to -60°C for 1 month, then -50 ± 5°C for 1 month, then 5 cycles of 1 month each at -20 ± 5°C and -90°C to -60°C (2 months data available for three primary stability lots)
- Thermal cycling 5: Five cycles each consisting of 4 days at -20 ± 5°C and 1 day at 25 ± 2°C/60 ± 5% RH, then storage at -50 ± 5°C until 2 months, then storage at -90 to -60°C for 24 months (data from 5 cycles available for three primary stability lots)

All available results from the thermal cycling studies have met acceptance criteria; however, the evaluator notes that the available results show an increase in LNP size and decrease in IVE following the shift from storage at -20°C to storage at 2 – 8°C. The results to date support: i) -20°C storage for three months (Cycling study 3), ii) cycling at -20°C for 1 month followed by 2 – 8°C for 2 months (Cycling study 1), and iii) five cycles at -20°C for 4 days followed by 25°C for 1 day (Cycling study 5). All other results are pending.

Stability in use

The in-use period for the thawed vials is 10 weeks at 2 – 8°C, within the 6 month shelf-life.

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 to 30°C after first opening (puncture) or dilution in sodium chloride 9 mg/mL (0.9%) solution for injection (see section 3.2.P.2.6 of this report). From a microbiological point of view (since the product does not contain a preservative), the product should be used immediately.

Module 3.2.A.1. Facilities and Equipment

The sites involved in the manufacture of the 0.1 mg/mL Tris/sucrose presentations of Comirnaty are the same as those currently approved for the parent 0.5 mg/mL PBS/sucrose vaccine. Section 3.2.A.1 confirms that the Tris/sucrose and PBS/sucrose products are manufactured in the same buildings at Pfizer Puurs. The precautions taken to minimise cross-contamination between products manufactured at Pfizer Puurs are as described for the parent vaccine, and can be considered acceptable on the basis of the cGMP for the site.

Module 3.2.A.2. Adventitious Agents Safety Evaluation

The drug substance used to manufacture the Tris/sucrose drug product is identical to that used for the currently approved PBS/sucrose drug product. The only differences between the two formulations are the change in buffers, and the strength. Adequate testing for bioburden, endotoxins and sterility are included at appropriate stages of the manufacturing process of the lower strength drug product. The specifications for the new, non-compendial Tris hydrochloride excipient include testing for microbial contamination as per Ph. Eur. 2.6.12. The Tris base is compendial. The use of the new excipients is not considered to change the safety profile of the product with regards to the risk for the presence of viral and non-viral adventitious agents. Reference is therefore made to the Module 3.2.A.2 approved for the parent PBS/sucrose drug product.

Module 3.2.R.5. N-Nitrosamines Risk Assessment

The company has conducted an assessment of the potential nitrosamine risk factors associated with the drug substance, drug product and primary packaging components, in accordance with EMA/409815/2020. The assessment was initially performed for the PBS/sucrose formulation, and has been updated for the Tris/sucrose formulation. The main findings of this assessment are summarised below.

i) Nitrosamines that could potentially be derived from large biotherapeutic products are considered very unlikely to be associated with the potent toxicity that has been seen with some small molecule nitrosamines, due to a lack of the cytochrome P450 (CYP) metabolic activation required for formation of a reactive diazonium species. The active site of CYP enzymes is buried within the CYP protein, so access is restricted to small molecules. In addition, CYP enzymes are on the inside face of the endoplasmic reticulum inside the cell, further limiting the access of a biotherapeutic. The drug substance is a mRNA that contains over 4,000 bases and has a molecular weight of over 1,000,000 g/mol so is not a suitable substrate for CYP enzymes. The inability of the drug substance to undergo metabolic activations supports the conclusion that it is not susceptible to the formation of a nitrosamine.

ii) No nitrite sources or small molecule amine compounds are used in the drug substance manufacturing process.

iii) The Tris/sucrose drug product has also been assessed for potential nitrosamine risks associated with small molecule amines, and the amine functionality within the active substance molecule itself. The formation of a nitrosamine requires the presence of both a vulnerable, reactive amine (particularly secondary amines) and a nitrosating agent. In addition, nitrosamine formation occurs in an acidic environment, whereas the vaccine is formulated at pH 6.9 – 7.9. The drug product is therefore considered to be at low risk for nitrosamine formation even though some excipients carry an amine function such as distearoylphosphatidylcholine (a quaternary ammonium salt), ALC-0315 (a component of the lipid nanoparticle with a tertiary amine present in the structure) and tromethamine (Tris) and Tris (hydroxymethyl) aminomethane hydrochloride (a primary amine), and other excipients, e.g. sucrose, might contain low levels (sub-ppm) of nitrate.

iv) The drug product container closure system is a vial closed with a bromobutyl rubber stopper (coated with silicone oil). Neither the glass nor the stopper are considered to be at risk for the presence of nitrosamines.

In summary, the risk assessment did not identify a risk for nitrosamine formation in the drug substance, drug product or primary packaging processes. In addition, from a toxicological perspective, there is no risk of the BNT162b2 vaccine molecule itself forming a nitrosamine requiring cohort of concern control.

Quality Assessment Conclusion

Pfizer/BioNTech have developed a new drug product formulation using tromethamine buffer instead of phosphate buffered saline (PBS) buffer, to provide a vaccine with an improved stability profile and greater ease of use at administration sites. The new formulation, referred to as the ‘Tris/sucrose’ formulation, has a lower strength (0.1 mg/mL) and is presented as a suspension for injection and a concentrate for suspension for injection, which differ in fill volume and the requirement for dilution prior to administration. Both presentations are manufactured and tested at sites currently approved for the production of the parent PBS/sucrose vaccine (original formulation).

The formulation development studies performed by the company suitably justify the chosen formulation. Analytical comparability data demonstrated the comparability of the Tris/sucrose drug product lots to the currently approved PBS/sucrose drug product (original formulation).

The manufacturing process for the Tris/sucrose drug product is the same as that used for the production of the PBS/sucrose drug product, with the exception of the introduction of minor process changes for buffer exchange, concentration adjustment and fill volume. The proposed manufacturing process was validated at the maximum commercial scale and demonstrated that the drug product manufacturing site is able to consistently produce Tris/sucrose drug product that meets required quality control acceptance criteria. The finished product specifications for the Tris/sucrose drug product are identical to those currently approved for the PBS/sucrose drug product, with the exception of the acceptance criteria for osmolality (to reflect the different characteristics of PBS versus Tris buffer), and for the six content assays (RNA, ALC-0315, ALC-0159, DSPC, cholesterol, and vial content) as a consequence of the five-fold difference in RNA concentration and different fill volumes. The currently available stability data for the Tris/sucrose drug product support storage of the drug product at -90 to -60°C for up to 6 months, and 10 weeks at 2 – 8°C at the point of use. The 6 month shelf-life for the unopened drug product is shorter than that currently approved for the parent vaccine, but this is expected to be extended once further stability data is available. The 10 week shelf-life at 2 – 8°C is longer than currently approved for the parent vaccine (1 month refrigerated shelf-life), which will facilitate ease of handling and storage at the point of use.

Pending satisfactory resolution of the questions raised in the initial evaluation, the information provided to support the manufacture and quality control of new formulation, strength and presentations of Comirnaty is acceptable from a quality perspective. The company has committed to reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. This is one of the recommended conditions of approval. Additional conditions of provisional approval are listed at the end of this report.

Module 5. Safety and Efficacy

This is a novel medicine. The safety and efficacy of this medicine has been established in a pivotal clinical trial, Study C4591007. The evaluation of this trial is reported within the separate clinical evaluation report.

Clinical study C4591007 utilised drug product lots EE3813 (also denoted lot BCV40820-P) and ER5832. Both lots were manufactured using the same formulation as the currently approved PBS/sucrose product (0.5 mg/mL) but filled at 0.2 mL per vial. In preparation for administration at the 10 µg per dose level, the drug product was diluted with 1.8 mL of 0.9% sodium chloride (normal saline) to a concentration of 0.05 mg/mL, and 0.2 mL (10 µg) was then administered. This is the same strength (concentration and dose volume) as the Tris/sucrose product proposed for administration to children aged 5 to 11 years old. The company justifies the absence of clinical trial data for the Tris/sucrose formulation on the basis of the demonstrated analytical comparability of the product to the PBS/sucrose formulation used in study C4591007. In response to a request from Medsafe, the company also provided a justification for why the current PBS/sucrose parent vaccine cannot be administered to children aged 5 to 11 years old, even though this is the formulation that was used in the clinical trial of this age group. Both justifications are detailed below.

Justification for the absence of clinical trial data for the Tris/sucrose formulation

As discussed earlier in this report, the introduction of the proposed Tris/sucrose formulation is supported by the demonstrated analytical comparability of six lots of Tris/sucrose drug product (three primary drug product stability lots and three PPQ drug product lots) against pre-determined comparability acceptance criteria derived from 94 historic PBS/sucrose drug product lots (the comparability acceptance ranges represent the minimum and maximum measured values of the 94 drug product lots; refer section 3.2.P.2.3 of this report).

To demonstrate that the PBS/sucrose drug product used in the clinical studies is comparable to the Tris/sucrose drug product intended for approval, the company has also compared the results of analytical testing of the clinical drug product lots EE3813 and ER5832 against the six Tris/sucrose drug product lots included in the comparability assessment. With the exception of the parameters for osmolality, RNA content and lipid content, which due to the different formulations and target RNA and lipid concentrations in the PBS/sucrose drug product are not applicable to the comparability assessment, all results fell within the comparability acceptance criteria ranges. Of note, IVE results for the Tris/sucrose batches are higher (76 – 89%) than the clinical batch (one clinical batch was ‘65% the other was not tested for this parameter) and RNA integrity was similar between the batches (76 – 89% for the Tris/sucrose batches; 63 and 74% for the clinical batches).

On the basis of i) the relatively minor nature of the change in formulation (change in buffer, with no change in pH), ii) the proposed product and the product used in the clinical trial have the same dose form and route of administration, and iii) the demonstrated analytical comparability of the Tris/sucrose and PBS/sucrose formulations (both are controlled to the same specifications with different acceptance criteria relevant to the proposed formulation and strength); the Tris/sucrose formulated drug product can be considered suitably comparable to the drug product lots EE3183 and ER5832 used in the clinical study. In alignment with the EMA and FDA, the absence of clinical bridging and bioequivalence data for the Tris/sucrose drug product will not be pursued by Medsafe.

Table 1. Comparability Data for BNT162b2 Tris/Sucrose and Clinical Drug Product Lots

Quality Attribute	Analytical Procedure	PBS/Sucrose Formulation Min-Max[a]	Comparability Acceptance Criteria	Tris/Sucrose Lot Range: EX0490 EW4564 EW4565 FC8273 FE4394 FJ5682	EE3813	ER5832
Appearance	Appearance (Visual)	Meets Specification	White to off-white suspension	White to off-white suspension	White Suspension	White to off-white suspension
Appearance (visible particulates)	Appearance (Particles)	Meets Specification	May contain white to off-white opaque, amorphous particles	Meets Test	No particles observed	Meets
Subvisible particles	Subvisible particulate matter	0 – 53	Particles ≥10 µm: ≤6000 per container	15 - 64	2	140
		1 – 637	Particles ≥ 25 µm: ≤600 per container	0 – 3	1	30
pH	Potentiometry	6.9 – 7.6	6.9 – 7.9	7.3 – 7.5	7.2	7.2
Osmolality (mOsmol/kg)	Osmometry	N/A[b]	240 – 400	353 - 373	369	342
LNP size (nm)	Dynamic light scattering (DLS)	66 - 91[c]	65 - 93[c]	68 – 77[c]	65	69
LNP polydispersity	Dynamic light scattering (DLS)	0.1 – 0.2	≤ 0.3	0.1 – 0.2	0.1	0.1
RNA encapsulation (%)	Fluorescence assay	86 – 98	≥ 86	89 – 97	93	95
RNA content (µg/mL)	Fluorescence assay	N/A[b]	0.074 – 0.126	0.100 – 0.119	0.50	0.43
ALC-0315 content (mg/mL)	HPLC-CAD	N/A[b]	0.90 – 1.85	1.17 – 1.45	6.19	6.63
ALC-0159 content (mg/mL)	HPLC-CAD	N/A[b]	0.11 – 0.24	0.13 – 0.17	0.72	0.85
DSPC content (mg/mL)	HPLC-CAD	N/A[b]	0.18 – 0.41	0.26 – 0.31	1.23	1.37
Cholesterol content (mg/mL)	HPLC-CAD	N/A[b]	0.36 – 0.78	0.51 – 0.62	2.49	2.82

Quality Attribute	Analytical Procedure	PBS/Sucrose Formulation Min-Max[a]	Comparability Acceptance Criteria	Tris/Sucrose Lot Range: EX0490 EW4564 EW4565 FC8273 FE4394 FJ5682	EE3813	ER5832
Lipid identities	HPLC-CAD	Meets Specification	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)	Complies	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
Identity of encoded RNA sequence	RT-PCR	Meets Specification	Identity confirmed	Identity Confirmed	Complies	Confirmed
In vitro expression (% cells positive)	Cell-based flow cytometry	39 – 95	≥ 39%	76 – 89	Not tested	65
RNA integrity (%)	Capillary gel electrophoresis	55 – 86	≥ 55	64 – 72	63	74

a. Minimum and maximum measured values derived from 94 drug product lots, which were used to establish the pre-determined comparability acceptance criteria.

b. Due to the different formulation and target RNA and lipid concentration, the PBS/Sucrose drug product ranges are not applicable (N/A) to the comparability assessment and therefore the results for the clinical batches are not expected to be comparable to the Tris/Sucrose range.

c. Corrected LNP size range accounts for updated method viscosity value from 1.0200 cP to 0.91 cP, consistent with the Tris/Sucrose drug product test method. LNP size for PBS/Sucrose lots EE3813 and ER5832 were calculated prior to the viscosity value update in the test method.

