Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Spikevax Bivalent Original/Omicron

Active ingredients: elasomeran and imelasomeran

Sponsor: Moderna Australia Pty Ltd

August 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
CDC	Centers for Disease Control and Prevention (United States of America)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DLP	Data lock point
EMA	European Medicine Agency (European Union)
EU	European Union
EUA	Emergency Use Authorization (Food and Drug Administration, United States of America)
FDA	Food and Drug Administration (United States of America)
GLSM	Geometric least squares mean
GMFR	Geometric mean fold rise
GMR	Geometric mean ratio
GMT	Geometric mean titres
HIV	Human immunodeficiency virus
ID_{50}	50% inhibitory dilution
LLOQ	Lower limit of quantification
MAAE	Medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralising antibody

Abbreviation	Meaning
NHP	Non-human primate
PI	Product Information
PPSI	Per-protocol set for immunogenicity
PPSI-Neg	Per-protocol set for immunogenicity-SARS-CoV-2 negative at Baseline
PPSI-Pos	Per-protocol set for immunogenicity-SARS-CoV-2 positive at Baseline
PT	Preferred Term
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SRR	Seroresponse rate
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
VOC	Variant of concern
VOI	Variant of interest
WHO	World Health Organization

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Spikevax Bivalent Original/Omicron
Active ingredients:	Elasomeran and imelasomeran
Decision:	Approved for provisional registration
Date of decision:	29 August 2022
Date of entry onto ARTG:	30 August 2022
ARTG number:	389513
, *Black Triangle Scheme:*	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Moderna Australia Pty Ltd Level 6, 60 Martin Place Sydney, NSW, 2000
Dose form:	Suspension for injection
Strength:	0.1 mg/mL
Container:	Multidose vials
Pack size:	10 x 5 mL multidose vials (0.1 mg/mL) 10 x 2.5 mL multidose vials (0.1 mg/mL)
Approved therapeutic use:	*Spikevax Bivalent Original/Omicron (elasomeran/imelasomeran) COVID-19 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.*
Route of administration:	Intramuscularly

Dosage:	*Individuals 18 years of age and older* Spikevax Bivalent Original/Omicron may be given at least 3 months following a primary series and/or previous booster dose with Spikevax (original) or another authorised/approved COVID-19 vaccine, in accordance with official recommendations. Each 0.5 mL dose of Spikevax Bivalent Original/Omicron 0.1 mg/mL contains 25 µg of elasomeran and 25 µg of imelasomeran embedded in lipid nanoparticles. 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 submission by Moderna Australia Pty Ltd (the sponsor) to register Spikevax Bivalent Original/Omicron (elasomeran and imelasomeran) 0.1 mg/mL, suspension for injection for the following proposed indication:

> *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.*

Each 0.5 mL dose of the proposed vaccine (Spikevax Bivalent Original/Omicron) contains 25 µg of elasomeran and 25 µg of imelasomeran (the active ingredients in this bivalent vaccine) embedded in lipid nanoparticles.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) betacoronavirus responsible for COVID-19 (coronavirus disease 2019). Since its emergence, the SARS-CoV-2 virus has

spread rapidly around the globe. It was officially declared a pandemic by World Health Organization (WHO) on 11 March 2020.[1,2]

In November of 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant to date with more than 30 mutations in the spike protein compared to the original or 'wild-type' strain of SARS-CoV-2.[3] The Omicron variant shares antibody escape site mutations with the Beta variant and it also exhibits transmissibility advantages.[4,5,6] Soon after its emergence the Omicron variant rapidly became dominant worldwide.[7,8] The emergence of the Omicron variant resulted in the highest ever COVID-19 incidence rates globally, even in countries with high vaccination coverage. With the emergence of the Omicron variant, seven-day moving averages for cases eclipsed that of previous waves with peaks observed in excess of 807,000 with peaks in seven-day hospitalisation observed in excess of 159,000. Deaths during the Omicron wave exceeded those observed during Delta with seven-day moving averages peaking above 2,500.[9]

The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022 and Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, and BA.5) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). According to the NOWCAST report from the Centers for Disease Control and Prevention (CDC) (part of the United States (US) Food and Drug Administration)) reporting period from 29 May 2022 to 4 June 2022, the Omicron BA.2, BA.2.12.1, BA.4, and BA.5 subvariants comprised approximately 24.8%, 62.2%, 5.4%, and 7.6%, respectively, of the SARS-CoV-2 sequences analysed.[10]

