



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for BNT162b2 (mRNA)

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

July 2021

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

List of abbreviations	4
I. Introduction to product submission	6
Submission details _____	6
Product background _____	7
Regulatory status _____	8
Product Information _____	10
II. Registration timeline	11
III. Submission overview and risk/benefit assessment	11
Quality _____	12
Nonclinical _____	12
Clinical _____	12
Risk management plan _____	27
Risk-benefit analysis _____	29
Outcome _____	33
Attachment 1. Product Information	36

List of abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
ADR	Adverse drug reaction
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AusPAR	Australian Public Assessment Report
CDC	Centers for Disease Control and Prevention (United States of America))
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPD	Certified Product Details
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practice
GMR	Geometric mean ratio
GMT	Geometric mean titre
GVP	Good Pharmacovigilance Practices
LLOQ	Lower limit of quantitation
mRNA	Messenger ribonucleic acid
NAAT	Nucleic acid amplification test
NI	Non-inferiority
NT ₅₀	50% neutralising titre

Abbreviation	Meaning
PI	Product Information
PSUR	Periodic safety update reports
RMP	Risk management plan
RNA	Ribonucleic acid
S	Spike glycoprotein
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
VE	Vaccine efficacy
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Product name:</i>	Comirnaty
<i>Active ingredient:</i>	BNT162b2 messenger ribonucleic acid (mRNA)
<i>Decision:</i>	Approved for provisional registration
<i>Date of decision:</i>	22 July 2021
<i>Date of entry onto ARTG:</i>	23 July 2021
<i>ARTG number:</i>	346290
<i>, Black Triangle Scheme:¹</i>	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration.
<i>Sponsor's name and address:</i>	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney, NSW, 2000
<i>Dose form:</i>	Concentrated suspension for injection
<i>Strength:</i>	30 µg/0.3 mL
<i>Container:</i>	Multidose vial
<i>Pack size:</i>	195
<i>Approved therapeutic use:</i>	<i>Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine has provisional approval for the indication below:</i> <i>Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.</i> <i>The use of this vaccine should be in accordance with official recommendations.</i> <i>The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer</i>

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

term efficacy and safety from ongoing clinical trials and post-market assessment.

Route of administration: Intramuscular

Dosage: *Individuals 12 years of age and older*

Comirnaty is administered intramuscularly after dilution as a course of two doses at least 21 days apart. See dosing instructions below.

There are no data available on the interchangeability of Comirnaty with other COVID-19 vaccines to complete the vaccination course. Individuals who have received one dose of Comirnaty should receive a second dose of Comirnaty to complete the vaccination course.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Comirnaty (BNT162b2 messenger ribonucleic acid (mRNA)) 30 µg/0.3 mL concentrated suspension for injection vaccine for the following extension of indications:

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.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that appeared in late 2019.² SARS-CoV-2 is an enveloped, positive sense, single stranded ribonucleic acid (RNA) virus sharing more than 70% of its sequence with another coronavirus, SARS-CoV, and about 50% with the coronavirus responsible for Middle

² Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine. 2020;382(8):727-733.

Eastern respiratory syndrome (also known as MERS).³ The SARS-CoV-2 spike glycoprotein (simply referred to as 'S'), which is a main target for neutralising antibodies, binds to its receptor human angiotensin converting enzyme 2 to initiate infection.³

Coronavirus disease 2019 is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; and diarrhoea. Infections caused by SARS-CoV-2, and the resulting disease, COVID-19, have spread globally. On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak to be a pandemic.⁴

As of May 2021, the ongoing pandemic remains a challenge to public health and economic stability worldwide. Although the symptomology of COVID-19 in adolescents is usually mild, severe disease and death can occur, especially in adolescents with underlying medical conditions. The preventive vaccine available for this age group is an important aspect for Australia's fight against the pandemic. In Australia, there are currently three vaccines provisionally registered for prevention of COVID-19, one of which is Comirnaty (as discussed here). The other products are the COVID-19 Vaccine Astra Zeneca (sponsor: Astra Zeneca)⁵ and COVID-19 Vaccine Janssen (sponsor: Janssen-Cilag).⁶ However, neither of these are currently approved for people under the age of 16.

Regulatory status

The product received initial registration (provisional) on the Australian Register of Therapeutic Goods (ARTG) on 25 January 2021;⁷ for the following indication:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations. The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

Comirnaty (BNT162b2 (mRNA)) vaccine has received temporary authorisations for supply in 28 countries and conditional marketing authorisations in 39 countries globally.

At the time the TGA considered this application, similar applications had been approved in Canada on 5 May 2021, in the United States of America (USA) on 10 May 2021, in Singapore on 18 May 2021, in the European Union (EU) on 28 May 2021, in Switzerland on 4 June 2021 and in the United Kingdom on 4 June 2021. It was under consideration in New Zealand, with an application submitted on 24 May 2021.

³ Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.e278.

⁴ World Health Organization's General Director 11 March 2020; available at: <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>.

⁵ See the AusPAR for ChAdOx1-S, COVID-19 Vaccine AstraZeneca, published in February 2021 for further details: <https://www.tga.gov.au/auspar/auspar-chadox1-s>

⁶ See the AusPAR for Ad26.COV2.S, COVID-19 Vaccine Janssen, published in June 2021 for further details; <https://www.tga.gov.au/auspar/auspar-ad26cov2s>

⁷ See the AusPAR for BNT162b2 (mRNA), Comirnaty, published in January 2021 for further details; <https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty>

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
Canada	16 April 2021	Approved (interim order) on 5 May 2021	<i>For active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older</i>
United States of America	9 April 2021	Approved (emergency authorisation) on 10 May 2021	<i>For active immunisation to prevent COVID-19 in individuals 12 years of age and older.</i>
Singapore	13 April 2021	Approved (interim authorisation) on 18 May 2021	<i>Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Interim Authorization for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.</i>
European Union (via the Centralised Procedure)	30 April 2021	Approved (conditional authorisation granted) 28 May 2021	<i>Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in</i>

Region	Submission date	Status	Approved indications
			<i>individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.</i>
Switzerland	7 May 2021	Approved (temporary authorisation) on 4 June 2021	<i>Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. The use of the Comirnaty vaccine should be in accordance with official recommendations.</i>
United Kingdom	13 April 2021	Approved (temporary authorisation) 4 June 2021	<i>Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. The use of the Comirnaty vaccine should be in accordance with official recommendations.</i>
New Zealand	24 May 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Data was provided as a rolling submission. Under normal circumstances, TGA's assessment (for both provisional and general registration) begins once all information to support registration is available. As part of the Department of Health's response to the pandemic, the TGA has agreed to accept rolling data for COVID-19 vaccines, to enable early evaluation of data as it comes to hand.

Table 2: Timeline for Submission PM-2021-02187-1-2

Description	Date
Designation (Provisional) ⁸	11 May 2021
Submission dossier accepted	8 June 2021
Evaluation completed	11 June 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	11 June 2021
Sponsor's pre-Advisory Committee response	15 June 2021
Advisory Committee meeting	16 June 2021, adjourned to 5 July 2021.
Registration decision (Outcome)	22 July 2021
Completion of administrative activities and registration on the ARTG	23 July 2021
Number of working days from submission dossier acceptance to registration decision*	32

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The Delegate referenced the following guidelines:

- European Medicines Agency (EMA) Guideline on Clinical Evaluation of New Vaccines.⁹

⁸ The Provisional approval pathway allows for provisional registration of medicines on the basis of preliminary clinical data. However, we require comprehensive non-clinical data on safety, quality and compliance with Good Manufacturing Practice. These requirements are the same as in the standard registration process for prescription medicines.

⁹ EMA, Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Evaluation of New Vaccines EMEA/CHMP/VMP/164653/2005, October 2006. Available from the EMA website.

- Access Consortium statement on COVID-19 vaccines evidence.^{10,11}
- United States of America (USA) Food and Drug Administration (FDA), Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry (Section VI: Post-Licensure Safety Evaluation – Key Considerations).¹²
- FDA Emergency Use Authorisation for Vaccines to Prevent COVID-19, Guidance for Industry.¹³
- EMA considerations on COVID-19 vaccine approval.¹⁴

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier consisted of clinical study report for Study C4591001.

Study C4591001 is an ongoing Phase I/II/III randomised, multinational, placebo controlled, observer blind, dose finding, vaccine candidate selection, and efficacy study in healthy individuals.

The study is in two parts: Phase I, and Phase II/III. Phase I consisted of dose finding and safety assessment in 18 to 55 year old participants. This part was previously submitted in the new biological entity application for the initial provisional registration of Comirnaty in individuals 16 years of age and older.¹⁵

The clinical study report for the current extension of indication application includes Phase II/III study data, which is an expanded cohort that assessed the immunogenicity, safety and efficacy of Comirnaty in participants 12 to 15 years of age (termed adolescents) in blinded follow-up to a data cutoff date of 13 March 2021. The sponsor also submitted the six month safety data following the second dose as part of the post approval commitment to the original provisional approval for individual older than 16 years of age.