Abbreviations: LNP = Lipid nanoparticles; CAD = Charged aerosol detector; RT-PCR = Reverse transcription polymerase chain reaction; ddPCR = Droplet digital PCR; RP-HPLC = Reversed-phase high performance liquid chromatography

Justification for why the currently registered PBS/sucrose formulation (30 micrograms/0.3 mL) cannot be used for children aged 5 to 11 years

In a teleconference with Pfizer on 8/11/2021, Medsafe asked the company to provide a written justification for why the currently registered parent vaccine cannot be administered to children aged 5 to < 12 years of age, given that this is the formulation that was used in the paediatric clinical trial. In an email received 11/11/2021, the company responded as follows:

'As described in our 8-Nov-21 teleconference, Pfizer cannot support manipulation of the current PBS/Sucrose formulation for administration to children aged 5 to <12 years. The PBS/Sucrose formulation was used to administer COMIRNATY to children aged 5 to <12 years in Study C4591007, however it is important to clarify the fill volume used in the study

was a specific clinical trial fill volume of 0.2 mL to administer the correct paediatric dose. The commercially manufactured 0.45 mL fill volume was not used in the study.

The current PBS/Sucrose 30 microgram/0.3 mL dose vial does not have enough space to add the additional diluent necessary to obtain the required dosage for the injection volume. Furthermore, the paediatric injection volume of such manipulation at 0.1 mL is exceedingly difficult to accurately dose, is suboptimal for intramuscular injections and risks introducing errors in dosing and administration.

The new Tris/Sucrose formulation (10 microgram/0.2 mL and 30 microgram/0.3 mL presentations) is based on the current PBS/Sucrose formulation except that:

• The formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride or potassium chloride while maintaining the same target pH.

• The RNA concentration is lower, and

• The drug product does not require dilution for administration of the 30 microgram dose.

There are no changes to the drug substance, or the lipids used to produce the lipid nanoparticles (LNPs) that are formulated to produce the bulk drug product. Pfizer maintains this is a minor buffer change to the formulation for which clinical bridging and bioequivalence data is not required. The identical application, with no bridging data, submitted to the EMA and FDA has been approved for both strengths by the FDA (emergency use authorisation) and by the EMA for the 30 microgram/0.3 mL dose. The 10 microgram/0.2 mL dose is still under evaluation by the EMA.'

Although it is considered that the company could have registered an alternative fill volume (eg 0.2 mL) to enable dilution of the parent vaccine to the required strength for administration of the 10 µg dose, this is outside the scope of the current NMA. Medsafe acknowledges that the Tris/sucrose formulation was developed to provide a drug product with an enhanced stability profile, which will ultimately facilitate greater ease of handling by healthcare professionals (pending the response to RFI1 Q.20). It is also noted that the proposed Tris/sucrose drug product will eventually replace the current PBS/sucrose formulation in the New Zealand market. An expected date for when this will occur has not been disclosed by Pfizer; however, the evaluator notes that the [redacted], so it would seem reasonable to assume a similar time-frame would apply in New Zealand.

Questions raised in the initial evaluation

RFI1 Q.1. Please provide the questions from the EMA and TGA (and company responses) for the introduction of the Tris/sucrose formulations of Comirnaty. Please also provide the EMA/CHMP assessment report for the 10 microgram/dose presentation of the Tris/sucrose formulation, when available.

RFI1 Q.2. To minimise the potential for administration errors due to confusion over the different formulations and presentations of Comirnaty (since the same trade name is proposed and all are likely to be in the market at the same time) the company is asked to include the following identifiers in the product name in the data sheet, CMI and all communications with New Zealand healthcare professionals:
COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose)
COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)
COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose).
The identifiers have been added to the therapeutic product database reports (TPDRs).

RFI1 Q.3. Please confirm the EU vial labels for both the 30 microgram/dose and 10 microgram/dose presentations are printed with the expiry date and batch details. Please also clarify the purpose of the green box on the EU vial labels. For those labels where the green box is obscuring text (eg PAA181046, PAA173907), please confirm exactly what text is under the graphic.

RFI1 Q.4. Since the 0.1 mg/mL strengths of the Tris/sucrose formulation of Comirnaty will be supplied in international labelling that does not comply fully with New Zealand medicines regulations, the company must provide a 'Dear Healthcare Professional Letter' to accompany release of the products. Information included in the letter should address (but is not limited to) the following:
i) An overview of the new formulation, strength, dose forms and indicated age ranges, with reference to the vial cap colour for dose verification.
ii) A clear description of the proposed shelf-lives and storage conditions for the unopened, opened/diluted products (for example, some labels state that the product should be stored at 2 – 8°C upon receipt but the data sheet states the product can be stored at either -90°C to -60°C or 2 – 8°C upon receipt).
iii) A description of the international labelling that will be used for distribution of the vaccine in New Zealand. The inclusion of colour photograph(s)/artwork(s) of the labels in the letter is encouraged. If more than one version of the labels for each strength/presentation will be used concurrently, differences between the labels should be identified. Of particular note are the vial label for the 30 microgram/dose presentation identified as PAA173908, and the tray label identified as PAA173907, which will need to be clearly described to distinguish them from the current approved labels for the parent (PBS/sucrose) vaccine.
iv) Differences in dose form description (eg dispersion versus suspension), product name (Comirnaty versus Pfizer-BioNTech COVID-19 vaccine) and in use shelf-life (eg 6 hours versus the proposed 12 hours) on the applicable international labels should also be identified.
Please provide (or commit to do so prior to launch of the vaccine to the New Zealand market), a draft DHPL that addresses the above concerns.

RFI1 Q.5. To ensure the safe use of the medicine and minimise the risk for administration errors, the company is asked to prepare separate data sheets for the 10 micrograms/dose and 30 micrograms/dose presentations of the new formulation of Comirnaty. The individual data

sheets should use the naming terminology suggested in RFI1 Q.2, incorporate the changes requested in RFI1 Q.6 and be based on the respective EU SPC documents.

RFI1 Q.6. Please make the following changes to the proposed data sheet:
i) Replace references to the indicated age range of the 10 micrograms/dose presentation from '5 to < 12 years' with '5 to 11 years'.
ii) Section 1: Include 'dose' in the bracketed information so it reads '(30 micrograms/0.3 mL dose)' …'(10 micrograms/0.2 mL dose)'.
iii) Section 2: Remove the table, and align the information in this section with that in the respective SPC document.
iv) Section 2: Include the statement 'Do not dilute prior to use.' next to 'This is a multidose vial' in the first paragraph under the table.
v) Section 4.1: Since the 10 micrograms/0.2 mL dose presentation is restricted for use to individuals aged 5 to 11 years, and the 30 micrograms/0.3 mL presentation is restricted for use in individuals aged over 12 years, please amend the indication to reflect the indicated age ranges of each presentation of Comirnaty .
vi) Section 4.2: Add the statement from the EU SPC 'Comirnaty for children 5 to 11 years of age cannot be used for individuals 12 years of age and older'.
vii) Section 4.2 The proposed data sheet states 'Doses of COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] (30 micrograms/dose) and COMIRNATY COVID-19 VACCINE 0.5 mg/mL concentrated suspension for injection (30 micrograms/dose) are considered interchangeable'. Section 6.6 of the proposed data sheet states: 'If the vial has a purple plastic cap, refer to the Data sheet handling instructions for COMIRNATY (COVID-19 mRNA vaccine) Concentrate for injection 0.5 mg/mL TT50-10853.' These statements are clinically unclear and infers that the original PBS/sucrose COMINARTY presentation (with a purple vial cap colour) may be used in the 5-11 years of age group. The sponsor is asked to amend the proposed data sheet such that the appropriate vial is clearly documented for the respective age groups. A suggested amendment of the data sheet could be to either remove this sentence or to amend as follows: 'Doses of COMIRNATY (grey cap, do not dilute) new formulation (30 micrograms/dose) and COMIRNATY (purple cap, must dilute, original formulation (30 micrograms/dose) are considered interchangeable however only COMIRNATY (orange cap, must dilute) new formulation (10 micrograms/dose is recommended in the 5-11 year age group.'
viii) Section 4.2: Amend the statement 'primary course of 2 doses (0.3 mL) at least 21 days apart', to read '… of 2 doses (0.3 mL each) at least …'.
ix) Section 6.3: Include subheadings under the main heading 'Unopened vial' and separate out the storage information for the frozen vials and thawed vials, as per the storage information in the EU SPC.
x) Section 6.3: Please move the statement 'It the vaccine is received at 2°C to 8°C it should be stored at 2°C to 8°C' to be positioned under the heading 'Thawed vial' as per the EU SPC, so that it is separate from the storage information for the frozen vaccine.
xi) Section 6.3: Revise the storage condition for the opened vial of the 30 micrograms/0.3 mL dose presentation from '8 to 30°C' to '2 to 30°C' to align with the temperature range on the product labelling and in the EU SPC.
xii) Section 6.4: To improve clarity, please remove the information in this section that is already stated in section 6.3 (as this section includes a statement to refer to section 6.3 for storage conditions after thawing and dilution).
xiii) Section 6.5: State the fill volume (contents of container) for each presentation, as per the EU SPC.
xiv) Section 6.5: Include the statement 'Not all pack sizes may be marketed' if applicable.
xv) Section 6.6: Remove references to the TT50 file in the graphics.
xvi) Section 6.6: In the graphics for both presentations, section 'Handling prior to use', include the statement 'within the 6 month shelf-life' next to 'Unopened vials can be stored for up to 10 weeks at 2°C to 8°C'.
xvii) Section 6.6: In the graphic for COMIRNATY Dilute to use multidose (For Age 5 to <12

Years), section ‘Mixing prior to dilution, replace the reference to ‘dispersion’ with ‘suspension’. Both tracked changes and clean versions of the data sheets should be provided with the response.

RFI1 Q.7. Please provide copies of the EU and US package inserts that are referred to from the respective international product labels, or confirm that the package insert for product marketed in New Zealand will be the New Zealand data sheet, if applicable.

RFI1 Q.8. Please prepare individual CMI documents for each strength and presentation of Comirnaty. The naming terminology used in the CMI should reflect that described in RFI1 Q.2.

RFI1 Q.9. Please provide the New Zealand Medicines Terminology Listing Certificate for the 195 vial pack size of the 10 microgram/0.2 mL presentation of Comirnaty.

RFI1 Q.10. Please provide evidence of cGMP for the API manufacturing site Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, Germany, as the current GMP certificate held on file at Medsafe for the site expired on 31/03/2021.

RFI1 Q.11. The GMP certificate provided for Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, Ireland, authorises the site for API testing. Please provide evidence of cGMP that authorises the site for testing the finished product.

RFI1 Q.12. The GMP certificate provided for Pfizer Manufacturing Belgium NV , Rijksweg 12, Puurs B-2870, Belgium, will expire on 31/12/2021. Please provide a commitment to send Medsafe updated evidence of cGMP for this site, once it is available.

RFI1 Q.13. Please provide further information on the 94 historical drug product batches used to set the comparability acceptance criteria. The response should confirm that batch data from clinical drug product lots was included in the assessment, and provide the batch size ranges of the drug product lots used to establish the acceptance criteria.

RFI1 Q.14. Please clarify the quality of the aluminosilicate glass vials in terms of their hydrolytic resistance (ie Type I, II or III). If the vials are not Type I glass, section 6.5 of the data sheet should be updated accordingly.

RFI1 Q.15. Please provide the available results from the leachables studies currently in progress to support the Tris-sucrose commercial container closure system (for both the borosilicate and aluminosilicate vials). If only T_0 data is available, the company should commit to provide the results of the leachables studies post-approval.

RFI1 Q.16. Please confirm that the New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

RFI1 Q.17. Please commit to reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available, and indicate a time-frame for when this reassessment will be completed and provided to Medsafe.

RFI1 Q.18. Please commit to provide batch release data/CoAs for the first three batches of vaccine intended for the New Zealand market, prior to their distribution. Please also commit to provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.

RFI1 Q.19. Please provide representative supplier certificates of analysis for the new aluminosilicate glass vials. These should include supplier statements regarding compendial compliance.

RFI1 Q.20. Section 6.4 of the data sheet states that the vaccine may be received frozen at -90°C to -60°C or at -25°C to -15°C, which implies the product can be stored at -20°C; however, a shelf-life at this storage temperature is not proposed with this NMA. The parent

PBS/sucrose vaccine is currently approved for storage at -20°C for 2 weeks (unopened). On the basis of the demonstrated comparability of the Tris/sucrose and PBS/sucrose formulations, and since the available stability data for the primary stability lots supports the storage of the Tris/sucrose formulation for up to 10 weeks at -20 ± 5°C (within the 6 month shelf life), please consider introducing an allowable storage condition at -25°C to -15°C for the unopened Tris/sucrose vials, to facilitate ease of handling and storage at the point of use.

RFI1 Q.21. Please provide the updated stability data that should now be available for the primary stability and PPQ Tris/sucrose drug product lots in the ongoing stability studies.

Attachments

1. Therapeutic Product Database Report

Questions raised in the additional evaluation

RFI2 Q.1 Please commit to provide the EMA assessment reports for the 10 micrograms/ dose presentation of the Tris/sucrose formulation of Comirnaty, when available. Please also confirm the specific obligations imposed by the EMA/CHMP on the conditional marketing authorisations of both the 10 micrograms/dose and 30 micrograms/dose Tris/sucrose presentations of Comirnaty.