In Australia, the Omicron variant was first identified in November 2021 and quickly spread throughout the country by the end of 2021. This led to the fourth wave and has continued into the first half of 2022 [11]. In January 2022, the Communicable Diseases Genomics Network variant of concern (VOC) Taskforce demoted previously designated VOCs (Alpha (B.1.1.7); Beta (B.1.351) and Gamma (P.1)) to variant of interest (VOI) due to sustained absence of cases in Australia. Similarly, the Delta variant (B.1.617.2) was demoted from VOC to VOI, again due to sustained absence of cases in Australia. As of June 2022, the VOC reported in Australia is the B.1.1.529 (Omicron) lineage along with its BA. sub-lineages. There have been five major sub-lineages defined under the B.1.1.529 (Omicron) variant: BA.1, BA.2, BA.3, BA.4 and BA.5; and a large number of sub-lineages

[1] World Health Organization: Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 30 January 2020. Available at: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

[2] World Health Organization: WHO Director-General's opening remarks at the media briefing on COVID-19. 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

[3] Hastie, et al. Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: A global consortium study. *Science*, 2021: 374; 6566: 472-478.

[4] Global Initiative on Sharing Avian Influenza Data database accessible via https://gisaid.org/

[5] van der Straten, et al. Mapping the antigenic diversification of SARS-CoV-2. *medRxiv,* 2022*:* 2022.01.03.21268582

[6] Wilks, et al. Mapping SARS-CoV-2 antigenic relationships and serological responses. *bioRxiv*, 2022: 2022.01.28.477987

[7] European Centre for Disease Prevention and Control site accessible via https://www.ecdc.europa.eu

[8] Centres for Disease Control and Prevention, Variants & Genomic Surveillance site accessible via https://covid.cdc.gov/covid-data-tracker/#variants-genomic-surveillance

[9] Johns Hopkins University Coronavirus resource center. Available from: https://coronavirus.jhu.edu/

[10] Nowcast is a model by Centres for Disease Control and Prevention, that estimates more recent proportions of circulating variants and enables timely public health action. Accessible via https://covid.cdc.gov/covid-data-tracker/#variant-proportions

[11] Australia Bureau of Statistic, Measuring Australia's excess mortality during the COVID-19 pandemic. Accesible via https://www.abs.gov.au/articles/measuring-australias-excess-mortality-during-covid-19-pandemic

under these are all designated Omicron.[12] As of 19 August 2022, there were approximately 9.87 million total confirmed cases recorded and 13,000 total deaths registered in Australia.[13]

The sponsor claims that the morbidity and mortality associated with COVID-19 that is being caused by antigenically divergent variants such as the Omicron variant combined with decreasing Spikevax (elasomeran/mRNA-1273) booster vaccine effectiveness against Omicron, and this creates the need to develop a booster vaccine with enhanced immunogenicity. An enhanced immune response is likely to confer improved protection against COVID-19 and help decrease the burden on hospitals and healthcare systems thereby helping contain this dynamic pandemic.[14,15] Soon after the emergence of the Omicron variant, the sponsor evaluated the Omicron-containing bivalent vaccine candidate 'mRNA 1273.214', in the form of 50 µg given as a second booster dose, and the sponsor is seeking authorisation of the Omicron containing bivalent booster vaccine.

The World Health Organization (WHO) states:

> 'Available data … indicate that the inclusion of Omicron, as the most antigenically distinct SARS-CoV-2 Variant of Concern, in an updated vaccine composition may be beneficial if administered as a booster dose to those who have already received a COVID-19 vaccination primary series'. In addition, the International Coalition of Medicines Regulatory Authorities (ICMRA) states: 'With the increasing circulation of Omicron-descendent lineages, bivalent vaccines incorporating an Omicron descendent lineage and ancestral (index) virus would be preferred for adapted versions of vaccines already in use, as they may provide an improved level of cross-neutralization against previous VOCs as well as current Omicron and possibly future Omicron sublineages in the Northern hemisphere winter season of 2022'.[16,17]

Current vaccine options

There are currently five vaccines on the Australian Register of Therapeutic Goods (ARTG), and all are approved under the provisional pathway: [18,19],

[12] COVID-19 National Incident Room Surveillance report, COVID-19 Australia: Epidemiology June 2022 report. Accessible via https://www1.health.gov.au/internet/main/publishing.nsf/Content/C50CAE02452A48A7CA2587320081F7BF/$File/technical_supplement__covid_19_australia_epidemiology_reporting_last_updated_28_june_2022.pdf

[13] Australian Government Department of Health: Coronavirus (COVID-19) case numbers and statistics (as of 19 August 2022. Available at: https://www.health.gov.au/health-alerts/covid-19/case-numbers-and-statistics#total-covid19-cases-by-source-of-infection

[14] Gilbert, et al. Immune Correlates Analysis of the mRNA-1273 COVID-19 Vaccine Efficacy Trial. Preprint. *medRxiv*, 2021;2021.08.09.21261290.

