Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

# Advisory Committee on Vaccines Minutes
# Item 2.1
# Tozinameran (formerly BNT162b2[mRNA])

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

**7 September 2022**

# Contents

## Submission details

| | |
|---|---|
| *Type of submission:* | Major variation / PI change requiring evaluation – include a booster dose (10 micrograms) for individuals aged 5 to less than 12 years. |
| *Product name:* | Comirnaty |
| *Active ingredient:* | Tozinameran (formerly BNT162b2 [mRNA]) |
| *Submission number*: | PM-2022-02476-1-2 |
| *Strength / dose form:* | 10 microgram per 0.2 mL dose, embedded in lipid nanoparticles, as Concentrated suspension for injection, as tris/sucrose formulation |
| *Approved indication:* | COMIRNATY (tozinameran) COVID-19 Vaccine has **provisional approval** for the indication below:<br>Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.<br>The use of this vaccine should be in accordance with official recommendations.<br>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. |
| *Approved dosage (abridged):* | *Booster dose in individuals 12 years of age and older*<br>A booster dose of COMIRNATY may be administered intramuscularly at least 6 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older.<br>The decision when and for whom to implement a booster dose of COMIRNATY should be made based on available vaccine safety and effectiveness data (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations. |
| *Proposed dosage:* | *Booster dose in individuals 5 to <12 years of age*<br>A booster dose of COMIRNATY Dilute To Use Multidose (For Age 5 to <12 Years) may be administered intramuscularly at least 6 months after the second dose in individuals 5 to <12 years of age. |

## Documents submitted for ACV consideration

The ACV considered the following documentation:

A1 Delegate's Overview – 26 August 2022
A2 application letter - 28 June 2022
A3 Sponsor – pre-ACV response
response
adverse reactions update
comments on PI
foreign regulatory status
comments on foreign PI
A4 ACV 30 ratified minute on booster dose in 16- 17 year olds
A4a ACV 32 ratified minute on booster dose in 12-15 year olds
PI Product Information – clean and annotated – from pre-ACV response
CMI Consumer Medicine Information – clean and annotated – from pre-ACV response
CAN Canadian product monograph - from pre-ACV response
USA USA emergency use fact sheet – orange vial – from pre-ACV response

**Public domain information:**

ACIP Update to the Evidence to Recommendations for a Pfizer-BioNTech COVID-19 Booster in Children Ages 5-11 Years via https://www.cdc.gov/vaccines/acip/recs/grade/pfizer-biontech-covid19-booster-children-etr.html

Levy N, Koppel JH, Kaplan O, et al. Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel. JAMA 2022; 327(24):2452-2454. doi:10.1001/jama.2022.8025.

Shi DS, Whitaker M, Marks KJ et al. Hospitalisations of Children Aged 5-11 Years with Laboratory-Confirmed COVID-19 – CVOID-NET, 14 States March 2020 – February 2022. MMWR Morn Mortal Wkly Rep 2022; 71574-581

Taquet M, et al. (2021). Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. medRxiv: 2021.2010.2026.21265508

Vaccine Safety Datalink (VSD) data sets accessed 13 August 2022

VAERS Vaccine Safety data sets accessed 18 August 2022

## Delegate's Overview

### Delegate's summary of issues

The Sponsor proposes the booster dose to be administered at least 6 months after Dose 2. The total range for timing of Dose 3 administration after Dose 2 (in Study C4591007) was 5 to 9 months however, almost all participants (399 of 401) received the booster dose 7 - < 9 months after Dose 2, the majority at 8 - < 9 months (86.8%).

### Summary of data

Phase 1/2/3 Study C4591007 Interim Clinical Study Report. Study C4591007 is the ongoing, randomised, placebo-controlled, Phase 1/2/3 study including healthy children from 6 months to <12 years of age.

### Delegate's preliminary view

While a decision is yet to be made, at this stage the Delegate is inclined to approve the registration of the product. The final decision will be made following the ACV discussion. Conditions for Provisional Registration would be applied.