RFI2 Q.2 To ensure sufficient differentiation between the 0.5 mg/mL strength of Comirnaty and the new presentations of the 0.1 mg/mL strength, please commit to update Section 1 of the data sheet for the parent vaccine to incorporate the identifiers COMIRNATY (purple cap, must dilute), original formulation, 0.5 mg/mL concentrate for suspension for injection, 12 years of age and older (30 micrograms/dose).

RFI2 Q.3 The data sheets provided in the response to RFI1 Q.6 are acknowledged. Please make the following additional changes:
a) Both data sheets: Please include ‘new formulation’ and the indicated age range in the product name in Section 1 to be consistent with the naming nomenclature used in the headings throughout the data sheet. When not used as a heading, Medsafe considers it is appropriate to use only the product name (or the name and one identifier) when referencing the product to improve readability, since each product now has its own data sheet. For example, in section 6.3, the shelf-life is headed with the full name, so all subsequent references to the product in this section could be limited to ‘COMIRNATY (orange cap, must dilute)’ or simply ‘the vaccine’ where appropriate (as used currently in places). Please revise references to the product in the body of the data sheet accordingly.
b) Section 3 of the 30 micrograms/0.3 mL dose data sheet: Remove ‘(sterile concentrate)’ from description of the pharmaceutical form.
c) Section 4.1 of the 10 micrograms/0.2 mL dose data sheet: Please change the indication wording from ‘in individuals 5 to 11 years of age’ to ‘children aged 5 to 11 years’.
d) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Separate the heading ‘Dose’ onto a new line and replace references to ‘Individuals 5 to 11 years of age’ with ‘Children 5 to 11 years of age’. Please also consider including the explanatory statement ‘(ie 5 to less than 12 years of age)’ as appears in section 4.2 of the current SPC document.
e) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Remove the statement regarding the interchangeability of the COMIRNATY (grey cap, do not dilute) and COMIRNATY (purple cap, must dilute) presentations, as this is not relevant to the data sheet for the 5 to 11 year old vaccine.

f) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Add a heading ‘Paediatric population’ and include the statement ‘The safety and efficacy of Comirnaty in children aged less than 5 years have not been established.’
g) Section 4.2 of the 10 micrograms/0.2 mL dose data sheet: Include ‘after dilution’ in the statement ‘COMIRNATY should be administered intramuscularly, after dilution’.
h) Section 4.2 of the 30 micrograms/0.3 mL dose data sheet: Move the heading ‘Dose’ to a separate line.
i) Section 4.2 of the 30 micrograms/0.3 mL dose data sheet: Please include the heading ‘Paediatric population’ with the accompanying text ‘There is a paediatric formulation available for children 5 to 11 years of age. For details, please refer to the data sheet for COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose).’
j) Section 6.3 of both data sheets: Since the company is not proposing a shelf-life for storage at -20°C outside of Pfizer/BioNTech control, the statement ‘… may be received frozen at -90°C to -60°C or at -25°C to -15°C’ should be amended to remove reference to ‘at -25°C to -15°C’ to minimise the potential for confusion to healthcare professionals (who could interpret this to mean the product can be stored at -20°C). It is noted that this change has been made to the current EU SPC for the 10 micrograms/dose presentation.
k) Section 6.3 of both data sheets. Medsafe notes that the shelf-life information in the current EU SPC for the unopened vials has been amended from ‘Vaccine may be stored at temperatures between 8 to 30°C for up to 24 hours, including any time within these temperatures following dilution’ (as stated in the current data sheets) to ‘Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8°C and 30°C’, which is clearer and aligns with the storage information in the FDA fact sheets. Please make the same change to the New Zealand data sheets.
l) Section 6.3 of both data sheets: For ease of reference, please also include the thawing times in this section, in addition to appearing in the graphics, as per the EU SPC. For example for the 10 micrograms/0.2 mL presentation ‘When stored frozen at -90°C to -60°C, 10-vial packs of the vaccine can be thawed at 2°C to 8°C for 4 hours or individual vials can be thawed at room temperature (up to 30°C) for 30 minutes.’ Both tracked changes and clean versions of the data sheet should be provided with the response.

RFI2 Q.4 The CMI documents provided in response to RFI1 Q.8 are acknowledged; however, both are entitled COMIRNATY COVID-19 VACCINE. Please include an identifier such as the indicated age range and cap colour (at a minimum) in the headers, to clearly differentiate the two CMI documents.

RFI2 Q.5 The response to RFI1 Q.21 cites updated stability data included with the response; however, this could not be located by Medsafe. Please provide the updated stability data. Please note that Medsafe will only be approving a 6 month shelf life, when product is unopened and stored at -90 to -60°C. This is due to the limited stability data available for commercial scale batches with the new formulation. If the company wishes to extend the long term storage shelf life, then a CMN will be required post-approval along with appropriate supportive data.

Final Recommendation

A few quality and clinical issues arising from this application still remain unresolved. The applicant has committed to providing the outstanding information to address these issues. Due to the COVID-19 global pandemic situation and the clinical need for the product,

provisional consent under Section 23 of the Medicines Act 1981 may be considered for the following indications:

COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose)

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

It is proposed that any provisional consent for both products include the following conditions:

COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)

Provisional consent is to be granted for a period that expires on the same date as the provisional consent for the parent product (3 November 2023).

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1) Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
4) Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
5) Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6) Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7) Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8) Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
9) Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.
10) Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
11) Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
12) Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified,

especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

COMIRNATY (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose)

Provisional consent is to be granted for a period that expires on the same date as the provisional consent for the parent product (3 November 2023).

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1) Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
4) Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
5) Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6) Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7) Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8) Provide the six months analysis data from Study C4591007. Due date: 28 February 2021.
9) Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
10) Provide the final Clinical Study Reports for Study C4591007 within five working days of these being produced.
11) Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
12) Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
13) Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Due to the unresolved concerns and additional quality, safety and efficacy data to be provided at the time of completion of the evaluation, Medsafe is unable to recommend that this product be granted consent. It is therefore recommended that the application be referred to the Medicines Assessment Advisory Committee (MAAC) under section 22(2) of the Medicines Act 1981 for their consideration. In referring the application, it is requested that the MAAC focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given the data provided up to the time of referral, as well as whether any additional conditions should be applied.

- Whether the benefit risk balance of these products is positive for the proposed indications.

This recommendation is also subject to the following post-approval commitments:

a) To update Section 1 of the data sheet for the parent product with the identifiers proposed in RFI1 Q.2 (purple cap, must dilute, original formulation).
b) To provide updated evidence of cGMP for Pfizer Manufacturing Belgium NV , Rijksweg 12, Puurs B-2870, Belgium, when available.
c) To provide the results from the ongoing leachables studies for the Tris/sucrose drug product lots.
d) To move to labelling compliant with the requirements of New Zealand Medicines Regulations 1984, once manufacture is no longer constrained by pandemic conditions.

The following additional data sheet changes will be requested of the sponsor in the outcome of evaluation email:

- *Section 1 of the 10 micrograms/0.2 mL dose data sheet:* Please remove the comma in “0.1, mg/mL”.
- *Section 2 of the 30 micrograms/0.3 mL dose data sheet*: Please write the statement ‘Do not dilute prior to use’ in bold font.
- *Section 2 of the 10 micrograms/0.2 mL dose data sheet*: Please write the statement ‘must be diluted’ in bold font.
- *Section 4.2 of both data sheets*: Please replace the statement ‘COMIRNATY for children 5 to 11 years of age cannot be used for individuals 12 years of age and older’ with ‘COMIRNATY (orange cap, must dilute) should be used only for children 5 to 11 years of age’.
- *Section 6.6 of the 10 micrograms/0.2 mL dose data sheet*. Please use orange colour in the graphics as per the FDA approved fact sheets. Please also consider using purple colour in the graphics of the parent PBS/sucrose vaccine data sheet when this is updated as per the commitment made to RFI2 Q.2.
- *Section 9 of both data sheets*: The approval date should reflect the date of gazettal of the Tris/sucrose formulations of the drug product.
- *Section 10 of both data sheets*: This will need to be updated accordingly following the above revisions.

Summary

SARS-COV-2 epidemiology in children aged 5–11 years

- **Children are at least as likely to be infected with SARS-CoV-2 as adults**
  - Over 1.9 million reported cases; seroprevalence estimated ~38% among 5–11 years in Sept 2021
  - Infections in children less likely to be reported as cases than infections in adults
- **Children 5-11 years of age are at risk of severe illness from COVID-19**
  - >8,300 COVID-19 related hospitalizations as of mid-October
  - Cumulative hospitalization rate is similar to pre-pandemic influenza seasons
  - Severity comparable among children hospitalized with influenza and COVID-19, with approximately 1/3 of children 5–11 years requiring ICU admission
  - MIS-C most frequent among children 5–11 years
  - Post-COVID conditions have been reported in children
- **Secondary transmission from young school-aged children occurs in household and school settings**

Other pediatric vaccine preventable diseases:

Hospitalizations per year prior to recommended vaccines

	Hepatitis A[1]	Varicella[2] (Chickenpox)	Influenza[3]	COVID-19
Age	5–14 years	<20 years	5–17 years	5–11 years
Time period	2005	1988–1995	2003–2007	Oct 2020–Oct 2021
Hospitalization Burden (per 100,000 population)	**<1**	**4-31**	**30-80**	**25**

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5603a1.htm

[2] Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. *J Infect Dis*. 2000;182(2):383-390. doi:10.1086/315714

[3] https://www.cdc.gov/flu/weekly/weeklyarchives2007-2008/07-08summary.htm

Other vaccine preventable diseases:

Deaths per year prior to recommended vaccines

	Hepatitis A[1]	Meningococcal (ACWY)[2]	Varicella[3]	Rubella[4]	Rotavirus[5]	COVID-19
Age	<20 years	11–18 years	5–9 years	All ages	<5 years	5–11 years
Time period	1990–1995	2000–2004	1990–1994	1966–1968	1985–1991	Oct 2020–Oct 2021
Average deaths per year	**3**	**8**	**16**	**17**	**20**	**66**

[1]Vogt TM , Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis2008; 197:1282–8.
[2]National Notifiable Diseases Surveillance System with additional serogroup and outcome data from Enhanced Meningococcal Disease Surveillance for 2015-2019.
[3]Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. *J Infect Dis*. 2000;182(2):383-390. doi:10.1086/315714
[4]Roush SW , Murphy TV; Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA2007; 298:2155–63.
[5] Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. J Infect Dis. 1996 Sep;174 Suppl 1:S5-11.

Modeling the impact of COVID-19 vaccination in children ages 5–11 years

- Vaccination among 5–11-year-olds is expected to accelerate the decline in cases, reducing cumulative incidence nationally by an expected **8%** (~600,000 cases) from November 2021 to March 2022

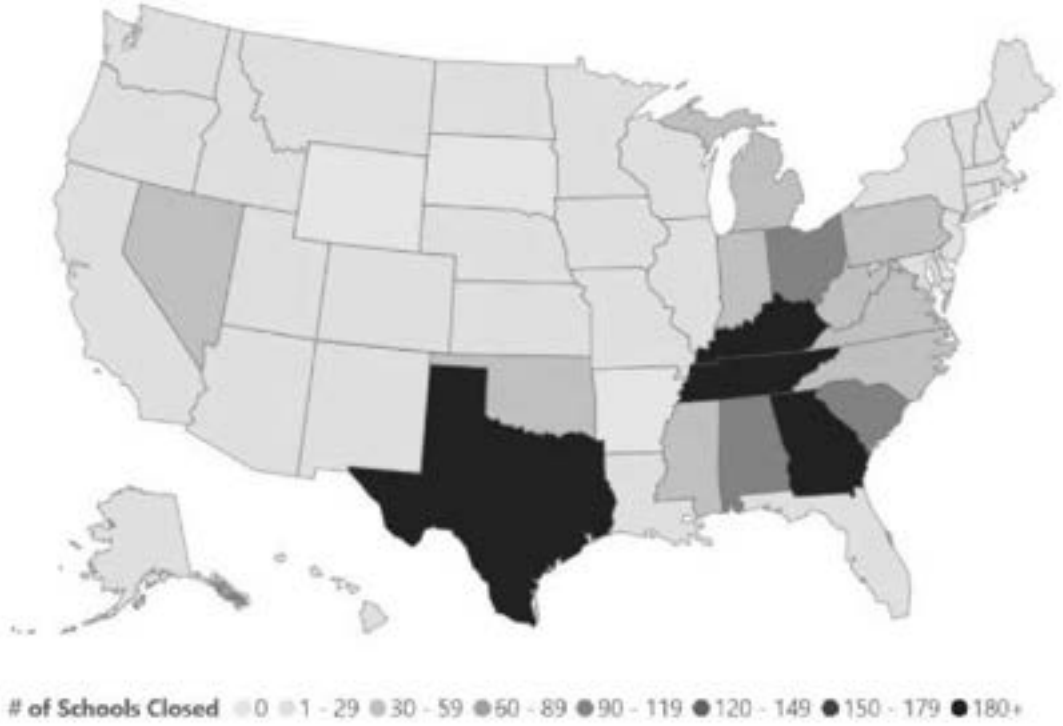
- Vaccination of 5–11-year-olds would dampen, but not eliminate, a new variant emergence

https://covid19scenariomodelinghub.org/

COVID-19 Related K-12 School Closures by State,

August 2, 2021 – October 22, 2021

School districts closed	Total # schools closed*	Estimated # students affected*	Estimated # teachers affected*
313	2,351	1,217,777	78,134



Data from the Unplanned School Closure Monitoring Project (DGMQ/CDC), ongoing research that uses systematic daily media searches (methods explained in https://doi.org/10.1371/journal.pone.0248925).

