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24 February 2022

s 9(2)(a)

By email: s 9(2)(a)
Ref: H202117877

Dear s 9(2)(a)

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) on 17 December 2021 for:

> *"The full meeting minutes from the 113th meeting of the Medicines Assessment Advisory Committee held on 14 December 2021 as outlined in the agenda (https://www.medsafe.govt.nz/committees/maac/Agenda113-14Dec21.htm).*
>
> *Please include all relevant correspondence (supporting evidence, email/text communications, memorandum, etc) for any applications for consent to distribute a new medicine under Section 20 / 23 / 24 of the Medicines Act 1981 that were discussed during the meeting in question."*

Information within scope of your request is itemised in Appendix 1 of this letter and copies of the documents are enclosed. The table in Appendix 1 outlines the grounds under which I have decided to withhold information. Where information is withheld, this is noted in the document itself.

I trust this information fulfils your request. Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Ministry website at: www.health.govt.nz/about-ministry/information-releases.

Yours sincerely

Chris James
Group Manager
Medsafe

Appendix 1: List of documents for release

#	Date	Document details	Decision on release
1	14 December 2021	Minutes of the 113th meeting of the Medicines Assessment Advisory Committee	Some information withheld under section 9(2)(g)(ii) of the Act to maintain the effective conduct of public affairs through the protection of such Ministers, members of organisations, officers, and employees from improper pressure or harassment.
2	N/A	Medsafe Evaluation Report - Clinical	Some information withheld under the following sections of the Act: • 9(2)(a) to protect the privacy of natural persons • 9(2)(b)(ii) where its release would likely unreasonably prejudice the commercial position of the person who supplied the information.
3	N/A	Medsafe Evaluation Report - Quality	Some information withheld under section 9(2)(b)(ii) of the Act.
4	N/A	Information supplied by Pfizer New Zealand in support of its application	Withheld in full under section 9(2)(b)(ii) of the Act..

Document 1

Minutes of the 113th meeting of the Medicines Assessment Advisory Committee by videoconference on 14 December 2021 at 9:30am

Present:

s 9(2)(g)(ii) [redacted]

s 9(2)(g)(ii) [redacted] (Secretary)

In Attendance (from Medsafe):

s 9(2)(g)(ii) [redacted] (Manager, Product Regulation Branch)

s 9(2)(g)(ii) [redacted] (Manager, Clinical Risk Management Branch)

s 9(2)(g)(ii) [redacted] (Team Leader, Product Regulation Branch)

s 9(2)(g)(ii) [redacted] (Principal Technical Specialist, Product Regulation Branch)

s 9(2)(g)(ii) [redacted] (Senior Advisor, Product Regulation Branch)

s 9(2)(g)(ii) [redacted] (Pharmacovigilance Advisor, Clinical Risk Management Branch)

s 9(2)(g)(ii) [redacted] (Pharmacovigilance Advisor, Clinical Risk Management Branch)

s 9(2)(g)(ii) [redacted] (Medical Advisor, Clinical Risk Management Branch)

s 9(2)(g)(ii) [redacted] (Senior Pharmacovigilance Advisor, Clinical Risk Management Branch)

Representatives from Pfizer:

s 9(2)(g)(ii) [redacted] (Head of Regulatory Affairs)

s 9(2)(g)(ii) [redacted] (Regulatory Affairs Manager)

s 9(2)(g)(ii) [redacted] (Senior Regulatory Affairs Associate)

s 9(2)(g)(ii) [redacted] (Vaccines Medical Lead Korea/AU/NZ)

s 9(2)(g)(ii) [redacted] (Cluster Safety Lead)

Apologies:

Apologies were received from s 9(2)(g)(ii) [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 s 9(2)(g)(ii) .

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.

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:

DATE:

This document was prepared and written by
s 9(2)(g)(ii)
the Medicines Assessment Advisory Committee Secretary.

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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
s 9(2)(b)(ii)			
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
s 9(2)(b)(ii)			
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 s 9(2)(b)(ii)

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 s 9(2)(b)(ii)

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.

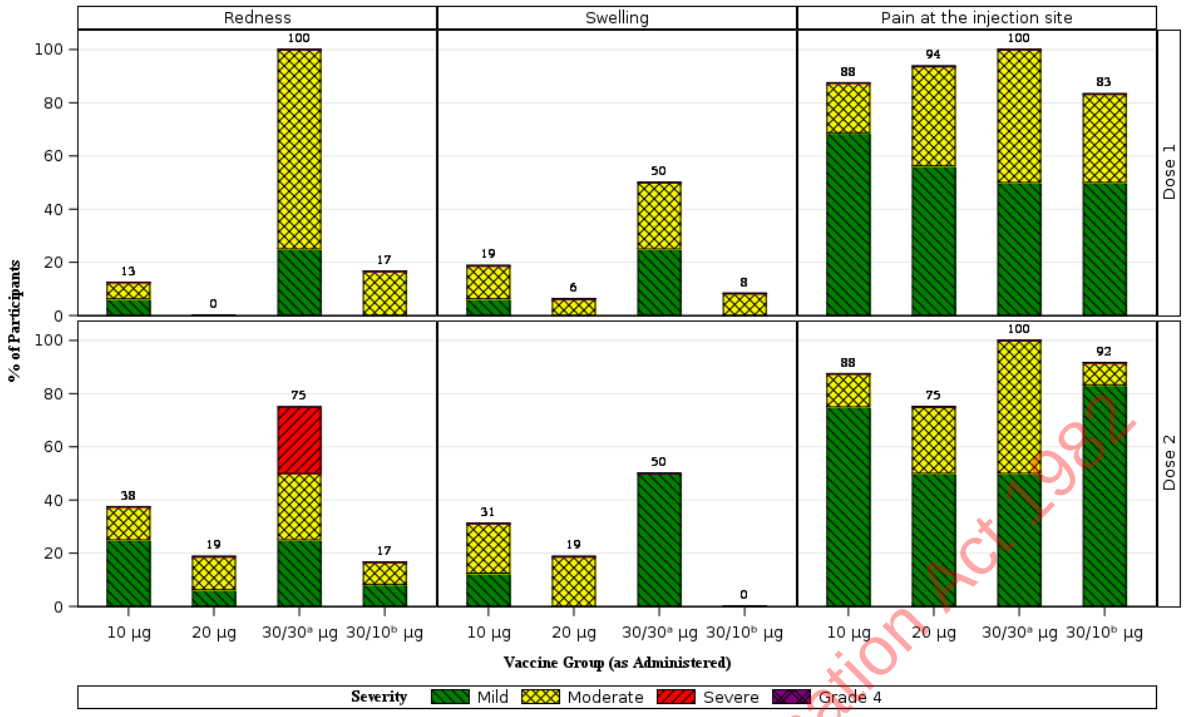
8.2 Evaluator's comments

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.