Previous efficacy analyses for individuals older than 16 years were conducted on 94 confirmed COVID-19 cases (interim analysis on 4 November 2020) and 170 confirmed cases (final analysis on 14 November 2020). At the time of the final analysis, there were few participants between 12 to 15 years of age enrolled and no COVID-19 cases reported in

¹⁰ Access Consortium statement on COVID-19 vaccines evidence (published on 4 December). Available from the TGA website at <https://www.tga.gov.au/access-consortium-statement-covid-19-vaccines-evidence>.

¹¹ The **Access Consortium** is a medium-sized coalition, which was formed in 2007 by 'like-minded' regulatory authorities to promote greater regulatory collaboration and alignment of regulatory requirements. The consortium currently comprises the national regulatory authorities of Australia, Canada, Singapore, Switzerland and the UK. For further information visit: <https://www.tga.gov.au/australia-canada-singapore-switzerland-united-kingdom-access-consortium>.

¹² FDA Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19 (published June 2020). Available from the FDA website.

¹³ FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (published 25 May 2021)

¹⁴ EMA, Committee for Medicinal Products for Human Use (CHMP), Considerations on COVID-19 vaccine approval EMA/592928/2020, 16 November 2020. Available from the EMA website.

this age group by 14 November 2020, as only with protocol amendment seven at 6 October 2020, the enrolment of adolescents 12 to 15 years of age was added.

The study design of Study C4591001 has been discussed in details in the initial Comirnaty BNT162b2 mRNA submission (PM-2020-05461-1-2, see relevant AusPAR for further details).¹⁵ The study participants were randomised to receive either the vaccine or placebo. The study treatments were administered as two doses, about 21 days apart. For this adolescent application, immunogenicity analysis is based on the non-inferiority (NI) comparison of adolescents to young adults (16 to 25 years of age) to a data cutoff date of 13 March 2021, and the efficacy was assessed in an updated analysis for the 12 to 15 years of age group based on all cases accrued for this group in blinded follow up to a data cutoff date of 13 March 2021.

Immunogenicity analysis

One of the secondary objectives in the Phase III part of Study C4591001 is to evaluate NI of the immune response to the Comirnaty BNT162b2 vaccine at one month after the second dose in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age (in those who had no serological or virological evidence of past SARS-CoV-2 infection). This NI analysis of neutralising titres was performed to provide immunobridging between adolescents (12 to 15 years of age) and young adults 16 to 25 years of age. Only a validated SARS-CoV-2 neutralisation assay was used.

Immunogenicity endpoints analysed for SARS-CoV-2 serum neutralising titres include:

- geometric mean titres (GMT) in each age group and geometric mean ratio (GMR) of 12 to 15 years group to 16 to 25 years group at one month after the second dose.
- geometric mean fold rise (GMFR) from before vaccination to one month after second dose in each age group
- seroresponse: percentage of participants with a ≥ 4 fold rise in neutralising titres from before vaccination to one month after the second dose in each age group.

The statistical analyses of immunogenicity data were based on the evaluable immunogenicity populations and all available immunogenicity populations. A random sample of 280 participants who received the Comirnaty BNT162b2 vaccine and 50 participants who received placebo was selected for each of the two age groups as an immunogenicity subset for immunogenicity assessment. This sample size was originally estimated to provide a power of 90.4% to declare NI in the specified analysis. Due to a testing laboratory supply limitation of the qualified viral lot used during the validation of the assay and clinical testing of samples, immunogenicity analyses were performed only on participants who had the required tests completed using the same available viral reagent lot. A blinded review of the samples tested at that time suggested a sufficient sample size properly balanced across age groups to perform the planned NI analysis. It was estimated that if the true GMR is ≥ 0.88 , there is approximately 90% power to demonstrate NI using the number of samples currently tested, and $> 99\%$ power if the true GMR is 1. NI was assessed based on the GMR of SARS-CoV-2 neutralising titres at one month after the second dose using a 1.5 fold margin. The GMR and its two sided 95% confidence interval (CI) were derived by calculating differences in means and CIs on the natural log scale of the titres based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale were 12 to 15 years minus 16 to 25 years. Non-inferiority was declared if the lower bound of the two sided 95% CI for

¹⁵ Australian Public Assessment Report for Comirnaty (BNT162b2 (mRNA)), first published on 25 January 2021. Assessable via <https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty>.

the GMR was greater than 0.67, using 1.5 fold non-inferiority margin. A supportive analysis was conducted for seroresponse rate and GMFR.

Result of immunogenicity analysis

The second dose evaluable immunogenicity population of adolescents included 209 participants in the Comirnaty BNT162b2 vaccine group and 36 participants in the placebo group, and the young adults (16 to 25 years of age) included 186 participants in the Comirnaty BNT162b2 vaccine group and 32 participants in the placebo group. The majority of exclusions were due to participants not having at least one valid and determinate immunogenicity result after second dose, mostly as the result of testing laboratory supply limitation of the qualified viral lot and were generally balanced across age and vaccine groups.

In the second dose adolescent evaluable immunogenicity population Comirnaty BNT162b2 vaccine group, 50.7% of participants were male; 88.0% were White, 7.7% were Black or African American, and 2.4% were Asian; 10.5% were Hispanic and/or Latino; and the median age was 14 years of age. The baseline SARS-CoV-2 status was positive for 4.8% of adolescent participants in the Comirnaty BNT162b2 vaccine group. Obese adolescents made up 8.3% (of the placebo group) to 11.5% (of the Comirnaty BNT162b2 vaccine treated group) of this age group in the evaluable immunogenicity population. Demographics were generally similar for Comirnaty BNT162b2 vaccine group and placebo, and in adolescents and young adults 16 to 25 years of age.

Demographics of the second dose evaluable immunogenicity population were similar to those in the second dose all-available immunogenicity population. The immunogenicity population demographics were also generally similar to those in the safety population.

Geometric mean ratio in neutralisation titres

In participants without evidence of prior SARS-CoV-2 infection, the immune response to the Comirnaty BNT162b2 vaccine in adolescents 12 to 15 years of age was non-inferior to that observed in young adults 16 to 25 years of age, based on SARS-CoV-2 50% neutralising titres at one month post second dose. The GMT ratio of adolescents to young adults was 1.76 (two sided 95% CI: 1.47, 2.10), meeting the 1.5 fold NI criterion (that is lower bound of the two sided 95% CI for GMR > 0.67) (see Table 2, below).

Table 2: Study C4591001 Summary of geometric mean ratio comparison of subjects between 12 to 15 years of age, and to subjects between 16 to 25 years of age (subjects without evidence of infection up to one month post second dose) (cutoff date 13 March 2021)

Assay	Dose/ Sampling Time Point ^a	Vaccine Group (as Randomized)				12-15 Years/16-25 Years	
		BNT162b2 (30 µg)				GMR ^d (95% CI ^e)	Met Noninferiority Objective ^e (Y/N)
		n ^b	12-15 Years GMT ^c (95% CI)	n ^b	16-25 Years GMT ^c (95% CI)		
SARS-CoV-2 neutralization assay - NT50 (titer)	2/1 Month	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT₅₀ = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Subjects who had no serological or virological evidence (up to one month after receipt of the last dose) of past SARS-CoV-2 infection (that is N-binding antibody (serum) negative at Visit One and SARS-CoV-2 not detected by NAAT (nasal swab) at Visit One and Two) and had negative nucleic acid amplification test (NAAT) (nasal swab) at any unscheduled visit up to one month after Dose 2 were included in the analysis.

^a Protocol specified timing for blood sample collection

^b n = Number of subjects with valid and determinate assay results for the specified assay at the given dose/sampling time point.

^c GMTs and two sided 95% CIs were calculated by exponentiating the mean logarithms of the titres and the corresponding CIs (based on Student t distribution). Assay results below LLOQ were set to 0.5 x LLOQ.

^d GMRs and two sided 95% CI were calculated by exponentiating the mean difference of the logarithms of the titres (Group one (12 to 15 years) – Group two (16 to 25 years)) and the corresponding CI (based on the Student t distribution)

^e Non-inferiority is declared if the lower bound of two sided 95% CI for the GMR is greater than 0.67.

Geometric mean titres

There were substantial increases in SARS-CoV-2 50% neutralising GMTs in both age groups at one month post the second dose of Comirnaty BNT162b2 vaccine, with a greater increase in the adolescent group compared with the young adult group. The neutralising GMT in adolescents at one month post the second dose was approximately 1.76 fold that of the young adult group. The neutralising GMTs were low in both placebo groups. Vaccination with the Comirnaty BNT162b2 vaccine induced an increased immune response at one month post Dose 2 for all participants, regardless of Baseline SARS-CoV-2 positive or negative status. Adolescents who were Baseline SARS-CoV-2 positive had SARS-CoV-2 50% neutralising GMTs approximately 1.89 fold that of adolescents who were Baseline negative. A similar pattern was seen for young adults.