* Number of schools closed in district-wide closures, total number of students, and total number of teachers are estimated by matching the public school district ID or school ID with the district/school data for school year 2019/20 and private school ID with school data for year 2017/18 as obtained from the National Center for Education Statistics (https://nces.ed.gov/ccd/elsi/tableGenerator.aspx, accessed on Apr 20, 2021). Due to missing information in 2019/20 data, the total number of public school teachers in California is estimated using 2018/19 NCES data.

Indirect impacts of COVID-19 pandemic on children


- Worsening of mental or emotional health


- Widening of existing education gaps


- Decreased physical activity and increased body mass index (BMI)


- Decreased healthcare utilization


- Decreased routine immunizations


- Increase in Adverse Childhood Experiences (ACEs)


- Loss of caregivers

Public health problem:
Summary of the available evidence

- **Children 5–11 years of age are at risk of severe illness from COVID-19**
  - Over 1.9 million reported cases and >8,300 hospitalizations through mid-October
    - Cumulative hospitalization rate similar to influenza season
    - MIS-C most frequent among children 5–11 years
  - Other post-COVID conditions have been seen in children
- COVID-19 in children leads to missed school for themselves and their communities
- **Wide use of an effective vaccine would reduce public health burden of COVID-19 in children 5–11 years of age**

Minutes of the 113th meeting of the Medicines Assessment Advisory Committee by videoconference on 14 December 2021 at 9:30am

Present:
[redacted]

In Attendance (from Medsafe):
[redacted] (Manager, Product Regulation Branch)
[redacted] (Manager, Clinical Risk Management Branch)
[redacted] (Team Leader, Product Regulation Branch)
[redacted] (Principal Technical Specialist, Product Regulation Branch)
[redacted] (Senior Advisor, Product Regulation Branch)
[redacted] (Pharmacovigilance Advisor, Clinical Risk Management Branch)
[redacted] (Pharmacovigilance Advisor, Clinical Risk Management Branch)
[redacted] (Medical Advisor, Clinical Risk Management Branch)
[redacted] (Senior Pharmacovigilance Advisor, Clinical Risk Management Branch)

Representatives from Pfizer:
[redacted] (Head of Regulatory Affairs)
[redacted] (Regulatory Affairs Manager)
[redacted] (Senior Regulatory Affairs Associate)
[redacted] (Vaccines Medical Lead Korea/AU/NZ)
[redacted] (Cluster Safety Lead)

Apologies:
Apologies were received from [redacted]

1 Welcome

The Chair opened the 113th meeting at 9.32am and welcomed members and guests to this meeting to consider a recommendation on the approval of Comirnaty (COVID-19 mRNA vaccine) 30 micrograms/0.3 mL suspension for injection and Comirnaty (COVID-19 mRNA vaccine) 10 micrograms/0.2 mL concentrate for injection, based on the new medicine application submitted by Pfizer New Zealand Limited. The Chair welcomed Committee members and guests.

2 Apologies

Apologies were received from [redacted]

3 Declaration of conflict of interest

Members submitted their conflicts of interest forms to the Secretary.

All members declared they have no additional interests that would pose a conflict with any of the items on the agenda.

4 Applications for consent to distribute a new medicine under section 20 / 23 / 24 of the Medicines Act 1981 (Referred by the Minister of Health under Section 22(2))

4.1 Comirnaty 30 µg/0.3 mL suspension for injection (TT50-10853/1) and Comirnaty 10 µg/0.2 mL concentrate for injection (TT50-10853/1a), Pfizer New Zealand Limited

On 4 November 2021, Pfizer New Zealand Limited (Pfizer) submitted an application for approval to distribute two new medicines based on a parent product, COVID-19 vaccine Comirnaty concentrate for injection 0.5 mg/mL (30 µg/0.3 mL dose delivered) (TT50-10853) (**Comirnaty**). These products are considered an additional dosage form, Comirnaty suspension for injection 30 µg/0.3 mL (TT50-10853/1) (**Comirnaty 30 µg**), and an additional strength, Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-10853/1a) (**Comirnaty 10 µg**), compared to the parent product. Comirnaty has provisional consent under section 23 of the Medicines Act 1981 (the Act). Therefore, Pfizer's application, being based on that approval, is also considered for provisional consent under section 23 of the Act.

The application has been submitted via an expedited priority review process and has been assessed under urgency due to the significant clinical need for a COVID-19 vaccine that can be administered to children. The initial application was received on 4 November 2021 and was formally accepted by Medsafe on 12 November 2021. Following assessment of the initial data submission, requests for additional information related to each of the aspects of the application (quality, clinical and Pfizer's risk management plan) were issued between 24 November and 7 December 2021. Responses from Pfizer were received on 7 December 2021. A second request for additional information related to product information and quality aspects was issued on 7 December 2021 and a response from Pfizer was received on 9 December 2021. All additional data provided by Pfizer had been assessed by Medsafe by the time of this MAAC meeting.

Comirnaty 30 µg and Comirnaty 10 µg are both based on the parent product Comirnaty. The parent product was given provisional consent under section 23 of the Act on 3 February 2021 and renewed provisional consent under section 23(4A) of the Act on 28 October 2021.

Comirnaty 30 µg has a different dosage form (suspension for injection, rather than concentrate for injection) and a different formulation to the parent product. The difference in formulation is related to a change in the buffering ingredients used, largely intended to support the stability of a more diluted solution. It is indicated for use in individuals aged 12 years and over and has been specifically developed to be used without prior dilution.

Comirnaty 10 µg has the same qualitative formulation as Comirnaty 30 µg but a different strength per dose compared to Comirnaty 30 µg and the parent product. It has been specifically developed for use in children aged between 5 and 11 years old, an indication which is not currently approved for the parent product.

A comparison of all three Comirnaty presentations is shown in the table below. The product names refer to the following medicines:

Original PBS/Sucrose (current indication/purple) = **Comirnaty (parent product)**

Tris/Sucrose (current indication/grey) = **Comirnaty 30 µg**

Tris/Sucrose (new indication/orange) = **Comirnaty 10 µg**

	Original PBS/Sucrose (current indication)	Tris/Sucrose (for current indication)	Tris/Sucrose (for new indication)
Vial cap colour	Purple	Grey	Orange
Age range	Over 12 Years	Over 12 Years	5 to <12 Years
Pharmaceutical form	Concentrate for dispersion for injection	Dispersion for injection	Concentrate for dispersion for injection
Fill Volume	0.45 mL	2.25 mL	1.3 mL
Volume/dose	0.3 mL	0.3 mL	0.2 mL
µg RNA/dose	30 µg	30 µg	10 µg
Dilution required	Yes (1.8 mL saline)	No	Yes (1.3 mL saline)
Doses/vial	6	6	10
Strength (RNA) in vial	500 µg/mL	100 µg/mL	100 µg/mL
Pack size	195	10, 195	10, 195

All three products have been developed in response to the global pandemic of SARS-CoV-2 virus that causes COVID-19.

Medsafe Presentation

Medsafe presented an overview of their assessment of the quality aspects of the application.

The Committee noted that both Comirnaty products have been granted emergency use authorization by the FDA and conditional/provisional approval by the EMA and TGA.

Evaluation

Quality evaluation report

The Committee considered the following documentation:

- Quality evaluation report

The Committee noted that the parent product formulation of Comirnaty uses a phosphate buffer, and the two proposed formulations use trometamol (tris) buffer.

The Committee discussed the use of buffers in parenteral medicines. Medsafe commented that a change in buffer is a minor formulation change and that under a standard changed medicine notification, a change in buffer would not typically require clinical data or a bioequivalence study to support it.

Additionally, Medsafe noted that the tris buffer is present in other vaccines approved in New Zealand such as Twinrix Junior and Nimenrix, which are indicated for paediatric use and historically have demonstrated good safety. The Committee was reassured and satisfied that the buffer change did not pose a risk to significantly impact the quality or safety of the product.

The Committee raised concerns about the potential for confusion between the products as the labels are very similar and all three Comirnaty presentations are generally referred to by the colour of their respective vial caps (purple, grey, orange) as the identifying component. The Committee identified a risk of confusion when selecting the correct vial/administering the correct dose, largely due to the different dilution and dosing instructions.

The Committee was satisfied that these risks are mitigated by the separation of product data sheets to ensure clarity on the administration of each of the products, as well as the need for the sponsor to produce a Dear Healthcare Professional letter or other instructive material.

Conclusion:

Overall, the Committee was satisfied by the quality evaluation and unanimously agreed that the quality report was sufficient to consider recommending provisional consent.

Medsafe Presentation

Medsafe presented an overview of their assessment of the clinical aspects of this application.

Clinical evaluation report

The Committee considered the following documentation:

- Clinical evaluation report

The Committee noted that covariate analysis stratified further by age in the Phase 2/3 C4591007 study was not performed. This was considered potentially useful given developmental and size differences in children 5 years versus 11 year of age. The Committee commented that if age stratification was performed, it likely would not have given enough power to provide a meaningful analysis, nor was the study designed for such sub-group analysis. The Committee noted that generally, adverse reactions appear to be more common/intense in younger age groups, however that these were still generally mild to moderate and reactogenic in nature.

The Committee discussed and accepted the rationale for utilising immunobridging analysis to support vaccine effectiveness in the children aged 5 to 11 years old in study C4591007. They acknowledged the acceptance of this approach for the clinical development of new COVID-19 vaccines by other international regulatory authorities and consortia. It was noted the GMR point estimate criteria for success increased from >0.8 to >1, as requested by the US Food and Drug Administration. The Committee noted that both thresholds were met. Overall efficacy was shown which was statistically significant and was reinforced by their geometric mean titre analysis.

The Committee noted that the study showed efficacy to be 90.7% in participants without prior COVID-19 infection (based on small numbers of infections), no cases had severe disease and there was no data on asymptomatic disease or transmission.

The Committee discussed adverse reactions in children aged 5 to 11 years old during the study. The Committee noted that the most common local reaction was pain at the injection site. Systemic reactions were mostly mild to moderate in severity and resolved within 48 hours. The most common unsolicited event was lymphadenopathy.

It was noted that no cases of myocarditis and pericarditis have been reported to date in study C4591007. The Committee commented that the study population of children aged 5 to 11 years old was likely too small to capture cases of myocarditis and pericarditis. However, data from the five million doses that have been rolled out in the US will provide more information in the post-market setting when it is made available. The Committee noted that post-marketing surveillance data will be available in the planned summary safety report due early next year.

The Committee acknowledged that spontaneous reporting to the Centers for Disease Control and Prevention would also detect any strong safety signals and that these would likely be communicated shortly after detection, before the next summary safety report is due. The Committee was made aware that Medsafe has been in contact with other regulators who have not indicated concerns at present with myocarditis or other events of interest in younger children.

Conclusion

Overall, the Committee was satisfied by the clinical evaluation and unanimously agreed that the clinical report was sufficient to consider recommending provisional consent.

Myocarditis and Pericarditis

Medsafe presented an overview of cases of suspected vaccine-associated myocarditis and pericarditis in New Zealand. Myocarditis and pericarditis are known rare adverse effects associated with mRNA vaccines. The reporting rate in New Zealand is similar to the rates seen internationally. Young males appear to be at highest risk of vaccine-associated myocarditis and pericarditis. It is currently unknown how children under 12 years of age might be affected by vaccine-associated myocarditis and pericarditis as these adverse events are too rare to be evaluated in clinical trials. It was noted that myocarditis and pericarditis of any aetiology is less common in younger children compared with adolescents.

The Committee raised questions around the background incidence of myocarditis compared to the reported cases of myocarditis in vaccinated children. The Committee agreed that increased incidence of myocarditis is a known feature of mRNA vaccines and that it was more common in young males. It was noted that the background hospitalisation rate in New Zealand is around 100-200 people per year. There has been an increase in the number of hospitalisations this year. The Committee considered whether the low threshold for suspicion by physicians could explain the increase in myocarditis cases in New Zealand. It was noted that local rapid cycle analysis showed an imbalance and confirmed the signal of myocarditis following Comirnaty. The underlying cause is not known.

Medsafe Presentation

Medsafe presented an overview of their assessment of the Comirnaty RMP (v3.0), including the ongoing and planned clinical studies and planned risk minimisation materials regarding the new formulation and product presentations.

Risk Management Plan (RMP) report

The Committee considered the following documentation:

- Risk Management Report

The Committee noted the questions issued to the company by Medsafe regarding the need for activities to collect additional information regarding children aged five to 11 years, including those of Māori and Pacific ethnicities and with prior SARS-CoV-2 infection. The company response indicated that routine pharmacovigilance activities include these groups and that the RMP includes a study to gather further information on cardiac adverse events in young people. Interaction studies will be conducted for pneumococcal and influenza vaccines but are not planned for other vaccines. Boostrix and Gardasil were noted as the only vaccines in the New Zealand immunisation schedule for children aged five to 11 years old.

The Committee noted that studies on the need for booster doses or third primary doses for immunosuppressed children are not yet planned, but that results from any such studies should be provided to Medsafe when available.

The Committee emphasised that the potential for administration errors with three different product presentations with different dilution requirements and dose volumes would need to be carefully managed with risk minimisation activities The Committee was satisfied with the RMP.

Discussion with Pfizer New Zealand Limited

Pfizer representatives joined the meeting to respond to questions from the Committee. The Committee asked questions regarding data to support the new buffer formulation, adverse reaction data collection, data stratification with the paediatric clinical study, safety signals being received from administration to children aged 5 to 11 years old internationally, immunogenicity against emerging variants and additional doses for the paediatric population. All questions were suitably addressed by Pfizer New Zealand Limited.