[15] Khoury, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med,* 2021; 27, 1205–1211.

[16] Interim statement on the composition of current COVID-19 vaccines. Accessible via https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines

[17] International Coalition of Medicines Regulatory Authorities SARS-CoV-2 Variant Workshop report. Accessible via https://icmra.info/drupal/en/covid-19/30june2022

[18] Available at: COVID-19 vaccine: Provisional registrations | Therapeutic Goods Administration (TGA). Last accessed on 19/08/2022.

[19] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.

- Comirnaty (tozinameran, previously known at BNT162b2 (mRNA));[20] also commonly known as the Pfizer/BioNTech (mRNA) vaccine is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 5 years of age and older.[21,22,23,24]
- COVID-19 Vaccine AstraZeneca (ChAdOx1-S), an adenoviral vectored vaccine, is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.[25,26]
- COVID-19 Vaccine Janssen (Ad26.COV2.S), an adenoviral vectored vaccine, is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.[27,28]
- Spikevax (elasomeran) COVID-19 vaccine, also known as the Moderna (mRNA) vaccine, is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.[29,30,31,32,33]
- Nuvaxovid (SARS-CoV-2 recombinant spike protein with Matrix-M adjuvant) COVID-19 vaccine, also known as the Novavax recombinant spike protein vaccine, is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.[34,35,36]

The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.

[20] Tozinameran, the active ingredient in the Comirnaty COVID-19 Vaccine was previously registered in Australia and overseas by the provisional drug name BNT162b2. Both the International non-proprietary name (INN) and the Australian Approved Name (AAN) is accepted as being tozinameran, and it is therefore referred to as Comirnaty (tozinameran) COVID-19 vaccine throughout this AusPAR. This is in contrast to the use of BNT162b2 as the name of the active ingredient in earlier AusPARs. The change is in name only; the composition of the active ingredient is unchanged in any way.

[21] Comirnaty was first registered on the ARTG on 25 January 2021 (ARTG number: 346290).

[22] AusPAR for Comirnaty (BNT162b2 (mRNA)) new biological entity, published on 25 January 2021. Available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty.

[23] AusPAR for Comirnaty (BNT162b2 (mRNA)) extension of indications, published on 23 July 2021. Available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna.

[24] AusPAR for Comirnaty (tozinameran) extension of indications; change to formulation (excipients), published on 13 December 2021. Available at: https://www.tga.gov.au/auspar/auspar-tozinameran-mrna-covid-19-vaccine.

[25] COVID-19 Vaccine AstraZeneca was first registered on the ARTG on 16 February 2021 (ARTG number: 349072).

[26] AusPAR for COVID-19 Vaccine AstraZeneca (ChAdOx1-S) new biological entity, published on 16 February 2021. Available at: https://www.tga.gov.au/auspar/auspar-chadox1-s.

[27] COVID-19 Vaccine Janssen was first registered on the ARTG on 25 June 2021 (ARTG number: 350150).

[28] AusPAR for COVID-19 Vaccine Janssen (Ad26.COV2.S) new biological entity, published on 25 June 2021. Available at: https://www.tga.gov.au/auspar/auspar-ad26cov2s.

[29] Spikevax was first registered on the ARTG on 9 August 2021 (ARTG number: 370599).

[30] AusPAR for Spikevax (elasomeran) new biological entity, adult indication, published on 9 August 2021. Available at: https://www.tga.gov.au/auspar/auspar-elasomeran.

[31] AusPAR for Spikevax (elasomeran) new biological entity, paediatric indication, published on 4 September 2021. Available at: https://www.tga.gov.au/auspar/auspar-elasomeran-0.

[32] AusPAR for Spikevax (elasomeran) extension of indications, published on 23 February 2022. Available at: https://www.tga.gov.au/auspar/auspar-elasomeran-1.

[33] AusPAR for Spikevax (elasomeran) extension of indications and major variation, paediatric indication for 6 months of age and above, published on 4 August 2022. Available at https://www.tga.gov.au/auspar/auspar-elasomeran-2

[34] Nuvaxovid was first registered on the ARTG on 20 January 2022 (ARTG number: 355139).

[35] AusPAR for Nuvaxovid (SARS-CoV-2 recombinant spike protein with Matrix-M adjuvant) new biological entity, published on 21 January 2022. Available at: https://www.tga.gov.au/auspar/auspar-sars-cov-2-rs-matrix-m-adjuvant.