Geometric mean fold-rise in titres

From before vaccination to one month post the second dose of Comirnaty BNT162b2 vaccine, there were greater increase of GMFRs of SARS-CoV-2 50% neutralising titres in the adolescent group (118.3) compared with that in young adult group (71.2). The GMFRs were numerically higher in those who were negative at Baseline compared to those who were positive at Baseline for both age groups.

Seroresponse rate

Proportions of participants with a ≥ 4 fold rise in SARS-CoV-2 50% neutralising titres from before vaccination to one month after the second dose of Comirnaty BNT162b2 (seroresponse rate) were 98.1% in adolescents and 99.3% in young adults. Very few

placebo recipients reached a ≥ 4 fold rise in SARS-CoV-2 neutralising titres from before to one month after the second dose. Seroreponse rate in adolescents who were Baseline SARS-CoV-2 positive or negative had similar seroreponse rates (100.0% versus 97.9%)

Efficacy analysis for adolescents 12 to 15 years of age

The updated efficacy analyses for individuals 12 to 15 years of age were not event driven. The number of cases of COVID-19 included in the updated efficacy analysis was not pre-specified. The cutoff date of 13 March 2021 was decided on the basis of safety and immunogenicity analysis.

The efficacy endpoints analysed for adolescents 12 to 15 years of age include the followings:

- COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen, cases confirmed ≥ 7 days after the second dose.
- Severe COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen, cases confirmed ≥ 7 days after the second dose.

The statistical analyses of efficacy data from Study C4591001 were based on the evaluable efficacy populations and all-available efficacy populations. The point estimate of vaccine efficacy (VE) and associated two sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time were provided as descriptive summary. Updated analyses for this submission include COVID-19 cases accrued in blinded follow-up in adolescents 12 to 15 years of age to the data cutoff date (13 March 2021).

In the efficacy analyses, adolescents in the efficacy populations included:

- Evaluable efficacy population without evidence of SARS-CoV-2 infection prior to seven days after the second dose: n = 1005 in the Comirnaty BNT162b2 vaccine group and n = 978 in the placebo group.
- Evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to seven days after the second dose: n = 1119 in the Comirnaty BNT162b2 vaccine group and n = 1110 in the placebo group.
- Dose 1 all available efficacy population: n = 1131 in the Comirnaty BNT162b2 vaccine group and n = 1129 in the placebo group.

As of 13 March 2021, confirmed COVID-19 cases in the evaluable efficacy population adolescent group without evidence of prior SARS-CoV-2 infection at least seven days after the second dose included 0 cases in the Comirnaty BNT162b2 vaccine group and 16 cases in the placebo group. The observed VE was 100% (two sided 95% CI: 75.3%, 100.0%) (see Table 3, below).

Table 3: Study C4591001 Vaccine efficacy, first COVID-19 occurrence from seven days post second dose (blinded placebo controlled follow-up period) subjects 12 to 15 years of age and without evidence of infection prior to seven days post second dose evaluable efficacy (seven days) population (data cutoff 13 March 2021)

Efficacy Endpoint	Vaccine Group (as Randomized)				VE (%)	(95% CI) ^e
	BNT162b2 (30 µg) (N ^a =1005)		Placebo (N ^a =978)			
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
First COVID-19 occurrence from 7 days after Dose 2	0	0.154 (1001)	16	0.147 (972)	100.0	(75.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SAR-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: subjects who has no serological or virological evidence (prior to seven days after receipt of the last dose) of SARS-CoV-2 infection (that is N-binding antibody (serum) negative at Visit One and SAR-CoV-2 not detected by NAAT (nasal swab) at Visit One and Two), had negative NAAT (nasal swab) at any unscheduled visit prior to seven days after Dose 2 were included in the analysis

^a N = Number of subjects in the specified group

^b n1 = Number of subjects meeting the endpoint definition

^c Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from seven days after Dose 2 to the end of the surveillance period.

^d n2 = Number of subjects at risk for the endpoint.

^e Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Confirmed COVID-19 cases in the evaluable efficacy population adolescent group (12 to 15 years of age) with or without evidence of prior SARS-CoV-2 infection at least seven days after Dose 2 included 0 cases in the Comirnaty BNT162b2 group and 18 cases in the placebo group. The observed VE was 100.0% (2-sided 95% CI: 78.1%, 100.0%) (see Table 4).

Table 4: Study C4591001 Vaccine efficacy, first COVID-19 occurrence from seven days post second dose (blinded placebo-controlled follow-up period) subjects 12 to 15 years of age and with or without evidence of infection prior to seven days post second dose evaluable efficacy (seven days) population (data cutoff 13 March 2021)

Efficacy Endpoint	Vaccine Group (as Randomized)				VE (%)	(95% CI) ^e
	BNT162b2 (30 µg) (N ^a =1119)		Placebo (N ^a =1110)			
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
First COVID-19 occurrence from 7 days after Dose 2	0	0.170 (1109)	18	0.163 (1094)	100.0	(78.1, 100.0)

Abbreviation: VE = vaccine efficacy

^a N = Number of subjects in the specified group

^b n1 = Number of subjects meeting the endpoint definition

^c Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

^d n2 = Number of subjects at risk of the endpoint.

^e Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Relative to the analysis of cases in participants without prior evidence of SARS-CoV-2 infection, two additional cases reported in the placebo group of the evaluable efficacy population with or without evidence of SARS-CoV-2 infection before and during vaccine regimen occurred in placebo recipients who were baseline negative serostatus for SARS-CoV-2, and had a negative nucleic acid amplification test (NAAT) at Visit One followed by a positive NAAT at Visit Two (scheduled visit for second dose).

As 13 March 2021, confirmed COVID-19 cases in the first dose only all available efficacy (modified intention to treat) population adolescent group included three cases in the Comirnaty BNT162b2 vaccine group and 35 cases in the placebo group, with an observed VE of 91.6% (two sided 95% CI: 73.5%, 98.4%) (see Table 5, below). The interval from after first dose to prior to receiving the second dose included three cases in the vaccinated group and 12 cases in the placebo group; these three cases in the Comirnaty BNT162b2 group, which comprised all COVID-19 cases reported in the Comirnaty BNT162b2 vaccine group in this population at any time, all occurred within the period from after first dose to less than 11 days after first dose (before a full immune response to the vaccine would be expected). All three of these cases in the Comirnaty BNT162b2 vaccine group occurred in participants who had Baseline SARS-CoV-2 negative status.

The observed VE for Comirnaty BNT162b2 in adolescents in the first dose all-available population was 100.0% (that is all cases were confined to the placebo group) for all time intervals starting from ≥ 11 days after the first dose to before the second dose, through ≥ 2 months after the second dose and < 4 months after the second dose.

Table 5: Study C4591001 Vaccine Efficacy first COVID-19 occurrence after the first dose (blinded placebo-controlled follow-up period) subjects 12 to 15 years of age. First dose, all available efficacy population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)				VE (%)	(95% CI ^e)
	BNT162b2 (30 µg) (N ^a =1131)		Placebo (N ^a =1129)			
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
First COVID-19 occurrence after Dose 1	3	0.257 (1120)	35	0.250 (1119)	91.6	(73.5, 98.4)
After Dose 1 to before Dose 2	3		12		75.0	(7.4, 95.5)
After Dose 1 to <11 days after Dose 1	3		4		25.0	(-343.3, 89.0)
≥ 11 Days after Dose 1 to before Dose 2	0		8		100.0	(41.4, 100.0)
Dose 2 to 7 days after Dose 2	0		5		100.0	(-9.1, 100.0)
≥ 7 Days after Dose 2	0		18		100.0	(77.3, 100.0)
≥ 7 days after Dose 2 to <2 Months after Dose 2	0		16		100.0	(74.1, 100.0)
≥ 2 Months after Dose 2 to <4 Months after Dose 2	0		2		100.0	(-432.5, 100.0)

No severe COVID-19 cases (per protocol definition or US Centers for Disease Control and Prevention (CDC) criteria) were reported in adolescents (12 to 15 years of age) as of the data cutoff date (13 March 2021).

Safety analysis

Safety analysis are presented for adolescents (12 to 15 years of age) in comparison with the safety results for young adults (16 to 25 years of age) who were in the reactogenicity subset. The data for young adults (16 to 25 years of age) were the same from the original provisional submission package.

Safety analysis were up to one month post the second dose and for all available data up to 13 March 2021. The median follow up duration for adolescents was > 2 months after the

second dose. Almost all (98.3%) of adolescent participants had at least one month of follow up after Dose 2, and 1308 out of 2260 adolescents (57.9%) had at least two months of follow up after Dose 2.