Discussion to Finalise Recommendation

Benefit-risk

The Committee discussed the overall benefit-risk of Comirnaty 30 µg and Comirnaty 10 µg. The Committee noted that the data provided to support the change in formulation was sufficient to support comparability between Comirnaty 30 µg and the parent product. The Committee noted that epidemiological data from overseas and New Zealand demonstrate that children are at risk of COVID-19, including from long-term symptoms and hospitalisation, and that there is a clear clinical need for immunisation of paediatric populations. They discussed the strong efficacy signal of Comirnaty 10 µg in children aged 5 to 11 years old and evidence suggesting a good safety profile, comparable to that observed in adults and adolescents to date. The Committee determined that, based on the information available, the benefit-risk profiles of Comirnaty 30 µg and Comirnaty 10 µg are favourable for the proposed indications.

Provisional consent

The Committee unanimously agreed to recommend that provisional consent be granted for both Comirnaty 30 µg and Comirnaty 10 µg valid until 3 November 2023. This period of consent was proposed by Medsafe to align with the current provisional consent granted to the Comirnaty parent product. The Committee agreed with this rationale.

PS.

Conditions of provisional consent

The Committee agreed to recommend that the conditions proposed by Medsafe be imposed on a provisional consent for both products as written (see Quality Evaluation Report).

Comirnaty (COVID-19 mRNA vaccine) 30 micrograms/0.3 mL suspension for injection.

The conditions include 12 obligations requiring information to be provided or actions to be taken by the sponsor within specified timeframes.

Comirnaty (COVID-19 mRNA vaccine) 10 micrograms/0.2 mL concentrate for injection

The conditions include 13 obligations requiring information to be provided or actions to be taken by the sponsor within specified timeframes.

Recommendation

The Committee recommended that the delegate of the Minister of Health should grant provisional consent to the distribution of these medicine under Section 23 of the Medicines Act 1981 with the conditions proposed by Medsafe. The Committee agreed to Medsafe's proposal that the provisional consent should be valid until 3 November 2023.

5 General Business

No general business was discussed.

6 Date of Next Meeting

No date has been set.

There being no further business, the Chair thanked members and guests for their attendance and closed the meeting at 1.21pm.

CHAIR'S SIGNATURE: [redacted]

DATE: 15/12/2021

This document was prepared and written by [redacted]

the Medicines Assessment Advisory Committee Secretary.

Memo

Date:	16 December 2021
To:	Chris James, Group Manager, Medsafe
Copy to:	[redacted] Secretary, Medicines Assessment Advisory Committee
From:	[redacted] Manager, Product Regulation Branch, Medsafe
Subject:	Pfizer New Zealand Limited's application for consent of **Comirnaty suspension for injection 30 µg/0.3 mL (TT50-10853/1) and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-1053/1a)** – decision required under section 23 of the Medicines Act 1981 and under regulation 52 of the Medicines Regulations 1984
For your:	Action and Decision

Purpose

This memo seeks your decision under section 23 of the Medicines Act 1981 (the Act) on whether to grant provisional consent to the sale or supply or use of Comirnaty suspension for injection[1] 30 µg/0.3 mL (TT50-10853/1) (**Comirnaty 30 µg)** and Comirnaty concentrate for injection 10 µg/0.2 mL (TT50-1053/1a) (**Comirnaty 10 µg)** and if so, on what conditions (if any) and for what period of time. The Minister of Health's (Minister) decision-making under section 20 and section 23 of the Act have previously been delegated to you.[2]

This memo also seeks your decision under regulation 52 of the Medicines Regulations 1984 (Regulations) on whether to approve the data sheets for Comirnaty 30 µg and Comirnaty 10 µg. The Minister's decision-making under regulation 52 of the Regulations has previously been delegated to you. [3]

Statutory framework

Under section 23 of the Act, you may, in your capacity as the Minister's delegate, give provisional consent to the sale or supply or use of a new medicine if you consider it is desirable that the medicine be sold, supplied, or used.

Therapeutic value weighed against the risk of injuriously affecting a person

In deciding whether to give provisional consent under section 23 of the Act, you must follow the procedure set out in section 22 which requires you to:[4]

(a) consider all of the particulars and information required to be submitted by an applicant, and such other matters as appear to be relevant to you; and

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1 The memo dated 10 December 2021 regarding referral of this application to the Medicines Assessment Advisory Committee incorrectly referred to this dosage form as "solution for injection", and a correction is made here.

2 Delegation made by the Minister of Health 11 September 2013 under section 28 of the State Sector Act 1988; and sub-delegated by Director-General of Health on 20 September 2013 under section 41 of the State Sector Act 1988.

3 Delegation made on 28 June 2021 by the Minister of Health under clause 5, Schedule 6 of the Public Service Act 2020; and sub-delegated on 30 June 2021 by the Director-General of Health under clause 2, Schedule 6 of the Public Service Act 2020

4 Medicines Act 1981, section 22(1).

(b) as far as practicable, weigh the likely therapeutic value of the medicine against the risk (if any) of the use of the medicine injuriously affecting the health of any person.

Desirable

Section 23 provides no explicit guidance on the circumstances when it would be desirable to give provisional consent to a medicine. However, the legislative history of section 23 indicates that it is desirable to give provisional consent to a medicine:[5]

(a) where limited information means that a full consent process under section 20 of the Act is not feasible;
(b) there is an identified public health need for the medicine; and
(c) if, having followed the process in section 22, you are satisfied that the assessment of therapeutic benefits and risks supports New Zealanders having timely access to the medicine.

Referral to a committee

If, after undertaking the above assessment, you are not satisfied that you should give consent, you are required to refer the application to an appropriate committee. In this case, that would be the Medicines Assessment Advisory Committee (MAAC). The MAAC would consider the application and who will provide you with a recommendation as to the decision you should make.[6]

You are not bound by that recommendation – it is open to you to make a different decision. However, if the recommendation is to refuse consent you must notify the applicant of the terms of the recommendation and the reasons for it. The applicant may then object to the recommendation. If this occurs you must refer the application to the Medicines Review Committee who will review the application and provide a further recommendation as to the decision you should make.[7]

Conditions

On giving provisional consent, you may impose conditions as you see fit.[8] These can be:

(a) conditions relating to the persons to whom the medicine may be sold or supplied;
(b) conditions relating to the area in which the medicine may be distributed; or
(c) any other conditions (provided such other conditions are not inconsistent with the purpose of section 23 of the Act).[9]

Time limited

The default position is that every provisional consent shall have effect for two years, however, you have the discretion to grant a shorter provisional consent. [10] Upon the expiry of the provisional consent, the provisional consent can be renewed for a period not exceeding two years.

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5 See the Medicines Amendment Bill, 41-1, explanatory note.
6 Medicines Act 1981, section 22(2).
7 Medicines Act 1981, section 22(5).
8 Medicines Act 1981, section 23(3).
9 There is no explicit purpose statement in section 23. However, the legislative history of section 23 indicates that the purpose of section 23 is to ensure that New Zealanders have timely access to safe and effective medicines where there is a public health need (see the explanatory note in the Medicines Amendment Bill, 41-1).
10 Medicines Act 1981, section 23(4).

Information
An applicant is required to provide certain information with their application for provisional consent. What they are required to provide is set out in section 21(2)(a) – (h) of the Act. This includes:

(a) details of the method of manufacture of the medicine;
(b) the proposed or recommended dosage and frequency of dose, and the manner in which the medicine will be recommended to be administered, applied, or otherwise used; and
(c) the purposes for which the medicine will be recommended to be used, and the claims or representations to be made in respect of its usefulness.

Data sheet
The Regulations require an applicant to provide a proposed data sheet for the medicine. A data sheet contains information relating to the safe and effective use of the medicine. Regulation 52 requires the data sheet to be approved by the Minister. Within 10 days of consent being given to the distribution of a prescription medicine or a restricted medicine, an applicant must send the Director-General of Health an electronic copy of the approved data sheet for the medicine. The data sheet is then made publicly available. While not explicit in the Regulations, in practice the data sheet needs to be approved before, or, on or around the same time as, any decision to grant provisional consent.

Pfizer New Zealand Limited's application
On 4 November 2021, Pfizer New Zealand Limited (Pfizer) submitted information to Medsafe relating to an application for approval to distribute Comirnaty 30 µg and Comirnaty 10 µg as extensions to the provisional consent for the parent product, Comirnaty concentrate for injection 0.5 mg/mL (30 µg/0.3 mL dose delivered) (TT50-10853) (**Comirnaty**), under section 23 of the Act. These two new products are considered new medicines as they are materially distinct (different strength of active ingredient, different qualitative and quantitative formulation) from Comirnaty and have not been previously available in New Zealand. On 12 November 2021, the application was complete and formally accepted by Medsafe.

By this application Pfizer has applied for provisional consent under section 23 for two new medicines: Comirnaty 30 µg and Comirnaty 10 µg. The application for these two new medicines has been assessed and progressed together, because the quality and manufacturing information for both products is the same and has been submitted in the same dossier. However, the application relates to two new medicines and you are required to make a separate decision on each new medicine.

Pfizer's application for provisional consent under section 23 for Comirnaty 30 µg has been considered for the following indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

Pfizer's application for provisional consent under section 23 of the Act for Comirnaty 10 µg has been considered for the following indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in children aged 5 to 11 years.*

The use of this vaccine should be in accordance with official recommendations.

Further detail about the application, Medsafe's evaluation and the therapeutic value and the risks of Comirnaty 30 µg and Comirnaty 10 µg was set out in MAAC referral memo attached at Appendix One.

Referral to the Medicines Assessment Advisory Committee
After considering Pfizer's application, you were not satisfied that you should give provisional consent to the distribution of either of the two medicines without first seeking a recommendation from MAAC, due to data limitations and the public interest involved. Accordingly, on 10 December 2021 you referred Pfizer's application to the MAAC in accordance with section 22(2) of the Act (see MAAC referral memo attached at Appendix One).

The MAAC met at the 113th meeting on **14 December 2021**. Attached as Appendix Two is a copy of the ratified minutes of the 113th meeting of the MAAC, which include the MAAC's recommendation in relation to the Comirnaty 30 µg and Comirnaty 10 µg application.

The MAAC discussed the overall benefit-risk of Comirnaty 30 µg and Comirnaty 10 µg. They noted that the data provided to support the change in formulation was sufficient to support comparability between Comirnaty 30 µg and the parent product. They also acknowledged that children are at risk of COVID-19, including from long-term symptoms and hospitalisation, and that there is a clinical need for immunisation of paediatric populations. They discussed the strong efficacy signal of Comirnaty 10 µg in children aged 5 to 11 years old and evidence suggesting a good safety profile, comparable to that observed in adults and adolescents to date. The MAAC determined that, based on the information available, the benefit-risk profiles of Comirnaty 30 µg and Comirnaty 10 µg are favourable for the proposed indications.

In summary, the MAAC recommended you should give provisional consent under section 23 of the Act to Comirnaty 30 µg and to Comirnaty 10 µg for period of time that expires on the same date as the existing provisional consent for Comirnaty (3 November 2023) with conditions imposed on that consent. The proposed conditions are set out in the draft *Gazette* Notice attached as Appendix Four.

Decision required
There are four decisions required:

(a) Whether to grant provisional consent to Comirnaty 30 µg under section 23 of the Act.

(b) Whether to approve the data sheet for Comirnaty 30 µg under regulation 52 of the Regulations.

(c) Whether to grant provisional consent to Comirnaty 10 µg under section 23 of the Act.

(d) Whether to approve the data sheet for Comirnaty 10 µg under regulation 52 of the Regulations.

Data Sheet

Attached at Appendix Two are the data sheets provided by Pfizer. A decision is sought from you as to whether to approve the data sheet under regulation 52 of the Regulations.

The data sheets contain information relating to the safe and effective use of Comirnaty 30 µg and Comirnaty 10 µg. Amongst other matters the data sheets provides that the vaccines are only suitable for use in those aged 12 years and older and between 5 and 11 years old, respectively, and that the vaccines should be used in accordance with official recommendations.

The data sheets comply with Medsafe's Guideline on the Regulation of Therapeutic Products in New Zealand. Medsafe is comfortable the data sheets accurately record the safety warnings, contraindications and when Comirnaty 30 µg and Comirnaty 10 µg are suitable for use. Medsafe recommends that you approve both data sheets.

Provisional consent (section 23 of the Act)
Now that you are in receipt of the MAAC's recommendation to give provisional consent to the sale or supply or use of Comirnaty 30 µg and Comirnaty 10 µg, you are required to make a decision under section 23 of the Act on Pfizer's application.

It is open to you to disagree with the MAAC's recommendation and/or to impose additional or different conditions to those recommended by the MAAC should you decide to grant provisional consent for either or both medicines under section 23 of the Act.

If you agree to give provisional consent to the sale or supply or use of Comirnaty 30 µg and/or Comirnaty 10 µg, you will need to sign a *Gazette* notice that will be published in the *New Zealand Gazette*. The *Gazette* notice, once published, will give effect to your decision to give provisional consent. A draft *Gazette* notice has been prepared on the basis of provisional consent for both medicines, and this is attached in Appendix Four. If you decide to grant provisional consent for only one of Comirnaty 30 µg or Comirnaty 10 µg, the draft Gazette notice will need to be amended to reflect that.

If you decide to give provisional consent to either or both medicines, please note:

(a) The MAAC has recommended that the consent for both medicines be for a period that expires on the same date as the existing provisional consent for the parent product (3 November 2023). This would enable consistency in the lifecycle management of all Comirnaty COVID-19 vaccines.

