Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines Meeting 26 Minutes on Item 2.1 BNT162b2 [mRNA] COVID-19 vaccine

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

October 2021

TGA Health Safety Regulation

Contents

Submission details

Type of submission:	Major variation / PI change requiring evaluation - addition of safety and immunogenicity data after a third dose of vaccine
Product name:	Comirnaty
Active ingredient:	BNT162b2 [mRNA] [1]
Submission number:	PM-2021-04582-1-2
Dose form:	Concentrated suspension for injection
Strength:	30 microgram per 0.3 mL injection
Approved indication:	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.
Approved dosage:	*Individuals 12 years of age and older* COMIRNATY is administered intramuscularly after dilution as a course of 2 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 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the vaccination course. *Elderly population* No dosage adjustment is required in elderly individuals ≥ 65 years of age.

[1] International Nonproprietary Name is tozinameran.

Dosage proposed by sponsor with initial submission on 12 October:

Individuals 12 years of age and older

COMIRNATY is administered intramuscularly after dilution as a primary course of 2 doses at least 21 days apart. See dosing instructions below.

A booster dose (third dose) of COMIRNATY may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.

~~There are no data available on the~~The interchangeability of COMIRNATY with other COVID-19 vaccines to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the primary vaccination course and for any additional doses.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Dosage subsequently proposed by sponsor during course of evaluation:

Individuals 12 years of age and older

COMIRNATY is administered intramuscularly after dilution as a primary course of 2 doses at least 21 days apart. See dosing instructions below.

A booster dose (third dose) of COMIRNATY may be administered intramuscularly approximately 6 months after the second dose in individuals ~~16~~18 years of age and older.

~~There are no data available on the~~The interchangeability of COMIRNATY with other COVID-19 vaccines to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the primary vaccination course and for any additional doses.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Dosage proposed by sponsor in pre-ACV response:

Dosage

Individuals 12 years of age and older

COMIRNATY is administered intramuscularly after dilution as a primary course of 2 doses at least 21 days apart. See dosing instructions below.

A booster dose (third dose) of COMIRNATY may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older.

The decision when and for whom to implement a third dose of Comirnaty should be made based on the available vaccine safety and effectiveness data (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

~~There are no data available on the~~The interchangeability of COMIRNATY with other COVID-19 vaccines to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the primary vaccination course and for any additional doses.

Severely immunocompromised aged 12 years and older

A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised (see section 4.4 Special warnings and precautions for use).

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Documents considered by ACV

The ACV considered the following documentation, provided between 11 October 2021 and 22 October 2021:

Background – Sponsor – COVID-19 Vaccine 2.5 Clinical overview – BNT162b2 30 mcg Booster (Dose 3) (Aug 2021) – dated 24 August 2021

Background – Sponsor – Interim Report ‑ BNT162b2 Booster (Dose 3): A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals – dated 23 August 2021

Background – Sponsor - C4591001 Phase 1 Booster Dosing and BETA Variant Ad Hoc report – Aug 2021 – dated 13 August 2021

Background – Sponsor - C4591001 Phase 1 Booster Dosing and DELTA Variant Ad Hoc report – Aug 2021 – dated 13 August 2021

A1 Delegate - Request for ACV advice and overview – ‘Delegate’s Overview’

A1a Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med 2021; 385:1393-400. DOI: 10.1056/NEJMoa2114255

A1b FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting held 17 September 2021 Booster protection against confirmed infections and severe disease - data from Israel

A1c FDA Vaccines and Related Biological Products Advisory Committee Meeting held 14 October 2021 - Booster protection across ages -data from Israel

A2 Sponsor - application letter dated 12 October 2021

A3 Sponsor – pre-ACV response - response

A3 Sponsor – pre-ACV response - adverse reactions update

A3 Sponsor – pre-ACV response – comments on PI

A3 Sponsor – pre-ACV response – foreign regulatory status

A3 Sponsor – pre-ACV response – comments on foreign PI

M5 TGA - Clinical - evaluation report – Round 1 draft dated 18 October 2021

PI Product Information – clean and annotated – from pre-ACV response

CMI Consumer Medicine Information – clean and annotated – from pre-ACV response

EMA European summary of product characteristics – dated 8 October 2021 - from pre-ACV response