The disposition of adolescents and young adults was similar in the vaccine and placebo groups through one month post the second dose. Most participants randomised in both age groups ($\geq 97.4\%$) received the first and second dosages. Among adolescents, seven participants (0.6%) in the vaccine group and 17 participants (1.5%) in the placebo group discontinued from the vaccination period and are continuing for safety follow up. Most participants across age groups completed the visit at one month after the second dose ($\geq 94.5\%$). Among adolescents who discontinued from vaccination period but continued in the study up to the one month post the second dose visit, two participants discontinued due to adverse events (AE), both in the vaccine group and none in the placebo group. No adolescents in the vaccine and two in the placebo group withdrew from the study before the one month post the second dose visit.

A total of 49 adolescents withdrew from the vaccination period when they turned 16 years of age and became eligible to be unblinded to receive BNT162b2 vaccination; of these, 19 out of 49 subjects received additional (third and fourth dosages) of the BNT162b2 vaccine.¹⁶ Participants originally randomised to placebo who received a third dose of Comirnaty BNT162b2 vaccine continued in open label follow up in the study, but their data were censored at the time of unblinding with regard to analyses in this submission. Information for these participants are provided for serious adverse events (SAE) or other significant AEs.

Demographic characteristics for adolescents and young adults were similar in their vaccine and placebo groups in the safety population. Most adolescents in the vaccine group were White (85.9%), with 4.6% Black participants and 6.4% Asian participants, and other racial groups were $< 3.0\%$. There were 11.7% Hispanic and/or Latino participants. The median age of adolescents in the vaccine group was 14.0 years and 50.1% were male. Obese adolescents made up 11.3% (placebo group) to 12.6% (vaccine group) of this age group in the safety population.

Reactogenicity

Reactogenicity was assessed via electronic diary in all adolescents and a reactogenicity subset of young adults up to seven days after each dose. Adolescents with electronic diary data included N = 1131 in the vaccine group and N = 1129 in the placebo group post the first dose, and N = 1124 in the vaccine group and N = 1117 in the placebo group post second dose. Young adults in the reactogenicity subset included N = 539 in the vaccine group and N = 564 in the placebo group post the first dose and N = 526 in the vaccine group and N = 537 in the placebo group post the second dose.

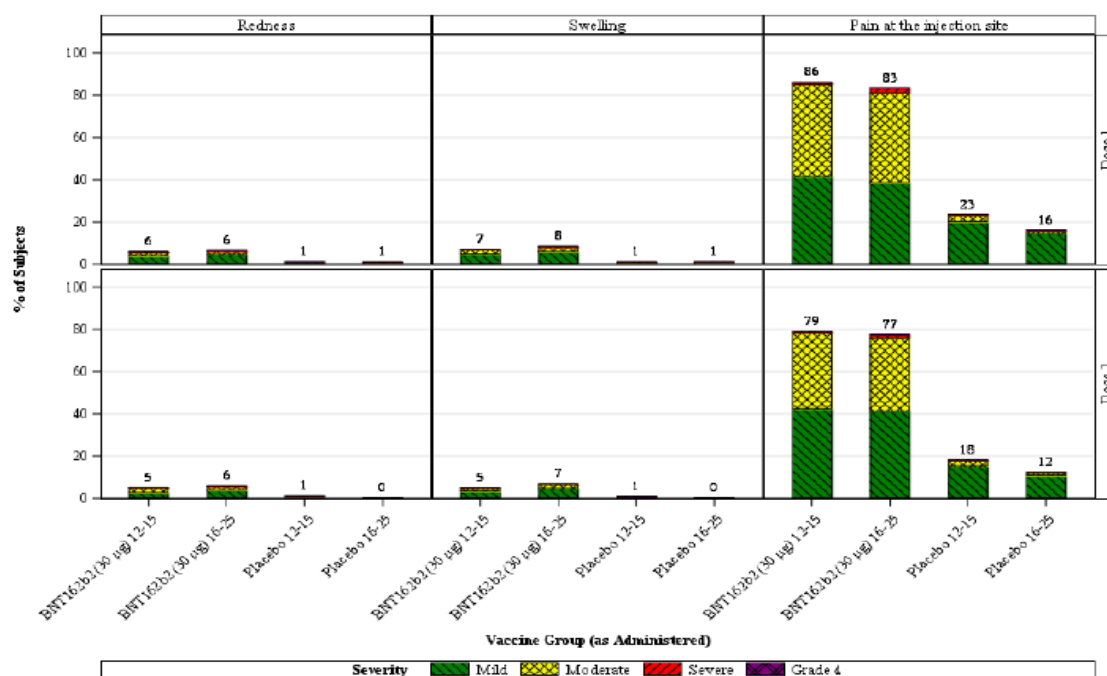
Local reactogenicity

In the vaccine group, pain at the injection site was most frequently reported in adolescents and young adults, and frequency was similar after the first and second dosages of the vaccine in adolescents (86.2% versus 78.9%) and in young adults (83.4% versus 77.5%). In the vaccine group, frequencies of redness and swelling were similar between the two age groups after the first and second dosages. Frequencies of redness and swelling were low post Dose 1 and Dose 2 of the vaccine in both age groups. After the first and second dosages in both age groups, most local reactions were mild or moderate. Severe reactions were infrequent and at lower incidence in adolescents ($\leq 1.5\%$) compared with young adults ($\leq 3.4\%$) across the vaccine and placebo groups after any dose. No Grade 4 local

¹⁶ The nature of the third and fourth dosage schedule does not comprise part of the application as submitted here, but is included on the basis of analysis of safety information. Participants originally randomised to placebo for their first two doses, would then go on to receive two doses of active vaccine.

reactions were reported in either age group. Across age groups, median onset for all local reactions after either dose of Comirnaty BNT162b2 vaccine was Day 1 to Day 3 and resolved with a median duration of 1 to 3 days (see Figure 1, below).

Figure 1: Local reactions, by maximum severity, within seven days after each dose-reactogenicity subset (Safety population by age group: 12 to 15 and 16 to 25 years of age)



Systemic reactogenicity

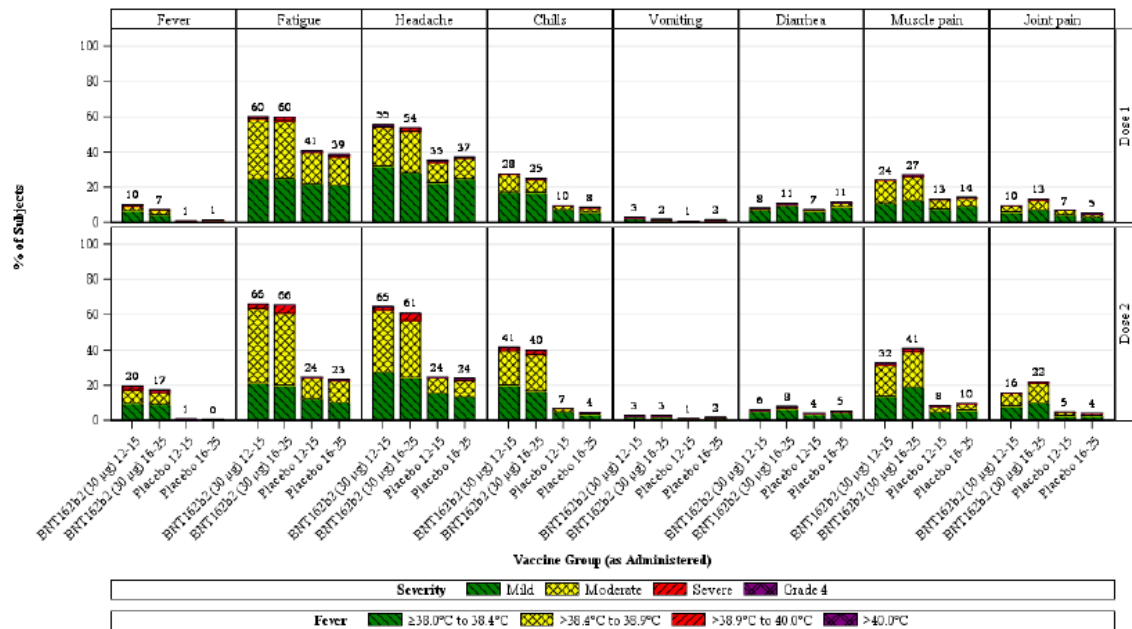
Systemic events were generally similar in frequency and severity in adolescents and young adults, with frequencies and severity increasing with number of doses for most events, with the exceptions of vomiting and diarrhoea which were reported infrequently and at similar incidences after each dose, and muscle and joint pain which was reported at higher frequencies in the young adults. Systemic events in the adolescent group compared with the young adult group, in decreasing order of frequency by dose (first dose versus second dose), were:

- fatigue: adolescents (60.1% versus 66.2%) compared to young adults (59.9% versus 65.6%)
- headache: adolescents (55.3% versus 64.5%) compared to young adults (53.9% versus 60.9%)
- chills: adolescents (27.6% versus 41.5%) compared to young adults (25.0% versus 40.0%)
- muscle pain: adolescents (24.1% versus 32.4%) compared to young adults (26.9% versus 40.8%)
- joint pain: adolescents (9.7% versus 15.8%) compared to young adults (13.2% versus 21.9%)
- fever: adolescents (10.1% versus 19.6%) compared to young adults (7.3% versus 17.2%)
- vomiting: reported infrequently in both age groups and similar after either dose
- diarrhoea: reported infrequently in both age groups and similar after either dose.