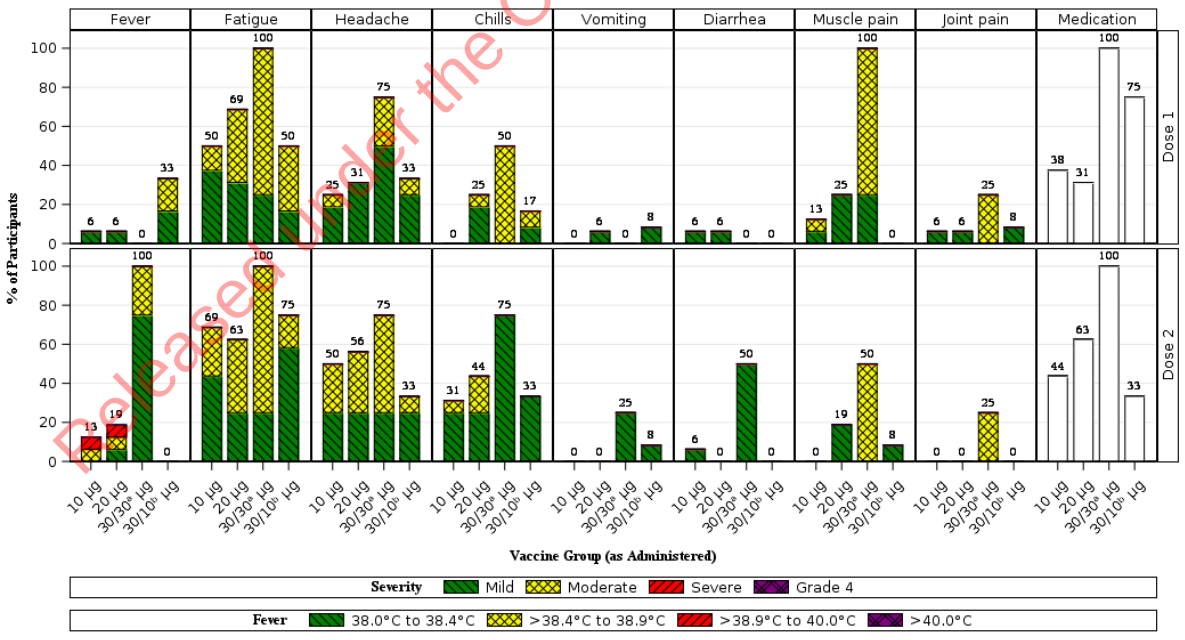
Safety review of reactogenecity data from the initial 4 participants who received the 30 microgram dose for both doses found that all participants developed mild to moderate redness at the injection and fever to 37.8c.

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: ./nda3/C4591007_Phase1_EUA/adce_f001_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.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2021 (13:36) Source Data: adfacevd Table Generation: 17AUG2021 (06:18)
(Cutoff Date: 16JUL2021, Snapshot Date: 11AUG2021) Output File: ./nda3/C4591007_Phase1_EUA/adce_f001_se_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)	30 µg 16-25 Years (C4591001)	5 to <12 Years (C4591007)	16-25 Years (C4591001)
	n[a] (%)	n[a] (%)	n[a] (%)	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).

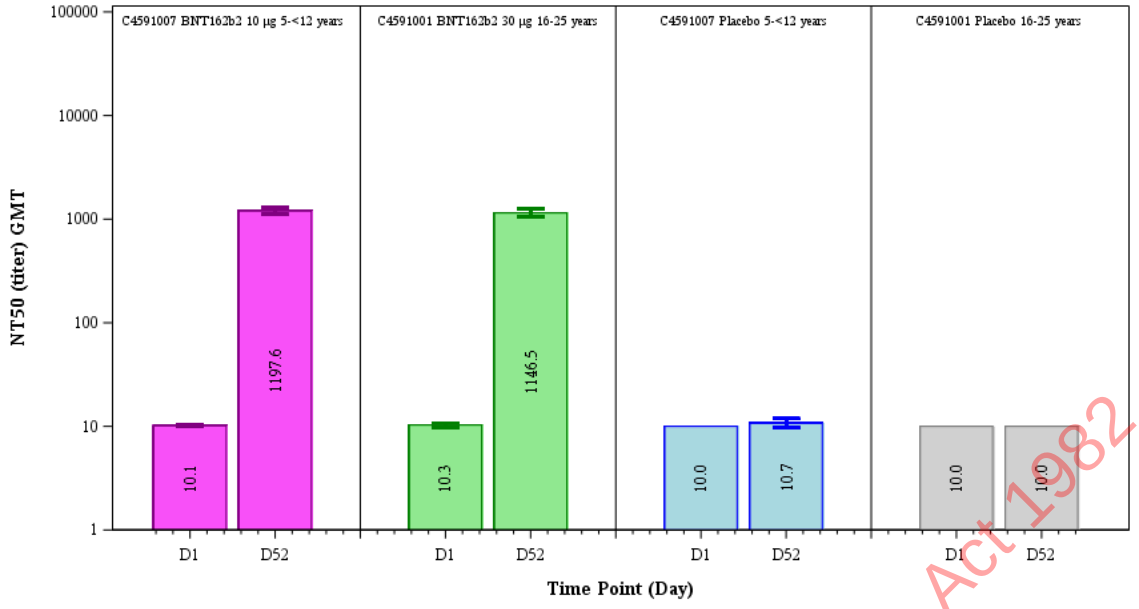
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.8.

PFIZER CONFIDENTIAL Source Data: adva Table Generation: 16SEP2021 (18:27)
(Cutoff Date: C4591001 [24MAR2021]/C4591007 [06SEP2021]) Output File: /nda2_ubped/C4591007_P23_5_12_Bridging/adva_s004_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_ubped/C4591007_P23_5_12_Bridging/adva_f002_sars_50_p2_12_evl

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[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])
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[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])
		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[b]								
		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 (657.3, 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]								
		POS	21	3270.0 (2032.1, 5261.8)	13	2253.8 (1497.7, 3391.5)	13	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: ./nda2_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[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
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 prevaccination 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_wee_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: ./nda2 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 s 9(2)(b)(ii) 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:

- s 9(2)(b)(ii)

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 at least 1 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_SAP_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.

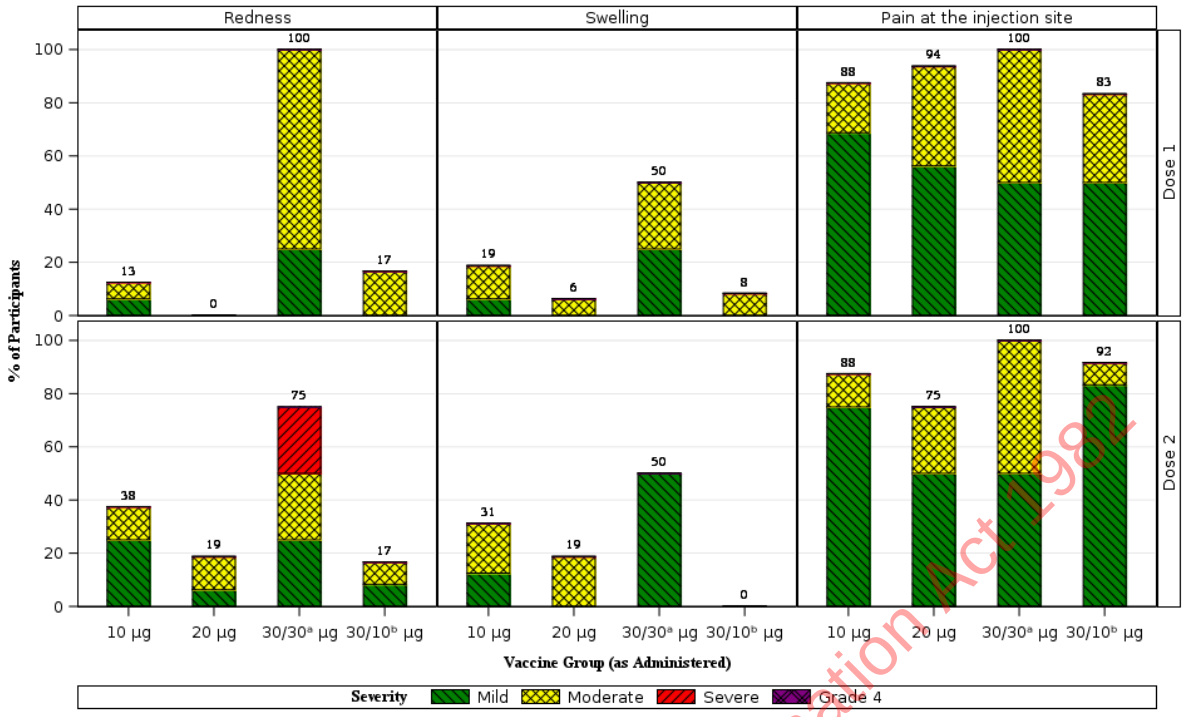
10.3.1 Local Reactions

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: /nda3/C4591007_Phase1_EUA/adce_f001_lr_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 s 9(2)(a) 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 s 9(2)(a) participant s 9(2)(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 s 9(2)(a) participant s 9(2)(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%).