(b) The MAAC has recommended imposing the proposed conditions, as written in the attached *Gazette* notice, on the provisional consent. These conditions will largely require Pfizer to provide additional information and data to support the quality, safety and efficacy of Comirnaty 30 µg and Comirnaty 10 µg as it becomes available. This will ensure Medsafe is kept up-to-date with the latest information, particularly as the manufacturing process continues to be upscaled to meet global demand and as clinical trials progress.

Recommendations
It is recommended that you:

1.	Note	the memorandum recording your decision to refer Pfizer's application to the MAAC (attached as Appendix One)	(Yes)/No

2.	Note	the minutes from the 113th meeting of the MAAC held on 14 December 2021, in particular the MAAC's recommendation in relation to Comirnaty 30 μg and Comirnaty 10 μg (attached as Appendix Two).	Yes/No
3.	Agree	that the likely therapeutic value of Comirnaty 30 μg outweighs any potential risk of Comirnaty 30 μg injuriously affecting the health of any person aged 12 years or older	Yes/No
4.	Agree	that it is desirable for Comirnaty 30 μg to be sold, supplied or used in New Zealand	Yes/No
5.	Agree	to give provisional consent to the sale or supply or use of Comirnaty 30 μg/0.3 mL suspension for injection under section 23 of the Act, with such consent to have effect until 3 November 2023 subject to the conditions set out in the draft *Gazette* notice (attached at Appendix Four).	Yes/No
6.	Agree	to approve the data sheet for Comirnaty 30 μg (attached as Appendix Three) under regulation 52 of the Regulations.	Yes/No
7.	Agree	that the likely therapeutic value of Comirnaty 10 μg outweighs any potential risk of Comirnaty 10 μg injuriously affecting the health of any person aged 5 – 11 years (inclusive)	Yes/No
8.	Agree	that it is desirable for Comirnaty 10 μg to be sold, supplied or used in New Zealand	Yes/No
9.	Agree	to give provisional consent to the sale or supply or use of the Comirnaty 10 μg/0.2 mL concentrate for injection under section 23 of the Act, with such consent to have effect until 3 November 2023 subject to the conditions set out in the draft *Gazette* notice (attached at Appendix Four).	Yes/No
10.	Agree	to approve the data sheet for Comirnaty 10 μg (attached as Appendix Three) under regulation 52 of the Regulations.	Yes/No
11.	Sign	the draft *Gazette* notice, which, when published, will give effect to your decision to give provisional consent to the sale or supply or use of Comirnaty 30 μg and Comirnaty 10 μg (attached as Appendix Four).	Yes/No
12.	Sign	the attached letter to the sponsor company, Pfizer New Zealand Limited, advising them of your decision to grant provisional consent to the sale or supply or use of the Comirnaty 30 μg and Comirnaty 10 μg (attached as Appendix Five).	Yes/No

Signature [redacted] Date: 16 Dec 2021

[redacted]

Manager, Product Regulation Branch, Medsafe

I have considered the particulars and information supplied, and I have weighed as far as possible the likely therapeutic value of Comirnaty 30 μg for use in those 12 years and older against the risk of the use of the vaccine injuriously affecting the health of those 18 years and older, and of Comirnaty 10 μg for use in those aged 5 to 11 years old against the risk of the use of the vaccine injuriously affecting the health of those aged 5 to 11 years old. I am satisfied, for the reasons set out in this memo, the associated Medsafe evaluation reports, the referral memo at Appendix One, and the enclosed MAAC minutes that it is desirable that Comirnaty 30 μg and Comirnaty 10 μg be able to be sold, supplied, and used in New Zealand.

Signature _____ Date: 16/12/2021

Chris James
Group Manager, Medsafe

Appendix One

MAAC referral memo (dated 10 December 2021)

Refer attached.

Appendix Two

MAAC minutes (113th meeting)

Refer attached.

Appendix Three

Data sheets

Refer attached.

Appendix Four

Draft *Gazette* notice

Refer attached.

Appendix Five

Draft letter to the sponsor

Refer attached.

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

COMIRNATY® (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/0.2 mL dose)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and **must be diluted** before use.

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see Section 4.2 Dose and method of administration and Section 6.6 Special precautions for disposal and other handling.

1 dose (0.2 mL) contains 10 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for suspension for injection (sterile concentrate).

COMIRNATY is a white to off-white frozen suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY (orange cap, must dilute) has provisional consent (see section 5.1) for the indication below:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

4.2 Dose and method of administration

Dose

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)

COMIRNATY (orange cap, must dilute) is administered intramuscularly as a primary course of 2 doses (0.2 mL each) at least 21 days apart.

The interchangeability of COMIRNATY with other COVID-19 vaccines to complete the primary vaccination course has not been established. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the primary vaccination course.

COMIRNATY (orange cap, must dilute) should be used only for children 5 to 11 years of age.

Elderly population

Refer to the Data Sheet for COMIRNATY (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose).

Method of administration

COMIRNATY should be administered intramuscularly, after dilution. The preferred site of administration is the deltoid muscle of the upper arm.

Do not inject COMIRNATY intravascularly, subcutaneously or intradermally.

COMIRNATY should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering COMIRNATY, see Section 4.4 Special warnings and precautions for use.

COMIRNATY (orange cap, must dilute)

Vials have an orange cap and after **dilution** contain ten doses of 0.2 mL of vaccine. In order to extract ten doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a tenth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on thawing, handling, dilution and dose preparation of COMIRNATY (orange cap, must dilute) see Section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of COMIRNATY.

The individual should be kept under close observation for at least 15 minutes following vaccination. A second dose of COMIRNATY should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Stress-related responses

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, COMIRNATY should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of COMIRNATY has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by COMIRNATY is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with COMIRNATY may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of COMIRNATY.

Use in the elderly

Clinical studies of COMIRNATY include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. See Section 5.1 Pharmacodynamic properties, Clinical trials, Efficacy against COVID-19.

Paediatric use

The safety and efficacy of COMIRNATY in children aged less than 5 years of age have not yet been established.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed.

Concomitant administration of COMIRNATY with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Fertility

In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 micrograms each, spanning between pre-mating day 21 and gestation day 20). SARS-CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate.

Pregnancy

There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Section 4.6 Fertility, pregnancy and lactation, Fertility). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

It is unknown whether tozinameran is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Section 4.6 Fertility, pregnancy and lactation, Fertility).

4.7 Effects on ability to drive and use machines

COMIRNATY has no, or negligible, influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 Undesirable effects may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of COMIRNATY was evaluated in participants 5 years of age and older in 3 clinical studies that included 24,675 participants (comprised of 22,026 participants 16 years of age and older, 1,131 adolescents 12 to 15 years of age and 1,518 children 5 to 11 years of age) that have received at least one dose of COMIRNATY.

Additionally, 306 existing Phase 3 participants at 18 to 55 years of age received a booster dose (third dose) of COMIRNATY approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.

Participants 16 years of age and older – after 2 doses

In Study C4591001, a total of 22,026 participants 16 years of age or older received at least 1 dose of COMIRNATY 30 micrograms and a total of 22,021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the COMIRNATY and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of COMIRNATY.

At the time of the analysis of Study C4591001 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25,651 (58.2%) participants (13,031 COMIRNATY and 12,620 placebo) 16 years of age and older were followed up for ≥4 months after the second dose. This included a total of 15,111 (7,704 COMIRNATY and 7,407 placebo) participants 16 to 55 years of age and a total of 10,540 (5,327 COMIRNATY and 5,213 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 subjects receiving COMIRNATY, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Study C4591001 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving COMIRNATY (n=100) in the individuals with stable HIV infection was similar to that seen in the general population.

Adolescents 12 through 15 years of age – after 2 doses

In an analysis of Study C4591001, 2,260 adolescents (1,131 COMIRNATY 30 micrograms; 1,129 placebo) were 12 through 15 years of age. Of these, 1,308 adolescents

(660 COMIRNATY and 648 placebo) have been followed for at least 2 months after the second dose of COMIRNATY. The safety evaluation in Study C4591001 is ongoing.

The most frequent adverse reactions in adolescents 12 through 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).

Children 5 to 11 years of age – after 2 doses

In an analysis of Study C4591007 Phase 2/3, 2,268 children (1,518 COMIRNATY 10 micrograms; 750 placebo) were 5 to 11 years of age. Of these, 2,158 (95.1%) (1,444 COMIRNATY 10 micrograms and 714 placebo) children have been followed for at least 2 months after the second dose. The safety evaluation in Study C4591007 is ongoing.

The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

Participants 18 years of age and older – after booster dose

A subset from Study C4591001 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original COMIRNATY 2-dose course, received a booster dose (third dose) of COMIRNATY approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common (≥ 1/10),

Common (≥ 1/100 to < 1/10),

Uncommon (≥ 1/1,000 to < 1/100),

Rare (≥ 1/10,000 to < 1/1,000),

Very rare (< 1/10,000),

Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from COMIRNATY clinical trials: Individuals 12 years of age and older

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy[a]		

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache		Lethargy	Acute peripheral facial paralysis[b]	
Gastrointestinal disorders		Nausea;			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia[c]; Injection site swelling	Injection site redness	Asthenia; Malaise;		Facial swelling[d]

[a] A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.
[b] Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COMIRNATY group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
[c] A higher frequency of pyrexia was observed after the second dose.
[d] Facial swelling in vaccine recipients with a history of injection of dermatological fillers

Table 2. Adverse Reactions from COMIRNATY clinical trial: Individuals 5 to 11 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Urticaria[a,b]; Pruritus[a,b]; Rash[a,b]			Anaphylaxis[a]

Table 2. Adverse Reactions from COMIRNATY clinical trial: Individuals 5 to 11 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					
Gastrointestinal disorders		Diarrhoea[a]; Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Injection site swelling; Injection site redness	Pyrexia	Malaise			

a. These adverse reactions were identified in the post-authorisation period. The following events were not reported in participants 5 to 11 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001: angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
b. The following events are categorised as hypersensitivity reactions: urticaria, pruritus, and rash

Post-marketing experience

Although the events listed in Table 3 were not observed in the clinical trials, they are considered adverse drug reactions for COMIRNATY as they were reported in the post-marketing experience. As these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 3:Adverse reactions from COMIRNATY post marketing experience

System Organ Class	Adverse Drug Reaction
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g. rash, pruritis, urticaria, angioedema)
Cardiac disorders	Myocarditis Pericarditis
Gastrointestinal disorders	Diarrhoea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)
General disorders and administration site conditions	Extensive swelling of vaccinated limb

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of COMIRNATY. The COMIRNATY recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03.

Mechanism of action

The nucleoside-modified messenger RNA in COMIRNATY is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. COMIRNATY elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

Clinical efficacy and safety

Efficacy

Study C4591001 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study C4591001, based on data accrued through 14 November 2020, approximately 44,000 participants were randomised equally and were to receive 2 doses of COMIRNATY or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COMIRNATY. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins through to conclusion of the study in order to receive either placebo or COMIRNATY.

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the COMIRNATY group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COMIRNATY group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COMIRNATY group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COMIRNATY group and in total 2,222 person-years for the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

COMIRNATY efficacy information is presented in Table 4.

Table 4: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY** **N[a] = 18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo** **N[a] = 18,325 Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY** **N[a] = 18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo** **N[a] = 18,325 Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided confidence interval (CI) for vaccine efficacy (VE) is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, efficacy of COMIRNATY in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% credible interval of 89.9% to 97.3%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through 13 March 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information is presented in Table 5.

Table 5: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine efficacy % (95% CI[e])**
All participants[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Efficacy against severe COVID-19 in participants 12 years of age or older – after 2 doses

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 6) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

Table 6. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on Food and Drug Administration (FDA)† Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time (n2[b])	Placebo Cases n1[a] Surveillance Time (n2[b])	Vaccine Efficacy % (95% CI[c])
After Dose 1[d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician
g. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

An analysis of Study C4591001 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 7.

Table 7: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2 – participants without evidence of infection and with or without evidence of infection prior to 7 days after Dose 2 – adolescents 12 to 15 years of age evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY **N[a] = 1005** **Cases** **n1[b]** **Surveillance time[c] (n2[d])**	**Placebo** **N[a] = 978** **Cases** **n1[b]** **Surveillance time[c] (n2[d])**	**Vaccine efficacy** **% (95% CI[e])**
Adolescents 12 to 15 years	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection			
	COMIRNATY **N[a] = 1119** **Cases** **n1[b]** **Surveillance time[c] (n2[d])**	**Placebo** **N[a] = 1110** **Cases** **n1[b]** **Surveillance time[c] (n2[d])**	**Vaccine efficacy** **% (95% CI[e])**
Adolescents 12 to 15 years	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time. CI not adjusted for multiplicity.

In Study C4591001 an analysis of SARS-CoV-2 neutralising titres in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to COMIRNATY in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 to 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titres at 1 month after Dose 2. The geometric mean titres (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67), which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

Immunogenicity in children 5 to 11 years of age – after 2 doses

Study C4591007 is a Phase 1/2/3 study comprised of an open-label vaccine dose-finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through to 11 years of age.

In C4591007, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 to 11 years of age in the Phase 2/3 part of Study C4591007 to participants 16 to 25 years of age in the Phase 2/3 part of Study C4591001 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 to 11 years of age to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 8.

