Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Advisory Committee on Vaccines Minutes
Item 2.3
Tozinameran / Riltozinameran

Proprietary Product Name: COMIRNATY ORIGINAL / OMICRON BA.1 COVID-19 VACCINE

Sponsor: Pfizer Australia Pty Ltd

5 October 2022

Contents

Submission details

Type of submission:	New active ingredient and New fixed dose combination Designated for Provisional registration 5 July 2022
Product name:	COMIRNATY Original / Omicron BA.1 COVID-19 VACCINE
Active ingredients:	Tozinameran (also referred to as BNT162b22) Riltozinameran (also referred to as BNT162b22 OMI)
Submission number:	PM-2022-03551-1-2
Proposed strength / dose form:	One dose (0.3 mL) contains tozinameran 15 micrograms and riltozinameran 15 micrograms, embedded in lipid nanoparticles, as a suspension for injection.
Indication proposed by sponsor:	COMIRNATY Original/Omicron BA.1 Vaccine has provisional approval for the indication below: As a booster dose for 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.
Indication proposed by Delegate:	COMIRNATY Original/Omicron BA.1 Vaccine has provisional approval for the indication below: As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 18 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.
Proposed dosage (abbreviated):	Booster Dose A booster dose of COMIRNATY ORIGINAL/OMICRON BA.1 may be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older.

Documents submitted for ACV consideration

The ACV considered the following documentation:

A1 Delegate's Overview and Request for ACV advice – 29 September 2022
Note: replaced 23 September 2022 version.
A2 Application letter
M3 Quality summary
M4 Nonclinical evaluation report
M5 Clinical evaluation report – round 1 - draft
M5a Sponsor's Clinical overview – Omicron BA.1 modified vaccine
RMP Risk Management Plan evaluation report – round 1

A3 Sponsor's response to Delegate's Overview dated 23 September 2022 – cover letter
A3a Sponsor's response to Delegate's Overview dated 23 September 2022
A3b Adverse reactions update
A3c Sponsor's comments on PI
A3d Foreign regulatory status
A3e Sponsor's comments on foreign PI
A3f PSUR for Comirnaty original for the period 19 December 2021 to 18 June 2022

PI Product Information – annotated and clean
CMI Consumer Medicine Information – annotated and clean
EU European Summary of Product Characteristics - draft
UK UK Summary of Product Characteristics – draft

Public domain information included:

Advisory Committee on Immunization Practices (ACIP), meeting of 1 September 2022, including from CDC COVID-19 Immunization Safety Unit

Richardson SI, Motlou T, van der Mescht MA, et al. SARS-CoV-2 BA.4 infection triggers more cross-reactive neutralizing antibodies than BA.1. bioRxiv 2022.07.14.500039; doi:https://doi.org/10.1101/2022.07.14.500039

Suryawanshi RK, Chen IP, Ma T, et al. Limited cross-variant immunity from SARS-CoV-2 Omicron without vaccination. Nature 2022;607:351–355. https://doi.org/10.1038/s41586-022-04865-0

Delegate's Overview

Delegate's summary of issues

Limitations to the current data include:

- No data for the bivalent vaccine in individuals under 55 years of age
- No data at all for the 12 years to 18 years population
- No data for the bivalent vaccine following 2nd and 4th doses of Comirnaty
- Immunogenicity against the currently circulating subvariant (BA.4/5) is not known
- Safety sample size was small and follow up was limited to 28 days post booster dose
- Immunogenicity follow up duration is short, and the long-term trend/duration of immune response post booster dose is unknown

- Clinical efficacy and efficacy against asymptomatic infection and viral transmission were not studied
- No data available for immunocompromised individuals, uncontrolled co-morbidities and frail elderly
- No data available in pregnant women and lactating mothers.

Delegate's preliminary view

While a decision is yet to be made, at this stage (23 September 2022), the Delegate is inclined toward thinking that the known and potential benefits likely outweigh the known and potential risks for the use of Comirnaty Original/Omicron BA.1 COVID-19 Vaccine as booster in individuals 18 years of age and older.

The Delegate is seeking advice from ACV on the issue of clinical safety and immunogenicity, especially regarding unavailability of immunogenicity and safety data for bivalent vaccine in the under 55 years age population and lack of data after the 2nd dose (primary series) and 4th dose ('winter' booster). Also, there are no data whatsoever for 12-17 years age group.