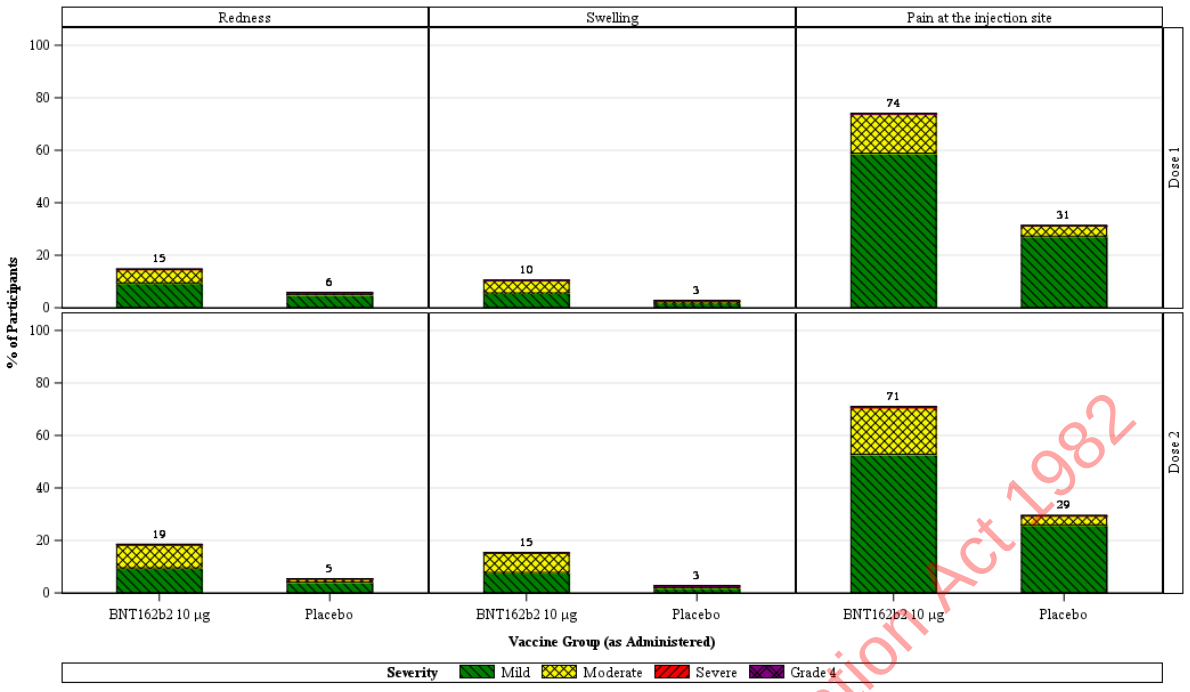
In the tozinameran group, frequencies of redness and swelling were similar after Doses 1 and 2. Frequencies of redness showed a modest increase from after Dose 1 compared to after Dose 2 of tozinameran (14.7% vs 18.5%). Frequencies of swelling also showed a modest increase after Dose 1 compared with 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.



Note: The number above each bar denotes the percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:18) Source Data: adfacevd
Table Generation: 15SEP2021 (23:02) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: /nda2_ubped/C4591007_P23_EUA/adce_f001_lr_p2_12

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

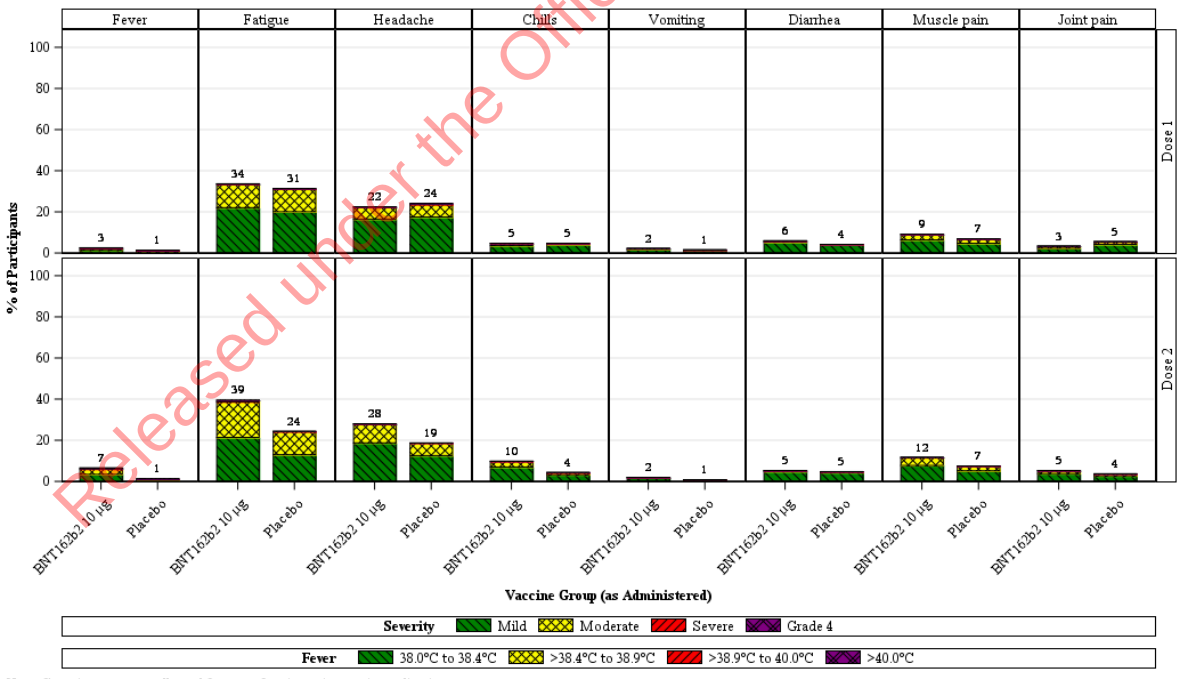
tozinameran and placebo groups after either dose. In the tozinameran group, highest frequencies of severe systemic events reported after Dose 1 and Dose 2 were fatigue (0.3% and 0.7%) and fever (0.2% and 0.5%).

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.