Table 8: Summary of geometric mean ratio for 50% neutralising titre – Comparison of children 5 to 11 years of age (Study C4591007) to participants 16 to 25 years of age (Study C4591001) – participants without* evidence of infection up to 1 month after Dose 2 – evaluable immunogenicity population

		COMIRNATY		5 to 11 years/ 16 to 25 years	
		10 microgram/dose 5 to 11 years n[a]=264	30 microgram/dose 16 to 25 years n[a]=253		
Assay	**Time point[b]**	**GMT[c] (95% CI[c])**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	**Met immunobridging objective[e] (Y/N)**
SARS-CoV-2 neutralisation assay - NT50 (titre)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

*Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (Group 1[5 to 11 years of age] - Group 2 [16 to 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%) as presented in Table 9.

Table 9: Difference in percentages of participants with seroresponse – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – comparison of 5 to 11 years of age to Study C4591001 Phase 2/3 16 to 25 years of age – evaluable immunogenicity population

		COMIRNATY		5 to 11 years/ 16 to 25 years	
		10 microgram/dose 5 to 11 years N[a]=264	30 microgram/dose 16 to 25 years N[a]=253		
Assay	**Time point[b]**	**n[c] (%) (95% CI[d])**	**n[c] (%) (95% CI[d])**	**Difference %[e] (95% CI[f])**	**Met immunobridging objective[g] (Y/N)**
SARS-CoV-2 neutralisation assay – NT50 (titre)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralising titre 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 to 11 years of age] – Group 2 [16 to 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of COMIRNATY was based on an assessment of 50% neutralising titres (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study C4591001, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 to 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise in NT50 from baseline (before Dose 1), These analyses are summarised in Table 10.

Table 10. SARS-CoV-2 neutralisation assay - NT50 (titre)† (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 to 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population±

	n	1 month after booster dose (95% CI)	1 month after primary series (95% CI)	1 month after booster dose/- 1 month after primary series (97.5% CI)	Met noninferiority objective (Y/N)
Geometric mean 50% neutralising titre (GMT[b])	212[a]	2466.0[b] (2202.6, 2760.8)	750.6[b] (656.2, 858.6)	3.29[c] (2.77, 3.90)	Y[d]
Seroresponse rate (%) for 50% neutralising titre[†]	200[e]	199[f] 99.5% (97.2%, 100.0%)	196[f] 98.0% (95.0%, 99.5%)	1.5%[g] (-0.7%, 3.7%[h])	Y[i]

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

† SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

± All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80.

e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is > -10%.

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of COMIRNATY (lipids and mRNA) are not expected to have genotoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

Distearoylphosphatidylcholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6 Special precautions for disposal and other handling.

6.3 Shelf life

COMIRNATY (orange cap, must dilute)

Unopened vial

Frozen vial

6 months when stored at -90°C to -60°C.

The vaccine will be received frozen at -90°C to -60°C. Frozen vaccine can be stored either at -90°C to -60°C or 2°C to 8°C upon receipt.

When stored frozen at -90°C to -60°C, 10-vial packs of the vaccine can be thawed at 2°C to 8°C for 4 hours or individual vials can be thawed at room temperature (up to 30°C) for 30 minutes.

Thawed vial

If the vaccine is received at 2°C to 8°C it should be stored at 2°C to 8°C. Once removed from frozen storage, the unopened vial may be stored refrigerated at 2°C to 8°C for a single period of up to 10 weeks within the 6-month shelf life.

Upon moving the product to 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90°C to -60°C, the vaccine can be thawed at either 2°C to 8°C or at temperatures up to 30°C.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8ºC to 30ºC.

Thawed vials can be handled in room light conditions.

Once thawed COMIRNATY (orange cap, must dilute) should not be re-frozen.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2ºC to 30°C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

COMIRNATY (orange cap, must dilute) can be stored in a refrigerator at 2°C to 8°C for a single period of up to 10 weeks, not exceeding the original expiry date (EXP). The expiry date for storage at -90°C to -60°C is printed on the vial and outer carton after “EXP”.

Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

Store in the original package to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For detailed instructions see Section 6.6 Special precautions for disposal and other handling.

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3 Shelf life.

For additional advice on storing COMIRNATY, contact Pfizer New Zealand on 0800 736 363.

6.5 Nature and contents of container

COMIRNATY (orange cap, must dilute) 1.3 mL fill volume in 2 mL clear multidose vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Each vial contains 10 doses, see Section 6.6 Special precautions for disposal and other handling.

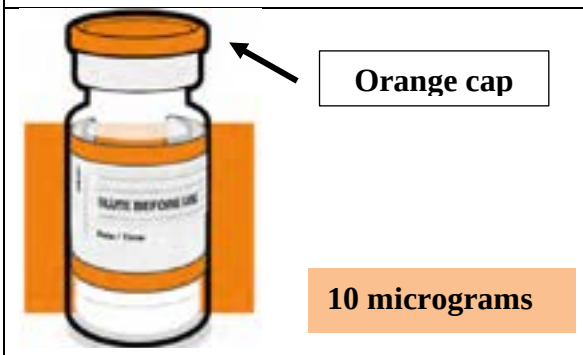
Pack size: 10 vials, 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

COMIRNATY (orange cap, must dilute)

The vaccine should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared diluted suspension.

<table>
<tr><th colspan="2">COMIRNATY (orange cap, must dilute)</th></tr>
<tr><td colspan="2">Dose Verification</td></tr>
<tr><td> 
</td><td>• Verify that the vial has an orange plastic cap.
• Only the orange cap vial can be used for children age 5 to 11 years.</td></tr>
</table>

<table>
<tr><th colspan="2">COMIRNATY (orange cap, must dilute)</th></tr>
<tr><td colspan="2">Handling Prior To Use</td></tr>
<tr><td> 
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If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2°C to 8°C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
Unopened vials can be stored for up to 10 weeks at 2°C to 8°C within the 6 month shelf life.
Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30°C for immediate use.

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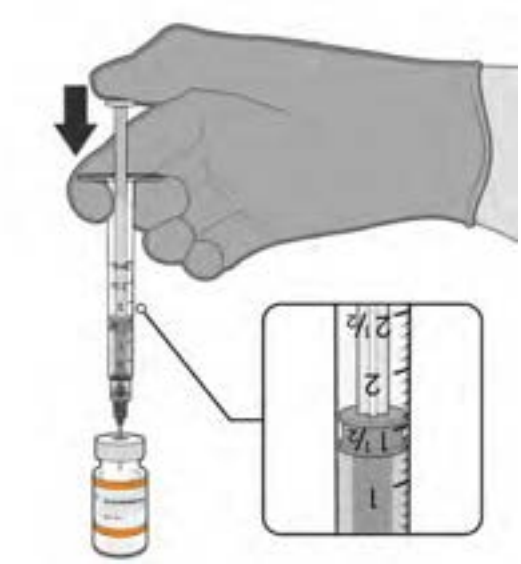
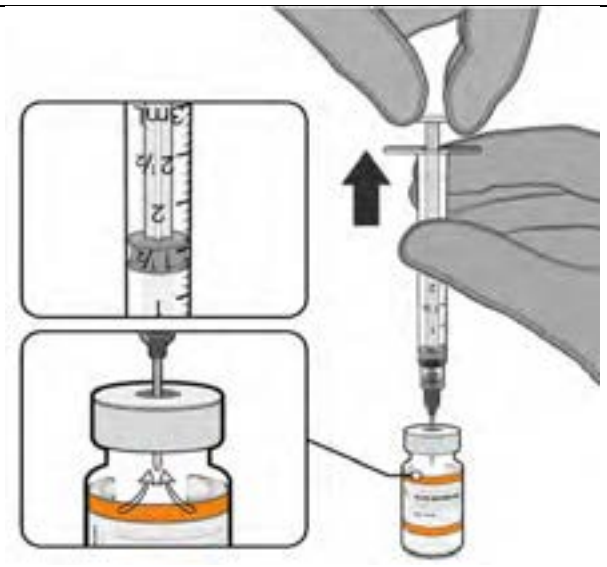
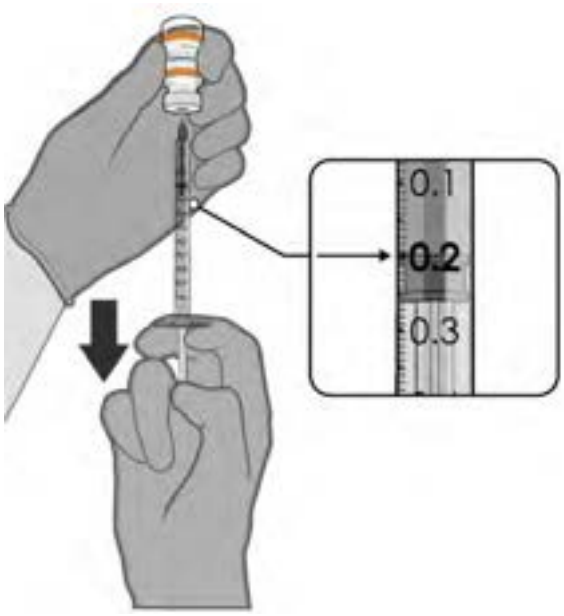
<table>
<tr><th colspan="2">COMIRNATY (orange cap, must dilute)</th></tr>
<tr><td colspan="2">Mixing Prior To Dilution</td></tr>
<tr><td>  </td><td>• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
• Prior to dilution, the thawed suspension may contain white to off-white opaque amorphous particles.</td></tr>
<tr><td colspan="2">Dilution</td></tr>
<tr><td> 
1.3 mL of 0.9% sodium chloride</td><td>• The thawed vaccine must be diluted in its original vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.</td></tr>
</table>

COMIRNATY (orange cap, must dilute)	
Dilution (continued)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted suspension 10 times. Do not shake. • The diluted vaccine should present as a white to off-white suspension with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

COMIRNATY (orange cap, must dilute)	
Dilution (continued)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2°C to 30°C and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted suspension to come to room temperature prior to use.

<table>
<tr><th colspan="2">COMIRNATY (orange cap, must dilute)</th></tr>
<tr><th colspan="2">Preparation of Individual 0.2 mL Doses of COMIRNATY (orange cap, must dilute)</th></tr>
<tr><td> 

0.2 mL diluted vaccine</td><td>

Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
Withdraw 0.2 mL of COMIRNATY (orange cap, must dilute).

Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres.

If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
Each dose must contain 0.2 mL of vaccine.
Discard syringe and needle after administration to a single patient.
Use a new, sterile needle and syringe to draw up each new dose.
If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
Discard any unused vaccine within 12 hours after dilution.

</td></tr>
</table>

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute this medicine:

Dd mmm 2021

10. DATE OF REVISION OF THE TEXT

Not applicable

Summary of Updates

Section	Update
1	Update to include new product presentations and new INN Tozinameran
2	Update to describe COMIRNATY (orange cap, must dilute) new formulation
3	Update to describe COMIRNATY (orange cap, must dilute) new formulation
4.1	Update indication age group to individuals 5 to 11 years of age
4.2	Update to describe COMIRNATY (orange cap, must dilute) new formulation
4.8	Add Adverse Reactions patient population 'For Age 5 to 11 Years'
5.1	Update Clinical Trials for Study 4591007
6.1	Update for COMIRNATY (orange cap, must dilute) new formulation
6.3	Amend shelf life from 9 months to 6 months; include detailed instructions on refrigeration conditions shelf life
6.4	Update storage details and alternate refrigeration and thaw handling
6.5	Update for new presentations
6.6	Update handling and administration for new Tris/Sucrose presentations

Gazette Notice 16/12/2021

Provisional Consent to the Distribution of New Medicines

Pursuant to section 23(1) of the Medicines Act 1981, the Minister of Health hereby provisionally consents to the sale, supply or use in New Zealand of the new medicines set out in the Schedule hereto:

Schedule

Product:	**Comirnaty (10mcg/0.2mL dose)**
Active Ingredient:	Tozinameran 0.1mg/mL
Dosage Form:	Concentrate for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturer:	Pfizer Manufacturing Belgium NV, Puurs, Belgium

Provisional consent is granted until 3 November 2023.

This consent is given subject to the following conditions.

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1. Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3. Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
4. Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
5. Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6. Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
9. Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.
10. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
11. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
12. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Product:	**Comirnaty (30mcg/0.3mL dose)**
Active Ingredient:	Tozinameran 0.1mg/mL
Dosage Form:	Suspension for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturer:	Pfizer Manufacturing Belgium NV, Puurs, Belgium

Provisional consent is granted until 3 November 2023.

This consent is given subject to the following conditions.

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, the dates of which may be altered by mutual agreement with Medsafe:

1. Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3. Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
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5. Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6. Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8. Provide the six months analysis data from Study C4591007. Due date: 28 February 2022.
9. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
10. Provide the final Clinical Study Reports for Study C4591007 within five working days of these being produced.
11. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
12. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
13. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Dated this 16th day of December 2021.

CHRIS JAMES, Group Manager, Medsafe, Ministry of Health (pursuant to delegation given by the Minister of Health on the 11th day of September 2013).

MEDSAFE

New Zealand Medicines and

Medicines

Revised: 31 May 2019

Medsafe Product Detail

File ref: TT50-10853/1a

Trade Name	*Dose Form*	*Strength*	*Identifier*
Comirnaty	Concentrate for injection	0.1 mg/mL	(orange cap, must dilute) 10 mcg/0.2 mL dose
Sponsor	*Application date*	*Registration situation*	*Classification*
Pfizer New Zealand Limited P O Box 3998 AUCKLAND 1140	12/11/2021	Provisional consent Approval date: 16/12/2021 Expiry date: 3/11/2023 Labelling exemption expires 03/11/2023	Prescription

Comirnaty (grey cap, do not dilute), new formulation, 0.1 mg/mL suspension for injection, 12 years of age and older (30 micrograms/dose)

Provisional consent is granted until 3 November 2023.

This consent is given subject to the following conditions.