UK UK information for temporary supply authorisation – dated September 2021 - from pre-ACV response

USA USA prescribing information for emergency use authorization – dated 22 September 2021 - from pre-ACV response

Documents provided early and superseded:

PI Product Information – annotated - for 16+ - seq0088

PI Product Information – annotated – provided to TGA via email on 11 October with the filename ‘proposed-pi-annotated-18+.pdf’ - as relied on by Clinical evaluator

EMA https://www.ema.europa.eu/en/documents /product-information/comirnaty-eparproduct-information_en.pdf – as per Delegate’s overview

UK https://www.medicines.org.uk/emc/product/12634/smpc - as per Delegate’s overview

Other materials discussed at the meeting included:

Pfizer press release dated Thursday 21 October 2021 (06:45am)

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and biontech-announce-phase-3-trial-data-showing

Altmann DM, Boyton RJ. Waning immunity to SARS-CoV-2: implication for vaccine booster strategies. Lancet Respir Med 2021. https://doi.org/10.1016/ S2213-2600(21)00458-6. Published online 21 October 2021.

Milne G, Harnes T, Scotton C, et al. Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity? Lancet Respir Med 2021. https://doi.org/10.1016/S2213-2600(21)00407-0. Available online 21 October 2021.

UK Health Security Agency. COVID-19 vaccine surveillance report Week 42. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1027511/Vaccine-surveillance-report-week-42.pdf

Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. New Engl J Med 2021.DOI: 10.1056/NEJMoa2114114

MMWR: Safety Monitoring of an Additional Dose of COVID-19 Vaccine — United States, August 12–September 19, 2021 https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7039e4-H.pdf

Kamar N, Abravanel F, Marion O, et al. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021 Aug 12;385(7):661-662. doi: 10.1056/NEJMc2108861. Epub 2021 Jun 23. https://www.nejm.org/doi/full/10.1056/NEJMc2108861

Preprints:

Goldberg et al
https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1.full.pdf

Tartof et al
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3909743

Pouwels et al
https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombinedve20210816.pdf

Andrews et al
https://khub.net/documents/135939561/338928724/Vaccine+effectiveness+and+duration+of+protection+of+covid+vaccines+against+mild+and+severe+COVID-19+in+the+UK.pdf/10dcd99c-0441-0403-dfd8-11ba2c6f5801

Delegate's Overview

Delegate's summary of issues

The Delegate of the Secretary of the Department of Health identified the following in their request for ACV advice:

The clinical data submitted to this submission come from an ongoing Phase 1/2/3 study (C4591001), which is also the source of clinical data supporting the original approval of the 2-dose primary series for use in individuals 16 years of age and older. The BNT162b2 30 µg booster dose was initially assessed in a cohort of 23 Phase 1 study participants (11 participants 18-55 years of age and 12 participants 65-85 years of age), and then in 306 Phase 2/3 study participants 18 through 55 years of age. The sponsor is requesting approval of the booster dose for use in individuals 18 years of age and older. Effectiveness of the booster dose against the reference strain is being inferred based on immunobridging to the 2-dose primary series, as assessed by SARS-CoV-2 neutralizing antibody titres elicited by the vaccine. Immunobridging success criteria for the reference strain were met for both pre-specified co-primary immunogenicity endpoints of GMT ratio and difference in seroresponse rates among study participants with no evidence of SARS-

CoV-2 infection prior to 1 month after the booster dose. The submission also includes exploratory descriptive analyses of immunogenicity against the SARS-CoV-2 Delta variant among adults 18 through 55 years of age and 65 through 85 years of age enrolled in the Phase 1 portion of the study.