Note: Severity was not collected for use of antipyretic or pain medication.
Note: The number above each bar denotes the percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2021 (17:18) Source Data: adfacevd
Table Generation: 15SEP2021 (23:02) (Cutoff Date: 06SEP2021, Snapshot Date: 13SEP2021) Output File: ./nda2_ubped/C4591007_P23_EUA/adce_f001_se_p2_12

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 s 9(2) year-old s 9(2)(a) 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 s 9(2)(a) female participant s 9(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 s 9(2)(a) 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)* s 9(2)(b)(ii) [redacted] s 9(2)(b)(ii) [redacted] s 9(2)(b)(ii) [redacted] <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). s 9(2)(b)(ii) [redacted] *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****.*

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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)

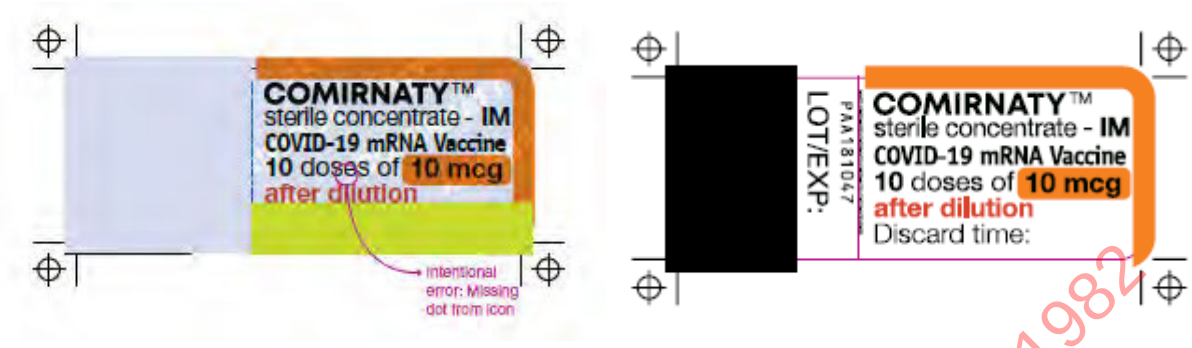
The information on this label is the same as on PAA173908. This version is more recent and has been updated to include the text 'Do not dilute' in bold font.

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'.

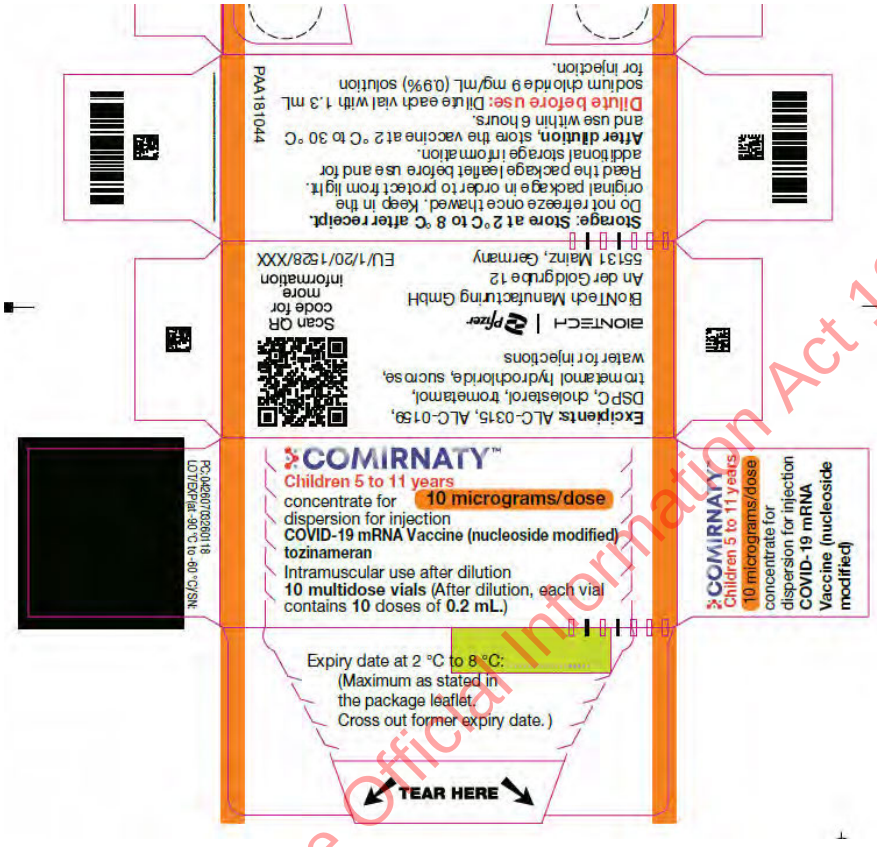
10 mcg PAA177913 (US EUA) (41 mm x 16 mm)

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)*



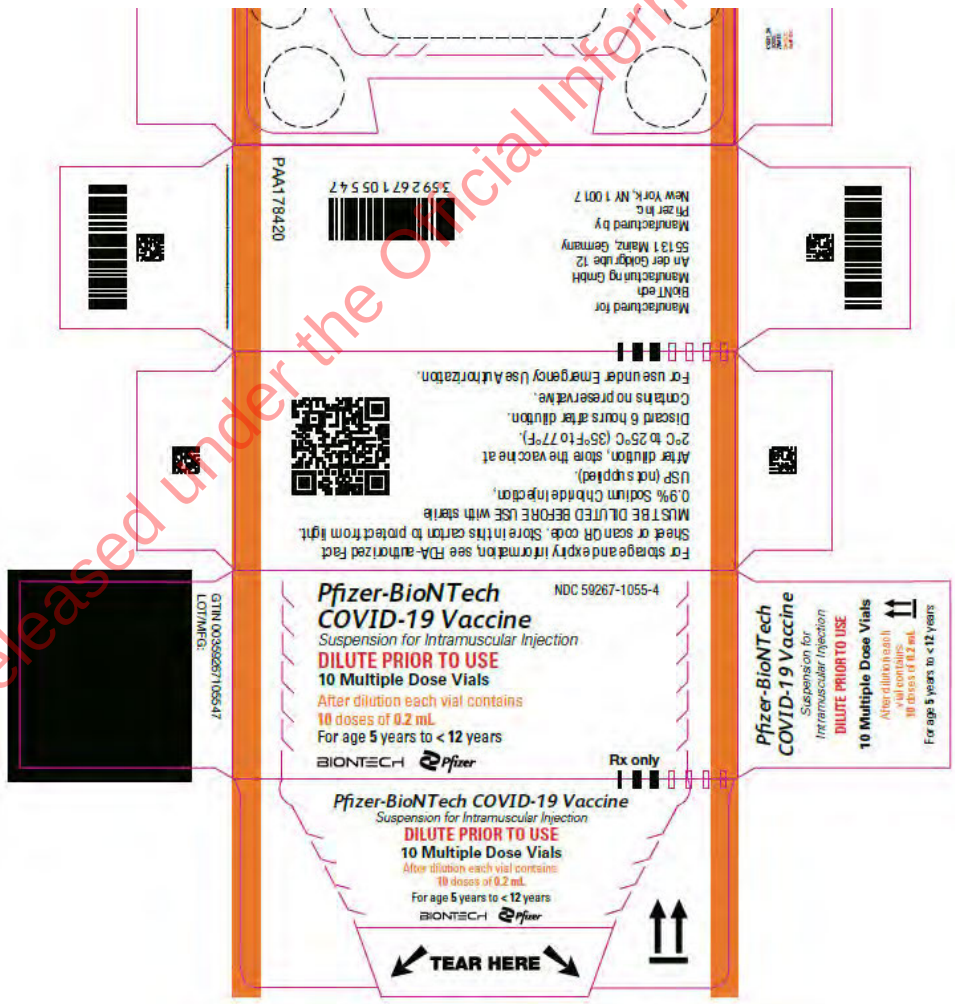
Two EU labels have been provided for the 10 pack size of the 10 micrograms/dose presentation: *PAA181044* (shown above) and *PAA181045* (same content as PAA181044 but slightly different dimensions). The sponsor states in the cover letter (and has signed the labelling declaration in the NMA form to this 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:

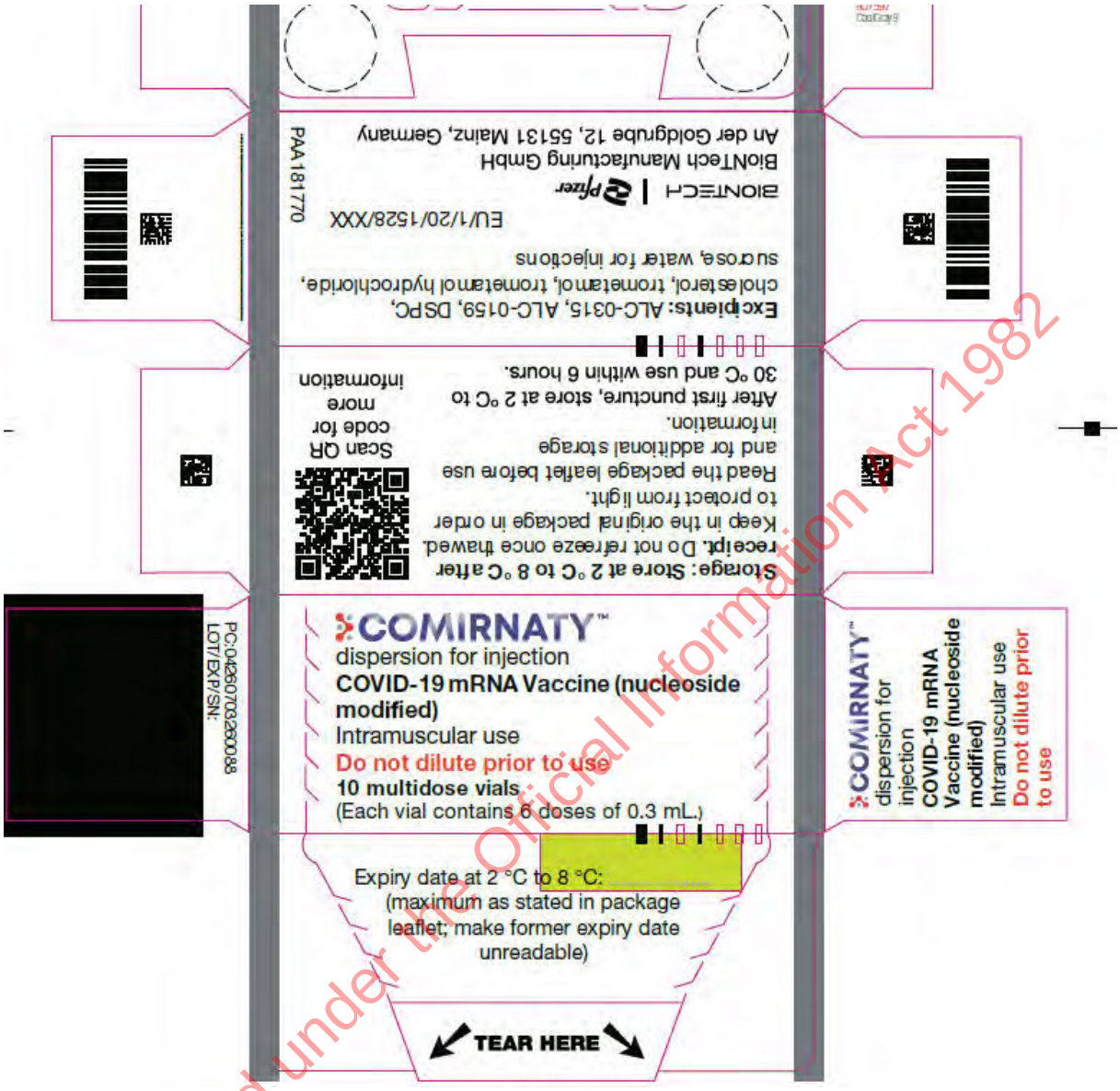
- the age range (5 years to < 12 years versus 5 to 11 years) and product name (Pfizer-BioNTech COVID-19 vaccine versus Comirnaty) on the FDA EUA labels differ from those on the EU labels
- the FDA EUA labels include the classification statement ('Rx only) but do not state the drug substance name or strength
- 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.

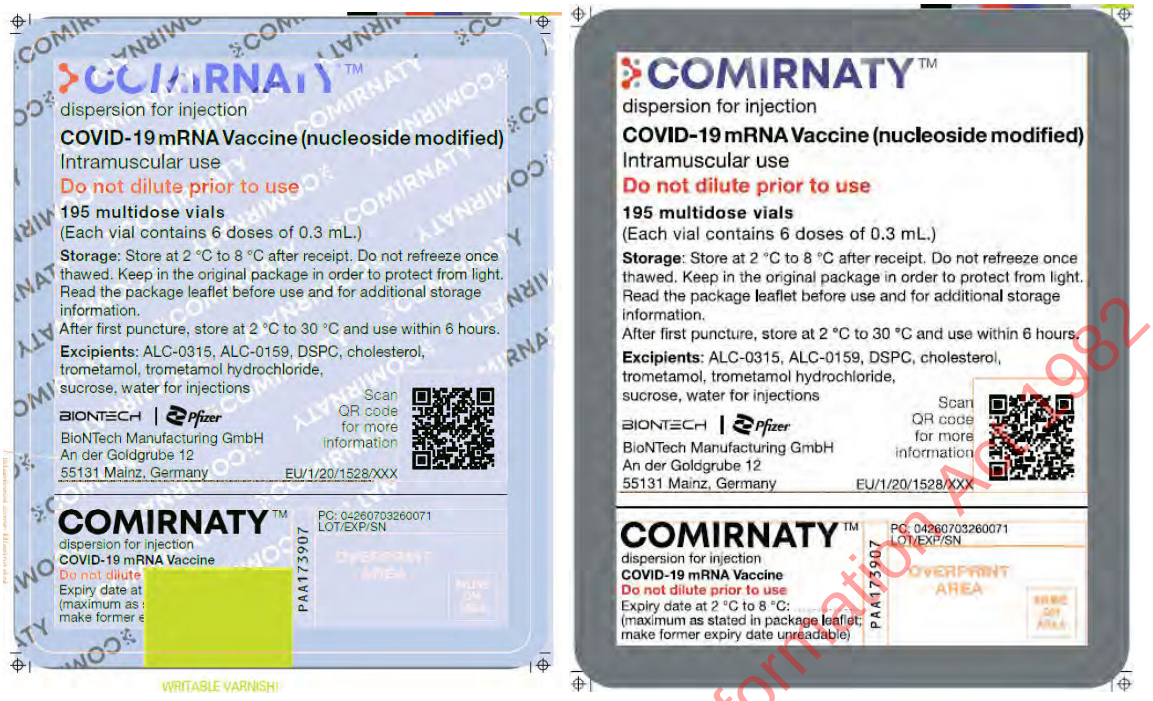
30 mcg PAA181770 (EMA approved for PPQ batches; shown below) (37 x 39 x 89 mm) and *30 mcg PAA181911 (EMA approved for PPQ batches) (37 x 47 x 89 mm)*



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.