**Advice sought by Delegate of the Secretary of the Department of Health and Aged Care**

1. Please advise on the Sponsors' proposal that the booster dose be administered at least 6 months after Dose 2.
2. Please comment on the benefit risk balance of Comirnaty COVID-19 Vaccine 10 μg (in this submission) as a booster following Dose 2 in children aged 5 - < 12 years for Provisional registration.

## ACV discussion

### Environment

The ACV noted that the vaccine was first provisionally registered on the ARTG on 25 January 2021 for use in persons from 16 years of age.

Dosage and PI changes for use of third doses have been incrementally approved for individuals aged 18+ years, 16+ years and 12+ years. The booster dose in these age groups is 30 micrograms.

***International regulatory status***

- On 17 May 2022 the US FDA extended the Emergency Use Authorization for Comirnaty to allow single booster dose of 10 microgram to individuals 5-11 years of age at least 5 months after completion of the primary series of Comirnaty.
- On 19 August 2022 Health Canada approved single booster dose of 10 microgram to individuals 5 years of age and older at least 6 months after completion of the primary series.
- Applications are under evaluation in the EU, Switzerland, New Zealand and Singapore.

### General comments

The ACV noted that the clinical presentation of SARS-CoV-2 infection in children is usually mild, with many asymptomatic. The ACV further noted the low risk of severe disease with hospitalisation within this population, with children with underlying medical conditions at a greater risk.

The ACV discussed Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) and noted that the majority of cases globally to date have occurred in individuals aged 5 to less than 12 years. It was noted that since the start of the pandemic to 3 July 2022 there have been 134 cases of PIMS-TS in Australia; to date there has been no PIMS-TS associated death. However, one COVID-19 associated death has been notified to the NNDSS in the 5 to 11 years age group. It was also noted in many settings rates of PIMS-TS were reduced while Omicron variants were the dominant strain compared with previous SARS-CoV-2 strains (Levy et al).

The ACV highlighted the benefits of vaccination within this age group, which includes protection from severe COVID-19 disease and death, potential prevention of post COVID-19 inflammatory syndrome (PIMS-TS) and long COVID.

### Immunogenicity

The ACV noted that the basis of demonstrating BNT162b2 effectiveness as a booster in children is via immunogenicity data from Study C4591007.

Study C4591007 is a Phase 1/2/3, randomised, placebo-controlled multicentre study in healthy paediatric participants aged 6 months to less than 12 years of age to evaluate the safety, tolerability, and immunogenicity of BNT162b2 vaccination. The ACV noted that Phase 2/3 study commenced on 7 June 2021 and is ongoing. The data cut-off for the interim report was 22 March 2022.

Participants aged 5 to less than 12 years in Phase 2/3 of the study were randomised to active vaccine (BNT162b2, 10 microgram) or saline placebo (2:1 ratio) administered in a 2-dose schedule given 21 days apart. Based on emerging clinical and real-world data, the protocol was amended to add a third (booster) dose. Safety and immunogenicity data are currently available for up to 1 month after a booster (third) dose.

The ACV noted that the protocol specified timing of booster vaccination for participants 5 to <12 years was ≥6 months after dose 2, with the booster doses administered in an open-label manner.

The immunogenicity data set comprised of up to 130 participants who received Dose 3 (3-Dose set) and up to 70 additional participants who received Dose 2 (2-Dose set). Secondary objectives to Study C4591007 included assessment of immunogenicity endpoints in participants without evidence of past SARS-CoV-2 infection. The ACV noted that the evaluable immunogenicity population without prior evidence SARS-CoV-2 infection was 67 (54.5%) participants, and that only 17 participants had a blood draw at one month post dose 2 resulting in a much smaller sample size in the Dose 2 evaluable immunogenicity population. Among the total evaluable immunogenicity population without prior evidence of infection, observed GMTs were 1253.9 (95% CI: 1116.0, 1408.9) at 1-month post-Dose 2 (n = 96), which waned to 271.0 (95% CI: 229.1, 320.6) prior to Dose 3, increasing to 2720.9 (95% CI: 2280.1, 3247.0) at 1-month post-Dose 3 (n = 67).

The ACV noted that in the Australian context many children have likely been exposed to SARS-CoV-2. The ACV acknowledged that it is important to ensure data are available for both seropositive and seronegative individuals.