Safety data from 306 Phase 2/3 booster recipients do not show evidence of increased local or systemic reactogenicity relative to Dose 2. While evaluated in only 12 participants in the age cohort of 65 through 85 years, the booster dose was less reactogenic in this age cohort compared to younger adults 18 through 55 years of age. Most reactogenicity events after the booster dose were of mild to moderate severity and self-limited in duration. Lymphadenopathy was observed more frequently following the booster dose than after primary series doses (5.2% compared to 0.4%). No deaths, vaccine-related serious adverse events, or events of myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's palsy were reported among study participants who received the BNT162b2 booster dose.

Delegate's preliminary view

While a decision is yet to be made, at this stage [18 October 2021] I am inclined to approve the variation of the product pending ACV deliberation.

The outstanding issue is PI wording on booster dosing: additional information should be provided in the PI in relation to a third dose for immunocompromised people at least 28 days after the primary series.

Advice sought by Delegate of the Secretary of the Department of Health

1. Does the ACV agree that the immunogenicity and safety data support the administration of a booster dose?
2. Advice on the qualifying statement on booster dosing in the PI.
    a. Option 1

        A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data (see sections 4.4 and 5.1).

    b. Option 2

        A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older when the potential benefits outweigh any potential risks.
3. Does the ACV think that additional information should be provided in the PI in relation to a third dose for immunocompromised people at least 28 days after the primary series (similar to the US EUA PI and EU SmPC)?
4. 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.

ACV discussion

General comments

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

evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment. (See ACV 18, held 15 January 2021, providing advice on new biological entity).

Supply of the vaccine commenced on 21 February 2021.

The ACV also noted the provisional registration on 22 July 2021 for use in persons from 12 years of age. (See ACV 22, held 16 June 2021, providing advice on extension of indication).

International regulatory status of booster doses

The ACV noted the following in regard to the international regulatory status of a booster dose:

- Israel approved a third dose of Comirnaty on 30 July 2021 for persons 60 years and older and at least 5 months post primary vaccination. The program has now extended to other age groups.
- The MHRA (UK) issued an authorisation for temporary supply on 9 September 2021, for administration of a third dose at least 8 weeks after the second dose of an mRNA or adenovirus-vectored COVID-19 vaccine when the potential benefits outweigh any potential risks [see also Option 2 in Question 2].
- The FDA issued an Emergency Use Authorization on 22 September 2021 for administration at least 6 months after the primary series, to persons: 65 years and older; 18-64 years and at high risk of severe COVID-19; 18-64 years with frequent institutional or occupational exposure.
- The EMA granted conditional authorisation on 8 October 2021 for administration at least 6 months after the second dose in individuals 18+ years, the decision to be based on available vaccine effectiveness data taking into account limited safety data [see also Option 1 in Question 2].
- Evaluations are in progress in Canada, Singapore, Switzerland and New Zealand.

Immunogenicity and efficacy

The ACV discussed the data on waning neutralising antibody levels in Study C4591001, based on levels taken immediately prior to administration of the third dose.

The ACV noted the immunogenicity data for GMR showed the non-inferiority of booster response to initial regimen response was met. The immune response at one month after the booster dose was non-inferior to that observed at one month after Dose 2 in the same participants, based on SARS-CoV-2 50% neutralising titres. The GMT ratio (one month after Dose 3: one month after Dose 2) was 3.29, which meets the non-inferiority criterion of lower bound of 97.5% CI for GMR > 0.67. The GMTs were superior after Dose 3 compared with Dose 2, with a statistically greater response since lower bound of 97.5% CI for GMR > 1. The difference in neutralizing titres against the wild type and B.1.351 variant viruses narrowed after the third dose compared with those after the second dose.

The seroresponse was ≥ 4-fold rise from baseline before Dose 1. A high proportion of participants (99.5%) had seroresponse at one month after Dose 3 compared to 98% at one month after Dose 2. The difference in proportion of participants with seroresponse one month after the booster (Dose 3) and 1 month after Dose 2 was 1.5% (97.5%CI -0.7-3.7%), which met the 10% non-inferiority margin (lower bound of 97.5% CI > -10%).