Systemic events were generally reported less frequently in placebo versus vaccine groups.

Following both the first and second dosages, use of antipyretic/pain medication was similar in adolescents and young adults, and medication use increased in both age groups after the second dose as compared with first dose. Use of antipyretic/pain medication was less frequent in the placebo group than in the vaccine group and was similar after the first and second dosages in the placebo groups for both age groups (ranging from 8.8% to 11.9%). After the first and second dose and in both age groups, most systemic events were mild or moderate. Severe events were reported infrequently and at lower incidence in adolescents ($\leq 3.5\%$) compared with young adults ($\leq 6.0\%$) across the vaccine and placebo groups after any dose. One adolescent in the vaccine group had Grade 4 pyrexia (40.4°C) on Day 2 after the first dose, with temperature returning to normal by Day 4; it was also reported as an AE. Across age groups, median onset for all systemic events after either dose of vaccine was Day 1 to Day 4. Systemic events resolved post each dose with a median duration of 1 day, except fatigue and chills which resolved within a median of 1 to 2 days (see Figure 2, below)

Figure 2: Systemic events, by maximum severity, within seven days after each dose reactogenicity subset (Safety population by age group: 12 to 15 and 16 to 25 years of age)



Adverse events

The overviews of AEs for adolescents and young adults (reactogenicity subset) are reported from the first dose to one month after the second dose, and from the first dose until 13 March 2021.

From the first dose to one month after the second dose, the number of participants with any AE were similar in the vaccine and placebo groups for adolescents and young adults groups. Severe AEs, SAEs, and AEs leading to withdrawal were reported by $\leq 1.7\%$, $\leq 0.4\%$, and $\leq 0.4\%$, respectively, in both groups. No reported SAEs were considered by the investigator as related to study intervention. Withdrawals due to related AEs were reported in one adolescent in the vaccine group and none in the placebo group; among young adults, withdrawals due to related AEs were reported in one participant in the vaccine group and none in the placebo group. Discontinuations due to any AEs were reported in three participants in the vaccine group and two participants in the placebo group, across age groups. No death was reported for study participants 12 through 25 years of age.

From the first dose to data cutoff date (13 March 2021): the number of adolescents with any event was similar in the vaccine and placebo groups. Severe AEs, SAEs, and AEs leading to withdrawal were reported by $\leq 0.8\%$, $\leq 0.4\%$, and $\leq 0.2\%$, respectively, in both groups. No reported SAEs were considered by the investigator as related to study intervention. Discontinuation due to related AEs was reported in one participant in the vaccine group and none in the placebo group. As of the data cutoff date, no death was reported for study participants in the adolescent group.

Analysis of AE for adolescents and young adults are reported from the first dose to one month after the second dose, and from the first dose until the data cutoff date (13 March 2021).

Adverse events by System Organ Class and Preferred Term

From the first dose to one month after second dose:

Adverse events reported in adolescents were generally similar to young adults within the vaccine and placebo groups. Most of the AEs after the first dose up to one month after the second dose were reactogenicity events reported as AEs (that is headache, nausea, and diarrhoea). In adolescents, AE frequencies in these reactogenicity System Organ Classes (SOCs) (vaccine versus placebo) were:

- general disorders and administration site conditions (1.4% versus 1.0%)
- musculoskeletal and connective tissue disorders (0.8% versus 0.7%)
- nervous system disorders (1.1% versus 0.6%)
- gastrointestinal disorders (1.2% versus 0.3%)

In young adults, AE frequencies in these reactogenicity SOCs (vaccine versus placebo) were:

- general disorders and administration site conditions (3.9% versus 1.8%)
- musculoskeletal and connective tissue disorders (2.2% versus 1.4%)
- nervous system disorders (2.4% versus 1.2%)
- gastrointestinal disorders (0.9% versus 1.1%)

The AEs reported in adolescents and young adults at one month after the second dose were largely attributable to reactogenicity events.

From the first dose to the data cutoff date:

Adverse events reported in adolescents through the data cutoff date were similar in the vaccine and placebo groups. The most frequently reported AEs in adolescents through the data cutoff date included lymphadenopathy (0.8%), injection site pain (0.6%), fatigue (0.6%), pyrexia (0.4%), nausea (0.4%), and headache (0.4%). No deaths were reported in adolescent (12 to 15 years of age) or young adult (16 to 25 years of age) groups evaluated in safety analyses up to the data cutoff date (13 March 2021).

Related adverse events

From the first dose to one month following the second dose, AEs assessed as related to study intervention in adolescents and young adults were similar in the vaccine and placebo group. Most related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, and these were reported by 15 adolescents (1.3%) and 19 young adults (3.5%) in the vaccine group compared with nine adolescents (0.8%) and nine young adults (1.6%) in the placebo group. Related events of lymphadenopathy were reported in seven adolescents in the vaccine group and one adolescent in the placebo group, compared with one young adult in the vaccine group and none in the placebo group.

Immediate adverse events

After the first dose, immediate AEs reported by adolescents and young adults were low in frequency ($\leq 0.4\%$) and were reported only in the placebo groups. All immediate AEs after the first dose were in the SOCs of general disorders and administration site conditions (injection site pain and injection site erythema) and nervous system disorders (dizziness and headache). After the second dose, adolescents and young adults with immediate AEs were low in frequency ($\leq 0.4\%$) in vaccine and placebo groups. Most immediate AEs after second dose were in the SOC of general disorders and administration site conditions. Other immediate AEs after Dose 2 were reported in the SOC of nervous system disorders (dizziness; one participant in the vaccinated adolescent group) or skin and subcutaneous tissue disorders (rash maculo-papular; one participant in the placebo adolescent group). No allergic AEs were reported after either dose of vaccine within 30 minutes after vaccination.

Severe or life-threatening adverse events

From the first dose to one month post the second dose, severe AEs reported in adolescents and young adults were low in frequency: 0.6% in the vaccine group versus 0.2% in the placebo group among adolescents, and 1.7% in the vaccine group versus 0.5% in the placebo group among young adults. Among adolescents, two participants (one each in the vaccine and placebo groups) had at least one life threatening AE from first dose to one month after second dose. These included:

- focal peritonitis and appendicitis reported in one adolescent in the placebo group, occurring concurrently 19 days following the second dose with a duration of two days, and considered as not related to study intervention; both events were reported as SAEs, resolved, and the participant continued in the study;
- pyrexia (of 40.4°C) was reported as Grade 4 in one adolescent in the vaccine group, occurring two days after Dose 1 with temperature returning to normal on Day 4, and was considered as related to study intervention; the event was reported as non-serious, resolved, and the participant withdrew from the study. Additionally, two participants in the adolescent group had life threatening AEs that occurred after they turned 16 years of age during the study and were unblinded to receive Comirnaty BNT162b2 vaccine and were therefore not included in analyses of blinded data
- anaphylactoid reaction reported in one participant originally randomised to the placebo group, three days after receiving the first dose of Comirnaty BNT162b2 vaccine (Dose 3, but first dose of active vaccine) with a duration of one day, considered as related to study intervention; the event was reported as an SAE, resolved, and the participant withdrew from the study; this participant has an ongoing medical history of food allergy, seasonal allergy, and drug hypersensitivity
- depression reported in one participant originally randomised to the placebo group, seven days after receiving the first dose of Comirnaty BNT162b2 vaccine (Dose 3, but first dose of active vaccine) reported as ongoing at the time of the data cutoff date, considered as not related to study intervention; the event was reported as an SAE due to hospitalisation and reported as resolving, and the participant continued in the study.

Among young adults, there were no life threatening AEs reported from the first dose to one month after the second dose.

Serious adverse events

Serious adverse events analyses for adolescents and young adults are reported from the first dose to one month after the second dose, and from the first dose until the data cutoff date (13 March 2021).

From the first dose up to one month after second dose, there were similar proportions of adolescents and young adults who reported at least one SAE. Overall, $\leq 0.4\%$ in both age groups reported any SAE after receiving the vaccine or placebo. None in either age group had SAEs assessed as related to study intervention. In the adolescent group, SAEs were reported in the vaccine group in two participants with depression, one participant with concurrent events of anxiety and depression, and one participant with neuralgia; and one participant in the placebo group with concurrent events of appendicitis and focal peritonitis. All SAEs in the adolescent group were reported as resolved. The SAE of neuralgia was reported in a 12 years old girl who reported concurrent abdominal pain and constipation. She was diagnosed with functional abdominal pain. In the young adult group, SAEs up to one month after the second dose were reported by two participants in the vaccine group (one with abdominal pain and one with appendicitis) and two participants in the placebo group (one had inguinal hernia, and one had flail chest associated with a motor vehicle accident). All SAEs in the young adult group were reported as resolved.