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

1. Based on the overall evidence from the sub study E and supportive Sub study D, can the ACV advice whether the benefits-risks balance of Comirnaty Original/Omicron BA.1 as homologous and heterologous booster in individuals 12 years and older is positive in the current pandemic situation?
2. Does the ACV support the proposed indication for use of Comirnaty Original/Omicron BA.1 as homologous and heterologous booster in general population above 12 years, based on the submitted immunogenicity/safety data, especially in the view of no immunogenicity/safety data for bivalent vaccine in subjects under 55 years? Also, there is no immunogenicity data for subjects after primary series (post dose 2) or the 4th dose or subjects with natural infection after primary series and no validated immunogenicity data against BA.4/5 variant?
3. Can the ACV comment if overall Safety is acceptable, as the sample size was small, pivotal study only included subjects above 55 years and the follow up was only 4 weeks? There are no safety data for proposed booster dose after the primary series or the 4th booster dose.
4. Can the ACV comment on any specific risk mitigation strategies required for the booster dose?
5. 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 a purpose of variant COVID-19 vaccines in general is to increase the breadth and depth of immunity rather than to keep pace with the evolution of SARS-CoV-2 (as this is impossible). The role of an Omicron-specific booster is unclear:

> … Omicron infection enhances pre-existing immunity elicited by vaccines but, on its own, may not confer broad protection against non-Omicron variants in unvaccinated individuals. (Suryawanshi, 2022)

> … unlike SARS-CoV-2 Omicron BA.1, which triggered neutralizing antibodies with limited cross-reactivity, BA.4/5 infection triggers highly cross-reactive neutralizing antibodies. Cross-reactivity was observed both in the absence of prior vaccination and also in breakthrough infections following vaccination (Richardson 2022).

International regulatory status

In the USA, Comirnaty Original/Omicron BA.1 has not been pursued, being superseded by emergency use authorisation for bivalent Original/Omicron BA.4/BA.5 vaccine.

In Europe, Comirnaty Original/Omicron BA.1 was approved on 1 September 2022 for use from 12 years of age, at least 3 months after (any) primary series of a COVID-19 vaccine. The EMA's human medicines committee (CHMP) has recommended authorising an adapted bivalent vaccine targeting the Omicron subvariants BA.4 and BA.5 in addition to the original strain of SARS-CoV-2.

Immunogenicity

Immunogenicity data were derived primarily from Study C4591031 Substudy E, investigating the immune responses and safety following bivalent vaccine administered to individuals who had previously received 3 doses of original Comirnaty with the third dose administered 5-12 months prior to Comirnaty Original / Omicron BA.1. Immunocompromised individuals were excluded from the study.

Approximately 1840 healthy older adults (>55 years of age) were in 6 treatment groups: standard (30 µg) and high-dose (60 µg) BNT162b22; standard (30 µg) and high-dose (60 µg) BNT162b22 OMI; and combinations of BNT162b22 and BNT162b22 OMI (at 15 or 30 µg each for a total mRNA amount of 30 or 60 µg), given as a single booster dose.

The ACV highlighted the following results:

- In participants without evidence of infection up to one month after study vaccination:
  - GMRs for the two bivalent vaccine groups BNT162b22 + BNT162b22 OMI 30 µg, and BNT162b22 + BNT162b22 OMI 60 µg, to BNT162b22 30 µg group, were 1.56 and 1.97 respectively. As the lower bound of the 95% CIs in each instance were >1.0, superiority was demonstrated.
  - GMRs for the BNT162b22 OMI 30 µg group and BNT162b22 OMI 60 µg to BNT162b22 30 µg group were 2.23 and 3.15 respectively
- Non-inferiority for GMR for anti-reference strain response was established for both bivalent formulations (lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and point estimate of the GMR ≥0.8).

The Interim Clinical Study Report (1-month analysis) for the pivotal Substudy E included only participants aged over 55 years. There are no efficacy endpoints.

Study C4591031 Substudy D recruited adults aged 18-55 years. In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after first study (Dose 4) vaccination, the GMR (BNT162b22 OMI / BNT162b22) was 1.75 (2-sided 95% CI: 1.39, 2.22). This study did not use bivalent formulation, and so it is supportive on immunogenicity and safety in BNT162b22 OMI in younger adults.

Safety

The ACV noted the limitations to the current data outlined by the Delegate, especially:

- No data at all in individuals 12-18 years of age. The benefit risk balance in this age group cannot be decided in the absence of data, particularly where there are very

limited data in younger adults. Adolescents and young adults are at highest risk of the most important known safety risks following mRNA COVID-19 vaccines.