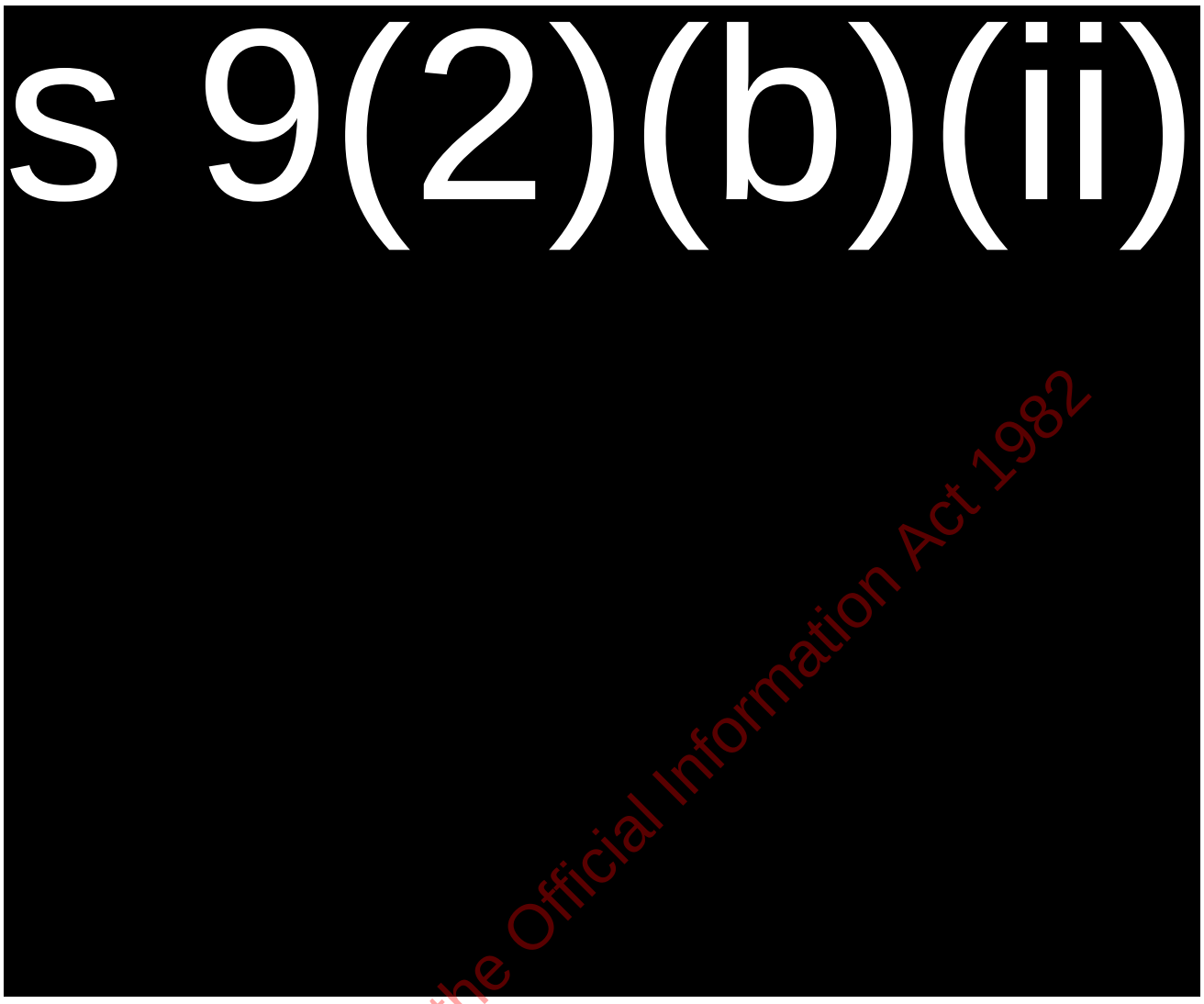
There are no ingredients of animal origin in the drug product.

3.2.P.2.2. Drug product

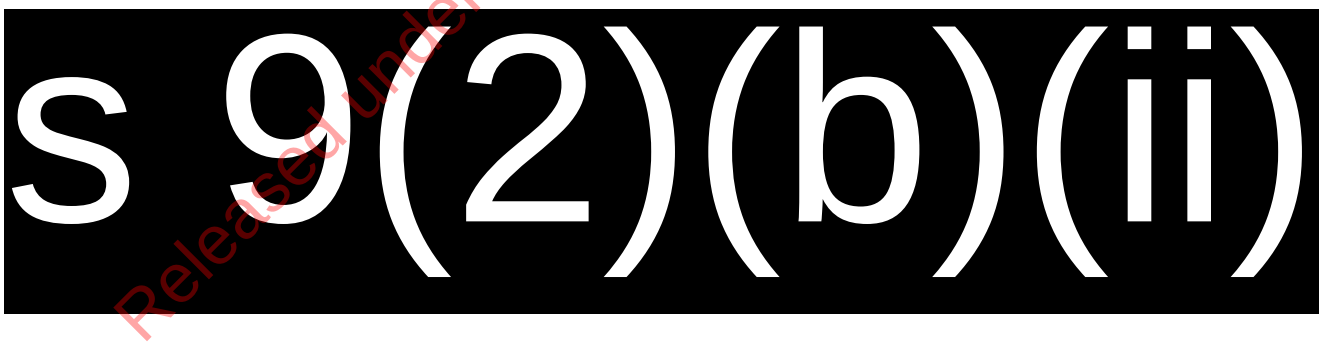
3.2.P.2.2.1. Formulation and test method development

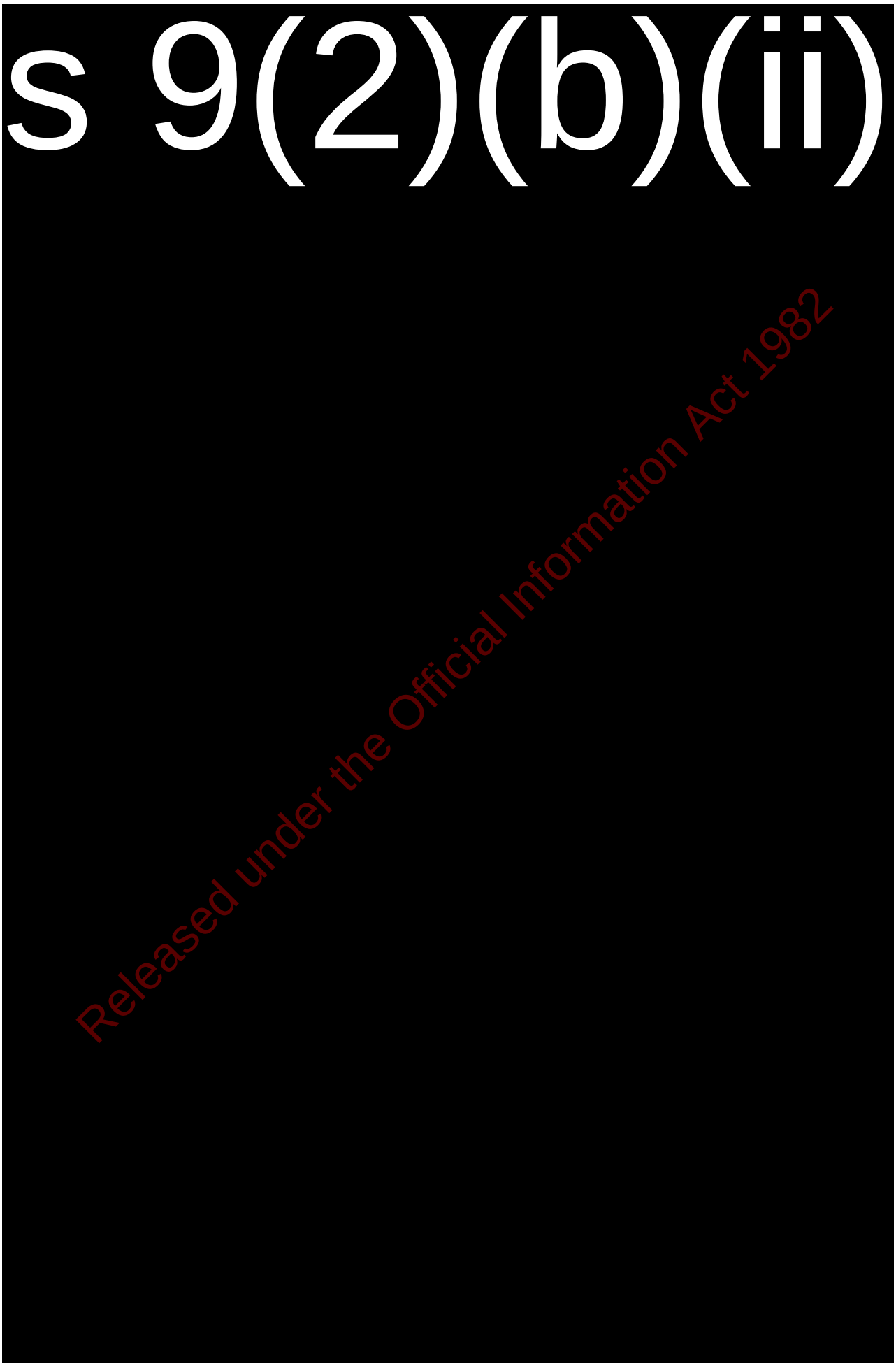
s 9(2)(b)(ii)