From the first dose to data cutoff date: the proportions of adolescents who reported at least one SAE were similar in the vaccine and placebo groups. Data for young adults are not included since they had different follow up time. Up to the data cutoff date, five adolescents (0.4%) in the vaccine group and two adolescents (0.02%) in the placebo group reported any SAE. None of the SAEs were assessed as related to study intervention. In addition to the SAEs that were previously reported up to one month following the second dose, SAEs reported from after one month post the second dose up to the data cutoff date included abdominal pain and constipation reported concurrently in one participant (who also previously reported neuralgia) in the vaccine group. An SAE of suicidal ideation was reported in one participant in the vaccine group and an SAE of appendicitis was reported in one participant in the placebo group. All SAEs were reported as resolved or resolving except for the events of abdominal pain and constipation. Additionally, two adolescents originally randomised to placebo had SAEs that occurred after they turned 16 and were unblinded to receive BNT162b2, therefore the data are not included in the blinded analyses. These events were also considered as life threatening: an anaphylactoid reaction reported in one participant three days after the first dose of Comirnaty BNT162b2 (third dose, first active dose following placebo), considered as related to study intervention and leading to study withdrawal; and depression reported in one participant seven days after the first dose of Comirnaty BNT162b2 (third dose, first active dose following placebo) reported as ongoing/resolving at the time of the data cutoff date, considered as not related to study intervention.

Adverse events leading to withdrawal

From the first dose to one month after the second dose, few adolescents and young adults in the vaccine group ($\leq 0.2\%$) and in the placebo group ($\leq 0.4\%$) were withdrawn due to AEs. In the adolescent group, one participant in the vaccine group had an AE leading to withdrawal that was considered as related to study intervention (pyrexia), and none in the placebo group. In the young adult group, one participant in the vaccine group had an AE leading to withdrawal that was considered as related to study treatment (severe injection site pain that started two days after the first dose and resolved after one day), and none in the placebo group.

Adverse events of special interest

As of 13 March 2021, there were very few AEs of clinical interest corresponding to the US Centers for Disease Control and Prevention (CDC) list of adverse events of special interest (AESI) in the adolescent population.

No cases of anaphylaxis or anaphylactoid reactions and of facial paralysis were reported in adolescent group as of the data cutoff date, 13 March 2021.

The AE of anaphylactoid reaction identified in the 16 to 25 years of age group is consistent with what has been observed in post-authorisation safety reviews in the ≥ 16 years of age population.

Lymphadenopathy is identified as an adverse reaction for this vaccine. In adolescents, seven subjects (0.6%) in the vaccine group and one subject (0.1%) in the placebo group had lymphadenopathy events assessed as related to study intervention. The majority of these events occurred in the arm and neck region, were reported within 2 to 10 days after vaccination, and about half of these events resolved within 1 to 10 days. In young adults, one related lymphadenopathy was reported up to the data cutoff date, occurring within one day of receiving the second dose and resolved within five days. In adults (16 to 55 years of age), 52 participants (0.4%) in the vaccine group and two subjects (0.0%) in the placebo group had lymphadenopathy events reported up to the unblinding date and assessed as related to study intervention. The majority of these events occurred in the arm and neck region, were reported within 2 to 4 days after vaccination (usually after the second dose), and typically resolved within approximately one week.

As of 13 March 2021, no severe COVID-19 cases were reported in adolescents 12 to 15 years of age in Study C4591001. The previously completed final analyses of efficacy for all study participants ≥ 12 years of age (data cutoff date: 14 November 2020) showed confinement of severe cases predominantly to the placebo group.

Safety data in adult population (*in comparison to adolescent population*)

In the context of the adolescent submission, the safety data for young and older adults were included for reference purposes. The safety data for adults is from approximately 26,000 adults 16 to 55 years of age, among whom a majority in the vaccine group have at least six months of blinded follow up after the second dose in the Phase II/III period of Study C4591001. These data showed that the reactogenicity was mostly mild to moderate and short lived (that is median onset between 1 to 2 days after dosing and resolution within 1 to 2 days after onset), with local reactions presenting predominantly as injection site pain with minimal effect of dose number, and systemic events generally increasing in frequency and/or severity with increasing dose number. The review of AEs and SAEs in the adult population (16 to 55 years of age) did not suggest new safety concerns. There was a slightly higher frequency noted in the adolescent group with regards to reactogenicity when comparing to that in adults population. Fever was highest for the adolescent group but was still considered acceptable and within tolerable limits. Arthralgia and muscle pain were higher in the young adult group than the adolescent group for both doses of the Comirnaty BNT162b2 vaccine. The differences in reported AEs were considered age appropriate. The review of AEs, SAEs, and events of clinical interest did not suggest any additional safety concerns among adolescents.

Unblinded clinical study data from Study C4591001 (data lock point, 13 March 2021) was searched for cases of myocarditis and pericarditis. During the blinded placebo controlled follow up period, there was one report of myocarditis in the placebo group and one report of pericarditis in the Comirnaty BNT162b2 vaccine group, a 66 year old white male who had pericarditis 29 days after the second dose of the vaccine which was ongoing at the time of the data cutoff. It was assessed as not related to study intervention by the investigator.

Post-approval safety data

Diarrhoea (very common), vomiting (common), rash (uncommon), pain in extremity (uncommon), urticaria (uncommon), and anaphylaxis (unknown) were identified as additional adverse drug reactions (ADRs) in the post approval period for individuals ≥ 16 years of age. A review of the sponsor's safety database for spontaneously reported AEs in individuals 12 to 15 years of age received up to 28 February 2021 returned with 11 cases. The cases were for individuals 15 years of age (four cases), 14 years of age (three

cases), 13 years of age (one case), and 12 years of age (three cases). The limited amount of safety information in these reports does not substantially contribute to the base of knowledge of the product safety profile in this age group.

The sponsor also submitted the six month duration post second dose safety data from the Phase III study as part of the agreed commitment post provisional approval. The TGA evaluator provided the following comments:

- The tolerability and safety profile up to six months after second dose was acceptable through the follow up period (to the data cutoff date) and consistent with results previously reported. The frequency of AEs is adequately captured in the Product Information (PI).
- The total number and frequency of related SAEs, related AEs/SAEs leading to withdrawal and deaths during the study (all apparently unrelated to vaccination) was very low and in keeping with previously reported data.
- There did not appear to be any clinically meaningful differences between subgroups by age, gender, ethnicity, baseline SARS-CoV-2 status, HIV status, or in relation to infection with COVID-19 in subsequently Comirnaty BNT162b2 vaccinated placebo recipients.
- Potentially significant adverse events identified by the FDA, CDC and through post marketing review appear to have been appropriately examined
- No new safety signals or concerns have emerged.

TGA's evaluator recommends the followings:

- The interim report: six month update be accepted by the TGA as fulfilling the condition of approval for provisional registration in relation to submitting a safety analysis at six months following use of the second dose
- The proposed updates to the PI in the recent safety related request submission is consistent with the data presented here along with their post authorisation experience
- Further safety data should be submitted in relation to follow up at six months following use of the second dose for all original Comirnaty recipients and at six months following the fourth dose for original placebo recipients subsequently vaccinated with Comirnaty (that is six months following their second dose), when the analysis is available.

Myocarditis and pericarditis

The sponsor's safety surveillance and risk management team conducted a review of spontaneous reports of myocarditis/pericarditis. The details regarding this were provided to the TGA in the April summary monthly safety report.

The sponsor's overall conclusion based on the totality of the available data is that there is not enough evidence to currently support a causal association between the vaccine and myocarditis and pericarditis. However, the sponsor commits to continue surveillance and review of any future data or research. The sponsor also commits to obtain further details on the Israel cases.

The TGA's evaluator states that while a plausible mechanism for a causal association of myocarditis and pericarditis with the vaccination is not yet clear, it may be postulated that myocarditis and pericarditis could be a systemic inflammatory reaction due to an immune response to the vaccine. The TGA's post market evaluation team will provide the detailed analysis on this issue to the Advisory Committee on Vaccines (ACV).

Risk management plan

The most recently evaluated EU-risk management plan (RMP) was version 1.0 (date 21 December 2020; data lock point (DLP) 17 December 2020) and Australia specific annex (ASA) version 0.2 (date 17 January 2021). In support of the extended indications, the sponsor has submitted EU-RMP version 2.0 (date 29 April 2021; DLP 28 February 2021 (Safety Database) 13 March 2021 (Clinical Database)). The sponsor submitted ASA (version 0.3, dated 11 June 2021) in response to TGA questions.