The dose interval between second and third doses was a median 6.8 months (range 4.8 – 8 months). The ACV noted that there was no sub-analysis of responses across this 3.2 month range.

Published literature, preprint literature and data presented to US FDA VRBPAC meetings, on Comirnaty and other COVID-19 vaccines, was also noted regarding vaccine effectiveness and waning, as well as the impact of Comirnaty booster dose program in Israel. Observational ecologic data from Israel suggests the age group targeted for booster vaccination were better protected against COVID-19 than age groups yet to receive booster doses. Additionally, short term protection against confirmed COVID-19 and hospitalisation appeared to be augmented in those >60 years of age in an Israeli report.[2] The press release published by the sponsor noting efficacy in a large clinical trial (n>10,000) was noted, but details have not been published or formally reviewed.

Safety

The ACV noted that safety data from 306 Phase 3 booster recipients did not show evidence of increased local or systemic reactogenicity relative to Dose 2. Most reactogenicity events after the booster dose were of mild to moderate severity and self-limited in duration. An increased rate of lymphadenopathy after the third dose was noted; increased rates of other inflammatory conditions such as myocarditis, pericarditis, and appendicitis, were not observed.

The ACV discussed Israeli post-marketing safety data following 3.7 million booster doses. Myocarditis (17 cases) and pericarditis (3 cases) have been reported. The crude rate of myocarditis reported following the booster dose was lower than the rate of myocarditis seen after dose 2 of the primary vaccination series.

Post-marketing safety surveillance in the USA V-safe program for people who received a third dose of Comirnaty (or Moderna's Spikevax) in the USA shows to date a pattern of adverse events after dose 3 consistent with those after dose 2, and no new safety signals have been seen.

Communication points

It was highlighted that there will be demand for booster doses from persons who did not receive Comirnaty as their primary vaccination. There is accumulating evidence internationally on mixed COVID-19 vaccine schedules, including as booster doses. Use of Comirnaty following another mRNA vaccine or viral vector vaccine is best addressed by official guidance and recommendations, such as from the Australian Technical Advisory Group on Immunisation (ATAGI).

Similarly, official guidance and recommendations that can assess emerging literature will likely address the issue of concomitant vaccinations, noting that the PI states 'Concomitant administration of COMIRNATY with other vaccines has not been studied'.

Consideration should be given to highlighting to relevant practitioners that facial swelling has occurred in vaccine recipients with a history of injection of dermatological filler.

ACV advice to the Delegate

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

1. Does the ACV agree that the immunogenicity and safety data support the administration of a booster dose?

The ACV agreed that the immunogenicity data supports the administration of a booster dose, that is, a third dose of Comirnaty administered at least 6 months after the primary

[2] Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med 2021;385: 1393-400. DOI: 10.1056/NEJMoa2114255

vaccination series, to restore waning neutralising antibody titres against wild type SARSCoV-2 to significantly higher levels than seen after primary vaccination course.

The ACV was of the view that the Phase 1 and 3 data from the pivotal study C4591001 demonstrated the induction of high levels of neutralising antibodies following the booster dose, and noted Geometric Mean Titres (GMTs) were significantly higher than those observed after Dose 2. The ACV commented that the data shows the booster dose substantially increased neutralising titres against variants of concern (Beta and Delta) one month after the booster dose, compared with one month after Dose 2 ~~in~~ **of** the primary course.

The ACV noted the limited data for the 65 to 85 years age group (n = 12) is confined to Phase 1 **participants**. In this group the initial responses following primary course waned to a greater extent than in younger individuals, followed by commensurate boosting.

The ACV commented that the duration of the sustained antibody response remains unknown and that there is no known serological correlate of protection. Therefore, the clinical relevance of restoring waning titres is not yet known.