s 9(2)(b)(ii)



3.2.P.2.3. Manufacturing process development





s 9(2)(b)(ii)

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). s 9(2)(b)(ii) [redacted] There is confirmation in the dossier that the samples are being tested using methods validated for the following potential leachables: s 9(2)(b)(ii) [redacted] (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 (but this was a recommendation (REC13) of the EMA), ***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	s 9(2)(b)(ii)		

a. Development LNPs made at laboratory scale have been demonstrated to be representative of those made at full scale for commercial manuafacture.

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	s 9(2)(b)(ii)		

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.

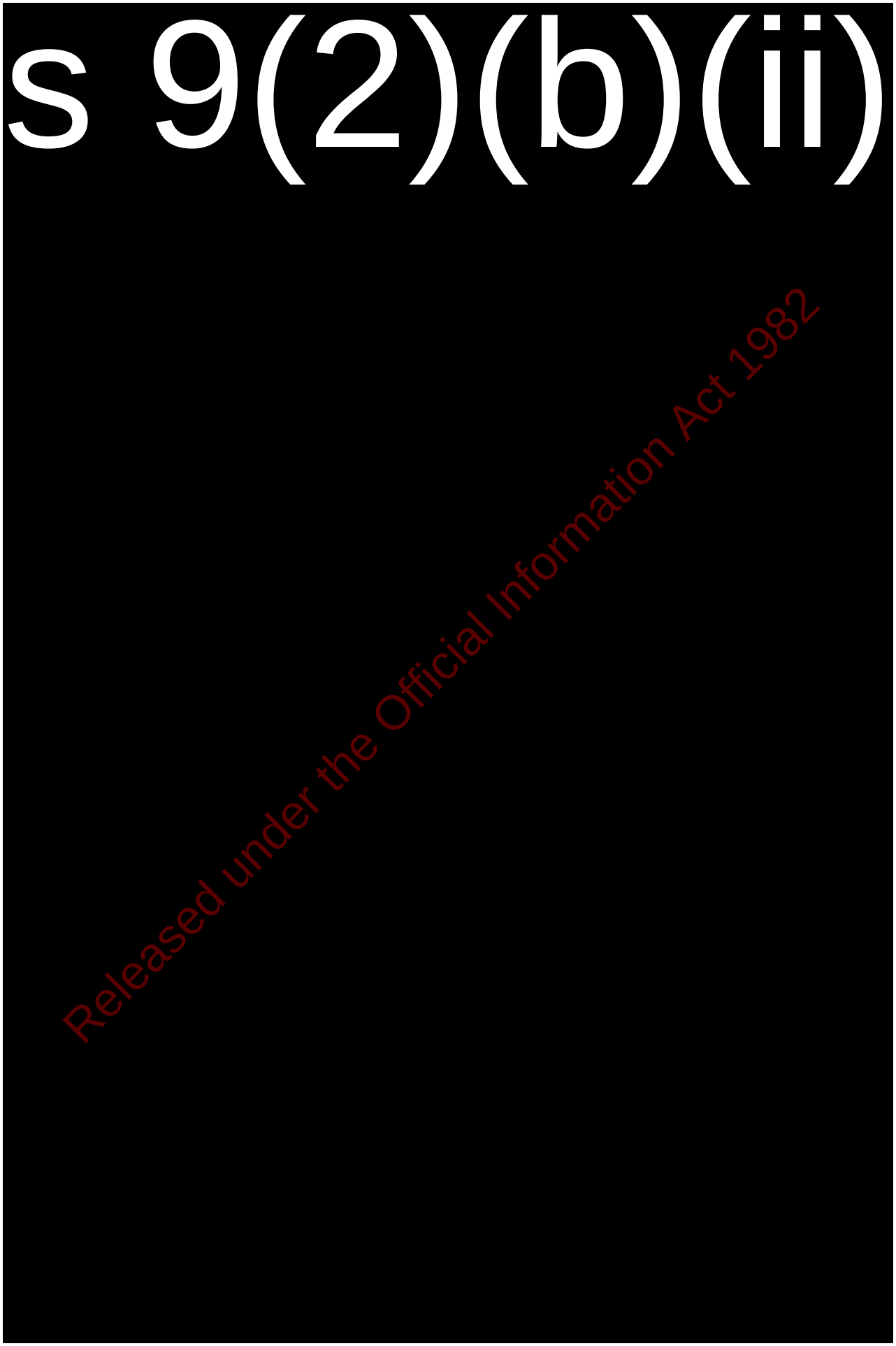
s 9(2)(b)(ii)

3.2.P.3.3. Description of manufacturing process and process controls

s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)



s 9(2)(b)(ii)

3.2.P.3.4. Controls of critical steps and intermediates

s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)