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1) Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.

2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.

4) Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.

5) Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.

6) Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.

7) Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.

8) Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.

9) Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-

01 within five working days of these being produced.

10) Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.

11) Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.

12) Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Comirnaty (orange cap, must dilute), new formulation, 0.1 mg/mL concentrate for suspension for injection, children 5 to 11 years of age (10 micrograms/dose)

Provisional consent is granted until 3 November 2023.

This consent is given subject to the following conditions.

The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1) Prepare a "Dear Healthcare Professional" letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.

2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.

3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.

4) Provide independent batch certification, such as UK National Institute for

Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.

5) Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.

6) Provide updated stability data for the primary stability and process performance
qualification supportive stability batches. Due date: 28 February 2022.

7) Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.

8) Provide the six months analysis data from Study C4591007. Due date: 28 February 2022.

9) Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.

10) Provide the final Clinical Study Reports for Study C4591007 within five working days of these being produced.

11) Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.

12) Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.

13) Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may

lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Composition

Component	*Ingredient*	*Manufacturer*
concentrate for injection, New Formulation	Active	
	Tozinameran 0.1 mg/mL equivalent to 10 µg/0.2mL dose after dilution	BioNTech Manufacturing Marburg GmbH Emil-von-Behring-Strasse 76 Marburg 35041 Germany Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC One Burtt Road Andover Massachussetts 01810 United States of America Rentschler Biopharma SE Erwin-Rentschler-Strasse 21 Laupheim 88471 Germany BioNTech Manufacturing GmbH An der Goldgrube 12 Mainz 55131 Germany
	Excipient	
	1,2-Distearoyl-sn-glycero-3-phosphocholine	
	ALC-0159	

ALC-0315

Cholesterol

Sucrose

Trometamol

Trometamol hydrochloride

Water for injection

Production

Manufacturing step	*Manufacturer*
Finished Product Testing	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin Dublin 22 Ireland
	Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs B-2870 Belgium
Manufacture of Final Dose Form	Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs B-2870 Belgium
Packing	Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs B-2870 Belgium
Secondary Packaging	Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs B-2870 Belgium

NZ Site of Product Release	Pfizer New Zealand Limited Level 10, 11 Britomart Place Auckland CBD Auckland 1010

Packaging

Package	*Contents*	*Shelf Life*
Vial, glass, multi-dose, (1.3 mL fill), closed with rubber stopper, aluminium overseal and orange flip-off plastic cap	10 dose units	6 months from date of manufacture stored in the freezer at -90°C to -60°C protect from light 24 hours unopened stored at or below 30°C. Applies to thawed vials. Do not refreeze. 10 weeks unopened stored at 2° to 8°C (Refrigerate, do not freeze). Applies to thawed vials within the 6 month shelf-life. Do not refreeze. 12 hours diluted stored at or below 30°C
Vial, glass, multi-dose, (1.3 mL fill), closed with rubber stopper, aluminium overseal and orange flip-off plastic cap	195 dose units	6 months from date of manufacture stored in the freezer at -90°C to -60°C protect from light 24 hours unopened stored at or below 30°C. Applies to thawed vials. Do not refreeze. 10 weeks unopened stored at 2° to 8°C (Refrigerate, do not freeze). Applies to thawed vials within the 6 month shelf-life. Do not refreeze. 12 hours diluted stored at or below 30°C

Indications

Comirnaty has provisional consent for the indication below:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by

SARS-CoV-2, in children aged 5 to 11 years.

The use of this vaccine should be in accordance with official recommendations.

Latest Regulatory Activity

Application Date	*Application Type*	*Change(s)*	*Status*	*Payment Date*	*Priority*
13/1/2022	Changed Medicine Notification	Active ingredient method of manufacture - Grade 1; Administrative fee (CMN)	Initial evaluation	19/1/2022	
10/1/2022	Changed Medicine Notification	Shelf life/storage conditions - finished product; Administrative fee (CMN)	Initial evaluation	19/1/2022	
10/1/2022	Changed Medicine Notification	Active ingredient manufacturing site; Finished product testing site; Administrative fee (CMN)	Initial evaluation	19/1/2022	
10/1/2022	Changed Medicine Notification	Active ingredient manufacturing site; Administrative fee (CMN)	Initial evaluation	19/1/2022	
10/1/2022	Changed Medicine Notification	Active ingredient method of manufacture - Grade 1; Administrative fee (CMN)	Initial evaluation	19/1/2022	

10/1/2022	Changed Medicine Notification	Active ingredient manufacturing site; Administrative fee (CMN)	Awaiting payment	
12/11/2021	Provisional Consent (Section 23)	Additional dose form - higher-risk medicine - Grade 1 or 2	Granted 16/12/2021	24/11/2021

Updated summary of risk management plan for Comirnaty.

This document is a summary of the updated risk management plan (RMP) for Comirnaty. the PfizerBioNTech COVID-19 mRNA vaccine. The RMP is created by the vaccine manufacturer and is submitted to medicine regulators as part of the vaccine approval and safety monitoring processes. The RMP details important risks of Comirnaty, how these risks can be minimised, and how more information will be obtained about Comirnaty's risks and uncertainties (missing information).

A summary of the initial RMP for Comirnaty is published on Medsafe's website. Over time, the RMP is updated as more information becomes available, including any new risks or changes to current ones. This RMP update was made in conjunction with the extension of the indication to children 5 to 11 years of age.

The Cominarty data sheet, consumer medicine information and the package leaflet give essential information for healthcare professionals and patients on how to use the vaccine.

RMP definitions

Important risks

Important risks need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks are classified as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of the medicine.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Activities to minimise or further characterise identified risks

Measures to minimise the identified risks for medicinal products may include:

- specific information for healthcare professionals and patients, such as warnings, precautions and advice on correct use, in the data sheet, consumer medicine information and package leaflet
- important advice on the medicine's packaging
- the authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- the medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously by the company and regularly analysed, so that immediate action can be taken by the company as necessary. These measures constitute *routine pharmacovigilance activities*.

Other non-routine Measures to further characterise the risks include safety and efficacy studies. The studies may be in particular risk groups or for particular safety concerns. They may also be a condition of the medicine's approval. These measures constitute *additional pharmacovigilance activities.*

Comirnaty RMP

The Medicine and what it is used for

Comirnaty is a vaccine for active immunisation to prevent COVID-19 caused by SARSCoV-2 virus, in individuals 5 years of age and older (see the data sheets for the full indication). The vaccine contains nucleoside-modified messenger RNA encapsulated in lipid nanoparticles as the active substance and it is given intramuscularly.

There are 2 different strengths of Comirnaty:

- 30 mcg/dose for immunisation of individuals 12 years and older
- 10 mcg/dose for immunisation of individuals aged 5 to 11 years

Important risks, missing information and additional pharmacovigilance activities

The tables below summarise the risks for Comirnaty, as described in the updated RMP.

- Table 1 is a list of the important risks (identified and potential) and missing information.
- Tables 2–10 provide the evidence for linking the risk to the medicine, risk factors and risk groups, risk minimisation measures and a list of additional pharmacovigilance activities.
- Table 11 summarise the additional pharmacovigilance activities.

Table 1. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Table 2. Important Identified Risk: Anaphylaxis

Evidence for linking the risk to the medicine	Events of anaphylaxis have been reported.
Risk factors and risk groups	Known allergy to the vaccine or its ingredients.
Risk minimisation measures	Routine: Data sheet sections 4.4. and 4.8. Additional: None.
Additional pharmacovigilance activities*	C4591001 C4591009 C4591010 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU)

* See Table 11 for a summary of the studies.

Table 3. Important Identified Risk: Myocarditis and Pericarditis

Evidence for linking the risk to the medicine	Events of myocarditis and pericarditis have been reported.
Risk factors and risk groups	Most frequently reported in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for males and females of broader age range and following the first vaccination also.
Risk minimisation measures	Routine: Data sheet sections 4.4. and 4.8. Additional: Letter to healthcare professionals (DHCP) and communication plan.
Additional pharmacovigilance activities*	C4591009 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 sub-study)

	C4591036 (former Pediatric Heart Network study)

* See Table 11 for a summary of the studies.

Table 4. Important Potential Risk: Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine: None Additional: None
Additional pharmacovigilance activities*	C4591001 C4591009[a] C4591011[a]

	C4591012[a] C4591021 (former ACCESS/VAC4EU)[a]

a The study addresses safety events of interest including vaccine associated enhanced disease.
* See Table 11 for a summary of the studies.

Table 5. Missing Information: Use in pregnancy and while breast feeding

Risk minimisation measures	Data sheet section 4.6
Additional pharmacovigilance activities*	C4591009[b] C4591010[b] C4591011[b] C4591015 C4591021 (former ACCESS/VAC4EU)[b]

b Studies C4591009, C4591010, C4591011 and C4591021 address only 'Use in pregnancy'.
* See Table 11 for a summary of the studies.

Table 6. Missing Information: Use in immunocompromised patients

Risk minimisation measures	Data sheet sections 4.4 and 5.1.
Additional pharmacovigilance activities*	BNT162-01 cohort 13 C4591010[a] C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and Immunogenicity in high-risk adults)

a The study addresses safety events of interest.
*See Table 11 for a summary of the studies.

Table 7. Missing Information: Use in frail patients with co-morbidities (e.g.chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Data sheet section 5.1.
Additional pharmacovigilance activities*	C4591001 subset C4591011 C4501012

	C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 11 for a summary of the studies.

Table 8. Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 11 for a summary of the studies.

Table 9. Missing Information: Interaction with other vaccines

Risk minimisation measures	Data sheet section 4.5
Additional pharmacovigilance activities*	C4591030 (Co-administration study with seasonal influenza vaccine)

*See Table 11 for a summary of the studies.

Table 10. Missing Information: Long term safety data

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591001 C4591010 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 substudy) C4591036 (former PHN)

*See Table 11 for a summary of the studies.

Table 11. Studies

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An unfavourable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.
C4591009	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System (FDA's national electronic system).
C4591011	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.
C4591012	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use (individuals in the US Veteran's Affairs Health System) of COVID-19 mRNA vaccine.
C4591010	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.
C4591015	To assess safety and immunogenicity in pregnant women. In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding women vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding women who received COVID-19 mRNA vaccine during pregnancy.
C4591014	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital due to SARS-CoV-2 infection.
W1235284	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
W1255886	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
BNT162-01 Cohort 13	To assess potentially protective immune responses in immunocompromised adults.

C4591024 (former Safety and immunogenicity in high-risk adults)	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).
C4591021 (former ACCESS/VAC4EU)	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine. Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.
C4591038 (former C4591021 substudy)	To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with Comirnaty as well as individuals not vaccinated with a COVID-19 vaccine.
C4591036 (former Pediatric Heart Network study)	To characterise the clinical course, risk factors, long-term effects, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis.
C4591030 (Co-administration study with seasonal influenza vaccine)	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Corrigendum—Provisional Consent to the Distribution of New Medicines

This corrigendum amends the notice with the above heading, published in the *New Zealand Gazette*, 16 December 2021, Notice No. 2021-go5403, by replacing the notice with the following:

Pursuant to section 23(1) of the Medicines Act 1981, the Minister of Health hereby provisionally consents to the sale, supply or use in New Zealand of the new medicines set out in the Schedule hereto:

Schedule

Product:	**Comirnaty (30mcg/0.3mL dose)**
Active Ingredient:	Tozinameran 0.1mg/mL
Dosage Form:	Concentrate for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturer:	Pfizer Manufacturing Belgium NV, Puurs, Belgium

Provisional consent is granted until **3 November 2023**.

This consent is given subject to the following conditions. The New Zealand Sponsor must fulfil the following obligations within the timelines specified, which may be altered by mutual agreement with Medsafe:

1. Prepare a “Dear Healthcare Professional” letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3. Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
4. Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
5. Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6. Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
9. Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.
10. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
11. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
12. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Product:	**Comirnaty (10mcg/0.2mL dose)**
Active Ingredient:	Tozinameran 0.1mg/mL
Dosage Form:	Suspension for injection
New Zealand Sponsor:	Pfizer New Zealand Limited
Manufacturer:	Pfizer Manufacturing Belgium NV, Puurs, Belgium

Provisional consent is granted until **3 November 2023**.

This consent is given subject to the following conditions. The New Zealand Sponsor must fulfil the following obligations within the timelines specified, the dates of which may be altered by mutual agreement with Medsafe:

1. Prepare a “Dear Healthcare Professional” letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of these products. Due date: 10 January 2022.
2. The New Zealand site of batch release will only release batches for distribution in New Zealand once the sponsor has verified that the shipping temperature profile meets specifications.
3. Provide Certificates of Analysis to Medsafe for the first three batches of vaccine of each presentation intended to be distributed in New Zealand, prior to distribution.
4. Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.
5. Reassess and revise the finished product specifications acceptance limits for RNA and lipid content as further data becomes available. Due date: 31 December 2022.
6. Provide updated stability data for the primary stability and process performance qualification supportive stability batches. Due date: 28 February 2022.
7. Provide any reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.
8. Provide the six months analysis data from Study C4591007. Due date: 28 February 2022.
9. Provide any reports on efficacy including asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.
10. Provide the final Clinical Study Reports for Study C4591007 within five working days of these being produced.
11. Provide Periodic Safety Update Reports according to the same schedule as required by the EMA.
12. Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.
13. Perform the required pharmacovigilance activities and interventions detailed in the agreed RMP and any agreed updates to the RMP. An RMP should be submitted at the request of Medsafe or whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important milestone being reached.

Dated this 17th day of December 2021.

CHRIS JAMES, Group Manager, Medsafe, Ministry of Health (pursuant to delegation given by the Minister of Health on 11 September 2013).

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