In regard to safety, the ACV commented that the safety data from the 306 Phase 3 booster recipients did not show any new safety concerns within 1 month of the booster dose and commented that these results are comparable with the reported data after Dose 2. There was no evidence of increased local or systemic reactogenicity relative to Dose 2. Most reactogenicity events after the booster dose were of mild to moderate severity and self-limited in duration. The rate~~s~~ of lymphadenopathy **was** ~~were~~ increased **following the** ~~post~~ booster dose (5.2%) compared to following dose 2 (0.4%), with most **cases** resolving within 5 days of onset.

The ACV noted the small numbers in the safety population (n = 306), predominantly aged 18 to 55 years. Rare but significant adverse events such as pericarditis/myocarditis were not observed but the power to detect these was very limited.

The ACV also reviewed data demonstrating **Comirnaty booster** safety and effectiveness from programs implemented in other countries, in particular the booster program in Israel, as presented to the FDA **VRBPAC meeting** on 15 October 2021 **and available in peer-reviewed published literature.** This **data** provided **reassurance on** population-level ~~reassurance on~~ safety and effectiveness **in a large number of vaccine booster dose recipients,** in addition to the small~~er~~ number of participants in the trial presented by the sponsor.

2. Advice on the qualifying statement on booster dosing in the PI.

a. Option 1

A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data (see sections 4.4 and 5.1).

b. Option 2

A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older when the potential benefits outweigh any potential risks.

The ACV advised that the qualifying statement on booster dosing in the PI should be worded as follows:

> A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the completion of a COVID-19 vaccine primary series in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available safety and vaccine effectiveness data (see sections 4.4 and 5.1), in accordance with official recommendations.

In providing this advice the ACV considered what primary course individuals will have received. While the ACV noted that the data in the submission are limited to booster dosing of Comirnaty following a primary course of Comirnaty, they agreed that adding 'the completion of a COVID-19 vaccine primary series' and 'in accordance with official recommendations' would provide flexibility for recommendations of the primary vaccination series to evolve as further data becomes available. The committee also noted considerable experience with mixed dose schedules in other countries, as well as in small studies.

Following on from this, the ACV advised the following clarifying wording should also be added to the PI, based on the current data:

> There are limited data on the interchangeability of COMIRNATY with other COVID 19 vaccines to complete the primary vaccination course or the booster dose (third dose). Individuals who have received 1 dose of COMIRNATY should preferably receive a second dose of COMIRNATY to complete the primary vaccination course and for any additional doses.

3. Does the ACV think that additional information should be provided in the PI in relation to a third dose for immunocompromised people at least 28 days after the primary series (similar to the US EUA PI and EU SmPC)?

The ACV acknowledged the ATAGI recommendation made on 7 October 2021 in regard to use of a third primary dose of COVID-19 vaccine in individuals who are severely immunocompromised.

The ACV was of the view that information on a third dose for immunocompromised people should be included in the PI and suggested the following wording:

> In accordance with official recommendations, a third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised.

The ACV emphasised that it should be made clear this is a third dose within the primary series rather than a booster dose.

4. 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 noted pending clinical trial data on immunogenicity and safety **in** ~~on~~ the balance of the 600 subjects who received the Beta variant vaccine construct **in the Comirnaty booster dose study.** The ACV also noted a recent press release detailing efficacy and safety in a trial (NCT04955626) of a booster dose **of Comirnaty** in more than 10,000 subjects that is yet to be published or formally reviewed. ~~(trial identifier to be confirmed by the sponsor).~~

The ACV suggested the following changes to the Comirnaty PI:

- Myocarditis and pericarditis

  'Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger ~~men.~~ **males**'

  Change 'men' to 'males', to use more inclusive wording for the younger age group.

- Duration of protection

'The duration of protection afforded by COMIRNATY is unknown as it is still being determined by ongoing clinical trials **and observational studies**.'

Add the text in bold to the sentence above.

ACV conclusion

The ACV recommended the approval of changes to the Product Information of Comirnaty to include a booster (third) dose for persons 18 years and older, and dosage for immunocompromised persons over 12 years.

Ratified and sent to the sponsor 4 pm on 26 October 2021

Therapeutic Goods Administration

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