3.2.P.4. Control of excipients

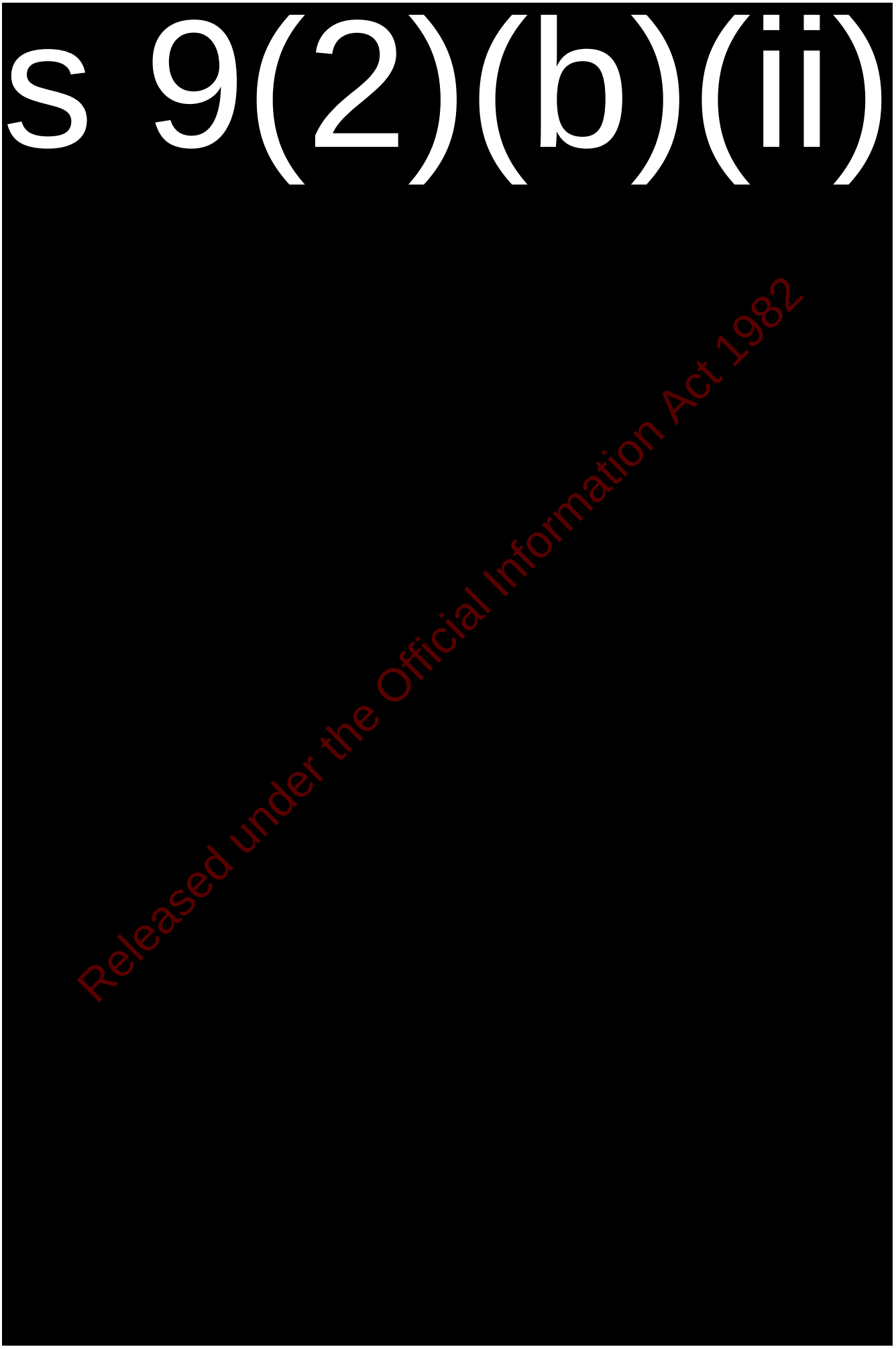
s 9(2)(b)(ii)

s 9(2)(b)(ii)

3.2.P.5. Control of drug product

s 9(2)(b)(ii)

s 9(2)(b)(ii)



s 9(2)(b)(ii)

s 9(2)(b)(ii)

s 9(2)(b)(ii)

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 s 9(2)(b)(ii) as reference materials for release and stability testing of the drug product using the s 9(2)(b)(ii) 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. The PPQ batches were placed on stability in June, July, and August 2021, so up to 3 months long-term data should now be available. Since the EMA approved a 6 month shelf-life for the unopened drug product on the basis of i) 3 months long-term stability data for the primary stability batches, and ii) the demonstrated analytical comparability of the Tris/sucrose and PBS/sucrose formulations, 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.

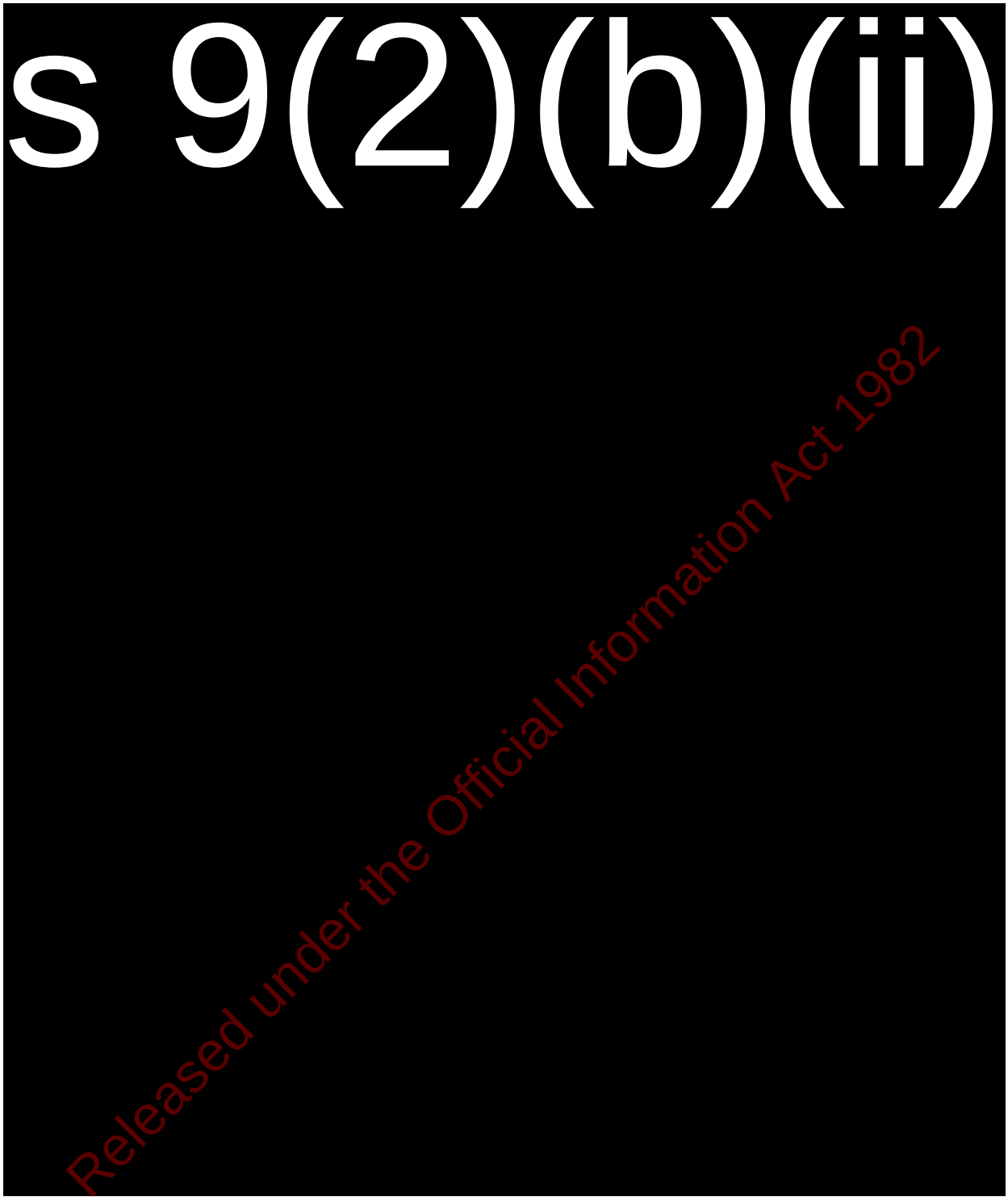
Clinical study C4591007 utilised drug product lots EE3813 (also denoted lot BCV40820-P) and ER5832. Both lots were manufactured using the same formulation as the currently approved PBS/sucrose product (0.5 mg/mL) but filled at 0.2 mL per vial. In preparation for administration at the 10 µg per dose level, 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 (s 9(2)(b)(ii)) than the clinical batch (one clinical batch was s 9(2)(b)(ii) the other was not tested for this parameter) and RNA integrity was similar between the batches (s 9(2)(b)(ii) for the Tris/sucrose batches; s 9(2)(b)(ii) 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.



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 EMA/CHMP report for the 30 micrograms/0.3 mL dose presentation states that the existing and new formulations of Comirnaty would co-exist on the EU market until the end of 2022, 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.

9(2)(b)(ii)

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.

9(2)(b)(ii)

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.