The summary of safety concerns and their associated risk monitoring and mitigation strategies proposed in the EU RMP version 2.0 are summarised below in Table 6.¹⁷

Table 6: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Anaphylaxis	ü [†]	ü*	ü	-
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	ü [†]	ü*	-	-
Missing information	Use in pregnancy and while breast feeding	ü	ü*	ü	-
	Use in immunocompromised patients	ü	ü*	ü	-
	Use in frail patients with co-morbidities (for example chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	ü	ü*	ü	-

¹⁷ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in patients with autoimmune or inflammatory disorders	ü	ü*	-	-
	Interaction with other vaccines	ü	ü*	ü	-
	Long term safety data	ü	ü*	-	-

†Data capture Aid *Clinical trials

The above summary of safety concerns is acceptable from an RMP perspective.

The pharmacovigilance plan is acceptable from an RMP perspective. The acceptability of the clinical study plan will be assessed by the clinical evaluator/TGA delegate.

Currently there are no additional risk minimisation measures implemented for Comirnaty BNT162b2 in Australia or in the EU. It is expected that the Australian Government's educational programs, activities to increase awareness of the public and the healthcare professionals would address some of the aspects of risk minimisation.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Comirnaty EU-Risk Management Plan (RMP) (version 2.0, date 29 April 2021; DLP 28 February 2021 (Safety Database) 13 March 2021 (Clinical Database)), included with submission PM-2021-02187-1-2, with Australian Specific Annex (version 0.3, dated 11 June 2021), will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than six calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than six monthly until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, Comirnaty safety summary reports (including safety data for patients in Australia) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

Comirnaty is to be included in the Black Triangle Scheme due to provisional approval. The PI and CMI for Comirnaty must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

Risk-benefit analysis

Delegate's considerations

The Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine has been provisionally approved by TGA on 25 January 2021 for active immunisation to prevent COVID-19 disease in individuals 16 years of age and older on the basis of short term efficacy and safety data. The sponsor has now submitted the data to support the indication extension to include adolescents group 12 to 15 years of age. The submitted data include immunogenicity, efficacy and safety analysis for adolescents 12 to 15 years old from Study C4591001 in blinded follow up to a data cutoff date of 13 March 2021.

The immunogenicity analysis demonstrated that the immune response to the Comirnaty BNT162b2 (mRNA) vaccine in adolescents 12 to 15 years of age was non-inferior to young adults between 16 to 25 year of age. At one-month following the second dose, the estimated GMT ratio in adolescents relative to young adults was 1.76 (95% CI: 1.47 to 2.10), meeting the non-inferior criterion. It is acknowledged that neutralising antibody responses were chosen here as an immune biomarker for inferring effectiveness through immunobridging, but a specific level of neutralising antibodies has not yet been established to correlate with protection, and other aspects of the immune response, such as cellular immunity, were not analysed. Although no data were presented on cellular immunity, this is not considered critical in the presence of available descriptive efficacy data.

It is noted that vaccine efficacy for adolescents was not a pre-specified endpoint and the data cutoff date (13 March 2021) was based on the immunogenicity and safety assessment, not based on the number of COVID-19 cases accrued for the adolescent group. The efficacy analysis is therefore considered as descriptive, not as hypothesis testing. The efficacy endpoints for adolescents are consistent with the endpoints assessed for adult population. The adolescent population is considered a subgroup rather than a separate study population. The results showed that in adolescents without evidence of prior infection with SARS-CoV-2, the estimate of VE against the first occurrence of confirmed SARS-CoV-2 infection from seven days following the second dose was 100% (95% CI: 75.3 to 100.0%). There were no cases of COVID-19 among 1,005 vaccine recipients and there were 16 cases of COVID-19 among 978 placebo recipients. The estimate of vaccine efficacy in all participants 12 to 15 years of age (including those with evidence of prior SARS-CoV-2 infection) was also 100% (95% CI: 78.1 to 100.0%). No cases meeting the severe COVID-19 case definition were reported in any participant 12 to 15 years of age as of 13 March 2021.

In term of safety data, a total of 2260 adolescents (1131 in the vaccine group and 1129 in the placebo group) have been included in the safety population up to the cut-off date. Around 98.3% of these participants had ≥ 1 month of follow up while 57.9% had ≥ 2 months of follow up after the Dose 2. Within this follow up period, the vaccine was well tolerated. Local reactions were mostly mild to moderate. Systemic events were predominantly fatigue, headaches, chills, muscle pain, fever, and joint pain and occurred more frequently after the second dose. In comparison to adult subjects, the adolescent group demonstrated increased frequency of headache, chills, and fever. Fever was reported in about 10% of adolescent participants after the first dose and in about 20% after the second dose, this is higher than that reported for young adults and adults. Up to 64.5% of adolescents reported headaches, up to 41.5% had chills, and up to 19.6% had

fever. Vaccination related lymphadenopathy in adolescents occurred in 0.6% of vaccine recipients, and no serious adverse events related to the vaccine and no deaths were reported.

The reactogenicity profile in adolescents in the trial is considered acceptable. The frequency of reported AEs and SAEs in adolescents were low. The sample size is relatively small and is not sufficient for the detection of rare adverse reactions. The safety database for adults in the real world setting is now quite extensive, which provide some reassurance for the use of this vaccine in the adolescent population.

The Delegate noted that the submitted data have the following limitations:

- The long-term efficacy and safety is not known.
- The VE against asymptomatic infection and viral transmission is not known.
- The number of adolescents in the study not sufficient to detect vary rare adverse events.
- No data available on the co-administration with quadrivalent seasonal influenza vaccine.
- Adolescents with immunodeficient status/high health risks are not specifically assessed.
- The VE against variants of concern has not been assessed.

These limitations are the same as these identified for individual 16 years and above with the previous submission. The submitted efficacy and safety data is short term at this stage, but the data have fulfilled the requirement as set out in the Access Consortium statement on COVID-19 vaccines evidence.¹⁰ The statement specified the minimum requirement that trial participants must be followed for a median of at least two months after receiving their final vaccine dose.¹⁰ The EMA has stated that conditional marketing authorisation for a COVID-19 vaccine could be based on review of at least six weeks post vaccination safety data.¹⁴

The benefit of this vaccine in adolescent population has been shown with the trial results of demonstrating the protection against symptomatic COVID-19 and the higher neutralising antibody levels. The safety profile in this age group is considered acceptable. The limitations regarding the short term data can be addressed by planned post market studies. The sponsor is requested to specify whether adolescent subjects will be included in some of the post market studies. Provision of six months post the second dose safety data in subjects 12 to 15 years are listed as one of the clinical conditions of the provisional registration. Further safety data are being collected in Study C4591001 for up to two years for all age groups. Real world use data and active surveillance will also provide long-term data in the vaccine recipients.

The Delegate has noted the recent international discussions on post market reports of rare cases of myocarditis and pericarditis following vaccination with the sponsor's COVID-19 vaccine in young people. The Vaccines and Related Biological Products Advisory Committee meeting on 10 June 2021 presented the safety data from the Vaccine Adverse Events Reporting System. The preliminary findings suggest there have been a higher than expected number of cases reported, especially after the second dose of mRNA vaccines, in individuals 16 to 24 years of age. The Advisory Committee on Immunisation (US CDC) meeting is scheduled for 18 June with further update on the analysis of myocarditis following mRNA COVID vaccination and benefit-risk assessment.

TGA's post market evaluation team has plans to discuss with the ACV the issue of myocarditis and pericarditis reports following vaccination with sponsor's COVID-19 vaccine.

Proposed action

Based on the evaluation of the submitted data and taking into consideration of the current pandemic and public health need, the Delegate is of the view that there is a favourable benefit-risk balance for the use of this vaccine in the adolescent population. The submitted data has satisfied the regulatory requirement for the extension of provisional registration to individual 12 to 15 years of age.

Pending the advice from the ACV and further review of the Product Information, the Delegate proposes the provisional approval of this vaccine for the indication below:

Comirnaty (BNT162b2(mRNA)) COVID-19 Vaccine has provisional approval for the indication below:

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.

The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

The final decision will be made following the ACV discussion and the satisfactory negotiation of the Product Information and the conditions of provisional registration.

Advisory Committee considerations¹⁸

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

- 1. Does the ACV consider that there is a favourable benefit-risk balance for the use of this vaccine in the adolescent population and the submitted data has met the regulatory requirement for the extension of provisional registration to individuals 12 to 15 years of age?***

The ACV advised that the benefit of the vaccine are:

- immunogenicity that is not inferior (and possibly superior) in the 12 to 15 years of age group compared to older persons;
- although limited, efficacy data are similar to that in young adults; and
- reactogenicity is similar to that in young adults.

Risks of the vaccine in the 12 to 15 years of age group include increase risks in myocarditis and/or pericarditis and lymphadenopathy.

¹⁸ The **Advisory Committee on Vaccines (ACV)** provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-market monitoring and safe use in national immunisation programs.

The Committee is established under Regulation 39F of the Therapeutic Goods Regulations 1990 and the members are appointed by the Minister for Health.

The ACV was established in January 2017, following consolidation of previous functions of the Advisory Committee on the Safety of Vaccines (ACSOV) and the pre-market functions for vaccines of the Advisory Committee on Prescription Medicines (ACPM).

Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues.