- Safety sample size in Substudy E for the proposed formulation was small (n=305).
- Follow up was limited to 28 days post booster dose. At the data cut-off, only 10.4% of participants had ≥ 2 months follow-up.

Presentation and administration errors

The ACV noted that the Comirnaty Original / Omicron BA.1 vaccine will be supplied in a multidose vial with a grey cap and does not require dilution prior to use. The ACV recalled that a grey capped multidose ready-to-use vial is also provisionally registered for tozinameran 30 microgram/0.3 mL for individuals 12 years and older. The committee was concerned that product differentiation may be inadequate, given the Comirnaty Original / Omicron BA.1 may be approved only for individuals 18 years and older rather than 12 years and older.

ACV advice to the Delegate

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

1. ***Based on the overall evidence from the sub study E and supportive Sub study D, can the ACV advice whether the benefits-risks balance of Comirnaty Original/Omicron BA.1 as homologous and heterologous booster in individuals 12 years and older is positive in the current pandemic situation?***

The ACV advised that the benefit-risk balance of Comirnaty Original/Omicron BA.1 as homologous and heterologous booster in individuals 18 years and older is positive.

The ACV advised that it was unable to assess the benefit-risk balance of Comirnaty Original/Omicron BA.1 in individuals aged 12-18 years, as no immunogenicity or safety data were available for this age group. The ACV noted that original Comirnaty is approved as a booster dose in the 12-18 year age group.

2. ***Does the ACV support the proposed indication for use of Comirnaty Original/Omicron BA.1 as homologous and heterologous booster in general population above 12 years, based on the submitted immunogenicity/safety data, especially in the view of no immunogenicity/safety data for bivalent vaccine in subjects under 55 years? Also, there is no immunogenicity data for subjects after primary series (post dose 2) or the 4th dose or subjects with natural infection after primary series and no validated immunogenicity data against BA.4/5 variant?***

The ACV advised that it did not support the proposed indication for use from 12 years of age. While immunogenicity bridging from older adults to younger adults (18+ years) was reasonable, bridging of reactogenicity and safety from older adults to adolescents was not supported.

Reactogenicity is known to be higher in adolescents and young adults than older adults following original Comirnaty administration. As all safety data are from individuals aged over 55 years, it is not appropriate to use Comirnaty Original/Omicron BA.1 in the 12-18 year age group.

Limitations in the submission are the absence of data on use of Comirnaty Original/Omicron BA for primary vaccination, after 4th doses of original Comirnaty, after natural infection after primary series, and validated immunogenicity against BA.4/5 variants. While the submitted data were solely in participants who had previous doses of Comirnaty, ACV agreed it would be reasonable to permit the use as a heterologous booster

after other primary vaccines. However, the lack of data for this group should be highlighted.

3. ***Can the ACV comment if overall Safety is acceptable, as the sample size was small, pivotal study only included subjects above 55 years and the follow up was only 4 weeks? There are no safety data for proposed booster dose after the primary series or the 4th booster dose.***

The ACV advised that the overall safety profile for adults was acceptable, noting the identified data limitations.

Adverse events occurring beyond 4 weeks are part of the 'long term safety data' identified as 'missing information' in the risk management plan.

4. ***Can the ACV comment on any specific risk mitigation strategies required for the booster dose?***

The ACV advised that the limitations on the available information on this vaccine need to be adequately communicated to potential recipients of the vaccine.

5. ***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 highlighted that Comirnaty (tozinameran 30 microgram/0.3 mL for individuals 12 years and older) and Comirnaty Original / Omicron BA.1 vaccine are each to be supplied in a multidose vial with a grey cap and as a formulation that does not require dilution prior to use. The committee was concerned that product differentiation may be inadequate for selection and safe administration of the appropriate vaccine. The ACV also highlighted the need for accurate record keeping given the enlarging range of COVID-19 vaccines.

ACV conclusion

The ACV considered this product to have an overall positive benefit-risk profile for the indication:

> COMIRNATY Original/Omicron BA.1 Vaccine has provisional approval for the indication below:
>
> As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 18 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 immunogenicity and short-term safety data. Continued approval depends on the evidence of longer term benefits and safety from ongoing clinical trials and post-market assessment.

Ratified and sent to the sponsor on 17 October 2022.

Therapeutic Goods Administration

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