The ACV noted that while one-quarter of children had comorbidities (including 4.5% with obesity), children with immunocompromise were excluded.

**Safety**

The ACV commented that the overall safety findings are generally consistent with those observed for primary series vaccination in this population.

The safety population within Study C4591007 comprised of all participants who received Dose 1, 2 and 3 by 22 February 2022 (n = 401). The median follow-up time after Dose 3 was 1.3 (1.0 to 1.8) months.

The ACV noted that no serious adverse events were reported among study participants and no deaths, cases of anaphylaxis or myocarditis were noted at the data cut off.

The proportion of participants with moderate pain at the injection site was higher after Dose 3 compared to the first 2 doses, however no Grade 4 local reactions were reported.

The most common systemic events within 7 days after Dose 3 were fatigue (45.6%) and headache (34.0%). The ACV noted that the incidence of headache and muscle pain increased after each dose, however no Grade 4 systemic events were observed.

The ACV noted that myocarditis is a rare event following mRNA COVID-19 booster vaccination. VAERS data do not indicate a statistical signal for myocarditis to date in children aged 5 to 11 years following the first booster.

The ACV highlighted that the USA post marketing data indicate that the most frequent reports following the first booster (third dose) within this age range were product

preparation and administration errors. 'Incorrect dose administered' reports may provide additional information on overdosage for the PI.

### ACV advice to the Delegate

The ACV advised the following in response to the Delegate's specific request for advice:

1. ***Please advise on the Sponsors' proposal that the booster dose be administered at least 6 months after Dose 2.***

The ACV supported changes to the PI to allow a 10 microgram booster dose to be administered at least 6 months after Dose 2 for children 5-12 years of age, based on limited immunogenicity and safety data.

This broadly aligns with USA and Canadian requirements and the clinical study criteria. The ACV noted that in the clinical study (C4591007) the booster dose (third dose) was administered between 5 and 9 months after Dose 2. However, almost all participants received the booster dose 7 to 9 months post primary series.

The ACV highlighted that the proposed booster timeframe for 5-12 year olds aligns with the current PI advice for the Comirnaty booster for 12-15 year olds. The ACV stated that alignment of administration timeframes / dosage intervals is an important consideration as the current differences can cause confusion for consumers and healthcare professionals using various COVID-19 vaccines across different age groups.

The clinical relevance of booster doses for this age group is unclear but may become important in the event of emergence of more transmissible/severe variants.

2. ***Please comment on the benefit risk balance of Comirnaty COVID-19 Vaccine 10 µg (in this submission) as a booster following Dose 2 in children aged 5 - < 12 years for Provisional registration.***

The ACV was of the view that overall there is a positive benefit risk profile for Comirnaty COVID-19 vaccine 10 microgram as a booster following Dose 2 in children aged 5 to less than 12 years of age when considered for provisional registration.

The ACV agreed that the demonstrated immunogenicity supports use in the population aged 5-11 years, although noted that an immunological correlate of protection is yet to be well defined.

The ACV acknowledged the limited data set, particularly for participants without prior evidence of COVID-19. However, the committee noted the increasing difficulties in recruiting participants without prior evidence of COVID-19.

The ACV highlighted that the USA post marketing data indicated that the most frequent safety reports following the booster within this age range were product preparation and administration errors. The ACV agreed that ongoing mitigation of these errors is important and noted that the Canadian PI provides some useful administration explanations. In addition, the ACV noted some confusion within the PI in regard to diluted and non-diluted preparations. The ACV discussed the potential for administration errors and reiterated the importance of post marketing surveillance and risk mitigation activities broadly to address administration errors for COVID-19 vaccines.

## ACV conclusion

The ACV considered this product to have an overall positive benefit-risk profile for use as a booster (third) dose in children aged 5 to less than 12 years of age when considered for provisional registration. This does not imply a booster dose is necessary or desirable for use across the Australian population aged 5-11 years.

The use and timing of Comirnaty booster in 5-11 year olds should be in accordance with official recommendations.

**Ratified and sent to the sponsor on 15 September 2022; minor revisions, re-ratified and sent to the sponsor on 16 September 2022.**

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**https://www.tga.gov.au**