Even apparently mild episodes of myocarditis may lead to long term sequelae, such as arrhythmias. However, additional data from the USA suggested that the majority of cases of myocarditis and/or pericarditis after mRNA COVID-19 vaccines (both the Pfizer [Comirnaty BNT162b2 (mRNA)] and Moderna [(mRNA) vaccines]) analysed to date occurred in older adolescents and young adults (aged 16 to 30 years), with highest risk in younger males within days after dose 2. Most cases were mild and recovered within days with a median duration of hospitalisation of 1 day.

Health authorities in the USA and other settings continue to recommend use of the vaccine in this age group and younger adolescents based on the balance of benefit over risk.

Thus, myocarditis / pericarditis is a small but significant risk of an important complication in otherwise healthy children.

Risks from COVID-19 infection in children include hospitalization (about 5%) and mechanical ventilation (about 0.25%), as well as MIS-C (multi-inflammatory syndrome in children, also known as PIMS-TS) and 'long COVID'.

Overall, the benefit-risk is favourable for provisional approval of the vaccine. The balance of risk and benefit will depend on the epidemiology of COVID-19 disease.

The benefit-risk will be higher in adolescents at greater risk of COVID-19 disease due to pre-existing health conditions.

2. *There are rare cases of myocarditis and pericarditis reported following vaccination with Comirnaty in young people in the global post-market setting, could the ACV please advise:*

a. *whether these rare events would change the benefit-risk balance for the use of this vaccine in the adolescent population?*

The ACV advised that incidence, severity and outcome data (the true size of the signal) are still emerging.

Most cases of myocarditis and pericarditis appeared to be mild and resolve with therapy.

Information on longer term outcomes or recurrences is not available.

b. *There are rare cases of myocarditis and pericarditis reported following vaccination with Comirnaty in young people in the global post-market setting, could the ACV please advise whether any regulatory action, such as adding relevant statements in the PI, should be taken at this stage?*

The ACV advised that relevant statements should be included in the PI:

- Reported events of myocarditis and pericarditis
- Risk appears to be greater in adolescents compared to older adults; in males; after the second dose
- A high index of suspicion for presentations within a risk time window, within 4 days of either first or second dose, but particularly the second dose; for people presenting with chest pain, dyspnoea, or suggestion of arrhythmia.
- Precaution for patients with a history of myocarditis or pericarditis, whether due to mRNA vaccine or not. Vaccination of such children should be considered on a case-by-case basis with specialist input, as required.

Suitable wording could be:

Rare cases of myocarditis and pericarditis have been reported following vaccination with Comirnaty, although a causal association is not established. Reported cases have occurred predominantly but not exclusively in male adolescents and young adults. Onset was typically within several days after vaccination, and cases have

occurred more often after the second dose than the first dose. Current available data from short term follow-up suggest most individuals have had resolution of symptoms, however information regarding potential long term sequelae is not known. Clinicians should consider myocarditis and pericarditis in adolescents or young adults presenting with acute chest pain, shortness of breath, or palpitations several days after vaccination, and should consider consultation with cardiologists or referral to an emergency department for assistance with cardiac evaluation and management.

Enhanced surveillance should be in place for myocarditis and pericarditis.

3. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACV suggested liaison with primary care, emergency and radiology clinical colleges and similar, regarding: recognition of presentation, specialist referral and management; availability of appropriate diagnostic tests (for example, echocardiogram; cardiac magnetic resonance imaging, if indicated); agreed case definitions. This should be done in conjunction with the Australian Technical Advisory Group on Immunisation, which develops clinical guidelines for immunisation use in Australia.

The ACV suggested liaison with paediatric cardiologists, including potential role in active surveillance.

Conclusion

The ACV considered Comirnaty to have an overall positive benefit-risk profile, and therefore supports provisional approval for the following:

Comirnaty (BNT162b2 (mRNA)) COVID-19 Vaccine has provisional approval for the indication below:

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.

The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Comirnaty (BNT162b2 mRNA) 30 µg/0.3 mL concentrated suspension for injection multiple doses vial, indicated for the following extension of indications:

Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine has provisional approval for the indication below:

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.

The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

Specific conditions of registration applying to these goods

- Comirnaty vaccine is to be included in the Black Triangle Scheme due to provisional approval. The Product Information (PI) and Consumer Medicines Information (CMI) for Comirnaty Vaccine must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- The Comirnaty EU-Risk Management Plan (RMP) (version 2.0, date 29 April 2021; DLP 28 February 2021 (Safety Database) 13 March 2021 (Clinical Database)), included with submission PM-2021-02187-1-2, with Australian Specific Annex (version 0.3, dated 11 June 2021), will be implemented in Australia.

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than six calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than six monthly until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, Comirnaty safety summary reports (including safety data for patients in Australia) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

Clinical

- Data relating to individuals 12 to 15 years old
 - Submit safety data for all adolescents 12 to 15 years of age in Study C4591001, 6 months post Dose 2, when the data becomes available.
 - Submit study report of Study C4591001, including data up to 24 months after Dose 2 in adolescents 12 to 15 years of age, when the data becomes available.
- Data relating to individuals 16 years and older
 - Submit safety data in relation to follow up at 6 months post-Dose 2 for all original Comirnaty recipients and at 6 months post-Dose 4 for original placebo recipients subsequently vaccinated with Comirnaty (that is 6 months following their second dose), when the analysis is available.
 - Submit the final completed study report for Study C4591001, including data up to 24 months after Dose 2 for individuals 16 years and older, when the data becomes available.

- Submit final study reports for Study BNT162-01 once completed, including data on healthy subjects.

When available, further data relating to vaccine efficacy against asymptomatic disease, vaccine efficacy in immunocompromised subjects, paediatric subjects, pregnant women, lactating mothers, and the information relating to post-market safety and effectiveness studies should be provided to the TGA, as separate submissions, to update the PI.

- **Medicine Labels**

- a) The New Comirnaty Medicine must only be supplied with the labels referred to in paragraph 8(a) of Attachment 4 to the decision dated 24 January 2021 to provisionally register the Existing Comirnaty Medicine.
- b) The sponsor will develop Australian-specific labels for the product, that conform with all relevant Australian labelling requirements, and will take all reasonable steps to implement such labelling before the end of the provisional registration period referred to in subsection 29(3) of the Act (being the period of 2 years starting on the day specified in the ARTG certificate of registration) (noting that, consistent with paragraph 28(5)(aaa) of the Act, changes to such matters as labels that have been agreed to as part of an evaluation under section 25 of the Act may only occur following submission under section 9D of a 'variation' application and approval by the TGA).
- c) The sponsor will provide information to the TGA on the proposed strategies and planned timelines for Australian dedicated supplies, as soon as possible, and no later than 24 January 2023.

- **Batch Release Testing and Compliance**

It is a condition of registration that all independent manufacturing batches of Comirnaty (BNT162b2 (mRNA)) COVID-19 Vaccine to be supplied in Australia are not released for supply by or on behalf of the sponsor until samples and the manufacturer's release data have been assessed by, and sponsor have received notification acknowledging authorisation to release from, the Laboratories Branch, TGA.

In complying with the above, the sponsor must supply the following for each independent batch of the product imported or proposed to be imported into Australia:

- a completed Request for Release Form, available from vaccines@health.gov.au ; and
- complete summary protocols for manufacture and quality control (QC), including all steps in production in the agreed format; and
- if the manufacturing batch has been released in Europe or United Kingdom a copy of the EU Official Control Authority Batch Release (OCABR) certificate (or equivalent from the UK) must also be provided; and
- any reagents, reference material and standards required to undertake testing as requested by Laboratories Branch, TGA.

The shipments (including reagents) to TGA are the responsibility of the Australian sponsor/agent who will be required to facilitate the import and customs clearance process.

- **Certified Product Details**

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription

Medicines (ARGPM) <https://www.tga.gov.au/guidance-7-certified-product-details> should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website <https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines>. The CPD should be sent as a single bookmarked PDF document to Vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

- Post approval commitments

As a provisionally registered medicine, extensive post-approval commitments are required of the sponsor. The additional requested quality data and notifications to the TGA should be provided as post approval commitments. This includes the following commitments:

- Commitment is required from the sponsor that they maintain the validity of all manufacturer Good Manufacturing Practice (GMP) clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP clearance approval is upheld.
 - Additional data should be provided in relation to the reference standards and materials.
 - Additional stability data and updated protocols should be submitted as it becomes available.
 - Any out of specification stability results for drug substance and/or drug product should be submitted to the TGA as soon as they are generated.
 - The sponsor must inform the TGA of any temperature deviation during shipment and not supply product that has been exposed to a temperature excursion outside of the approved storage conditions of -90°C to -60°C.
 - Additional information should be provided regarding batch analyses.
 - Additional data should be provided in relation to process validation of commercial scale batches.
 - Additional data should be provided in relation to validation of the proposed rapid sterility test.
 - Additional data should be provided in relation to the container safety.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Comirnaty approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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