[36] AusPAR for Nuavxovid (SARS-CoV-2 recombinant spike protein with Matrix-M adjuvant) extension of indications, published on 29 July 2022. Available at https://www.tga.gov.au/auspar/auspar-sars-cov-2-rs-matrix-m-adjuvant-nvx-cov2373

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

Spikevax Bivalent Original/Omicron is formulated with equal amounts of elasomeran and imelasomeran. Elasomeran, as a single biological entity, has had provisionally registration since August 2021 in the form of the sponsor's monovalent Spikevax COVID-19 vaccine.[29,30,31,32,33] Imelasomeran is a new biological entity with no regulatory history or history of use in Australia.

At the time the TGA considered this submission, a similar submission had been approved in the United Kingdom on 15 August 2022. A similar submission was under consideration in Canada, European Union (EU), Switzerland, Singapore and Japan. Furthermore, a similar, yet slightly different Omicron bivalent vaccine is under consideration in the United States of America (USA).[37]

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	24 August 2022	Under consideration	Under consideration
Canada	30 June 2022	Under consideration	Under consideration
European Union	16 June 2022	Under consideration	Under consideration
United Kingdom	21 June 2022	Approved on 15 August 2022	*Spikevax Bivalent Original/Omicron is indicated as a booster dose for active immunisation to prevent 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*

[37] Sponsor applied for Emergency Use Authorization (EUA) in United States of America for COVID vaccine booster candidate, mRNA-1273.222, a bivalent booster candidate containing the original and Omicron BA.4/BA.5 strain mRNA.

Region	Submission date	Status	Approved indications
Switzerland	22 June 2022	Under consideration	Under consideration
Singapore	22 July 2022	Under consideration	Under consideration
Japan	10 August 2022	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 PI/CMI search facility.

Registration timeline

Data were provided as a rolling submission. Under normal circumstances, the TGA's assessment (for both provisional;[19] 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 and treatments, to enable early evaluation of data as it becomes available. The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2022-02203-1-2

Description	Date
Determination (Provisional)	27 April 2022
Submission dossier accepted and first round evaluation commenced	22 June 2022
Evaluation completed	16 August 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	18 August 2022
Sponsor's pre-Advisory Committee response	19 August 2022
Advisory Committee meeting	24 August 2022
Registration decision (Outcome)	29 August 2022
Completion of administrative activities and registration on the ARTG	30 August 2022
Number of working days from submission dossier acceptance to registration decision*	49

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

The Delegate referred to the following guidelines and guidance documents as being applicable to this submission:

- TGA guidance 8: Product information.[38]
- TGA guidance on form for providing product information.[39]
- ACCESS Consortium statement on COVID-19 vaccines evidence.[40]
- ACCESS Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines.[41]
- European Medicine Agency (EMA) Committee for medicinal product for human use (CHMP): Guidelines on clinical evaluation of new vaccine.[42]
- EMA consideration on COVID-19 vaccine approval.[43]
- Food Drug Administration (FDA) United States (US), Guidance for industry: Development and licensure of vaccines to prevent COVID-19.[44]
- US FDA, Guidance for industry: Emergency Use Authorization for vaccine to prevent COVID-19.[45]
- US FDA, Guidance for industry. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention.[46]
- WHO; Design of vaccine efficacy trials to be used during public health emergencies – points of consideration and key principles.[47]

Quality

The Spikevax Bivalent Original/Omicron vaccine (drug development code: mRNA 1273.214) comprises of two specific nucleoside modified mRNA sequences that each encode for the viral spike protein of two SARS-CoV-2 variants. The mRNA is embedded in lipid nanoparticles.

[38] TGA Guidance 8: Product information. Available at https://www.tga.gov.au/guidance-8-product-information.
[39] TGA guidance on form for providing product information. Available at https://www.tga.gov.au/form-providing-product-information.
[40] ACCESS consortium statement on COVID-19 vaccines evidence published on 4 December 2020. Available at https://www.tga.gov.au/access-consortium-statement-covid-19-vaccines-evidence.
[41] ACCESS Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines published on 14 September 2021. Available at https://www.tga.gov.au/access-consortium-alignment-icmra-consensus-immunobridging-authorising-new-covid-19-vaccines.
[42] EMEA/CHMP/VWP/164653/2005. Guidelines on clinical evaluation of new vaccines published on 18 October 2006. Available at www.ema.europa.eu.
[43] EMA/592928/2020. EMA consideration on COVID-19 vaccine approval published on 16 November 2020. Available at www.ema.europa.eu.
[44] Food Drug Administration (FDA) United States, Guidance for industry: Development and licensure of vaccines to prevent COVID-19 published in June 2020. Available at www.fda.gov.
[45] FDA US, Guidance for industry: Emergency use authorization for vaccine to prevent COVID-19 published on 25 May 2021. Available at www.fda.gov.
[46] FDA US, Guidance for industry. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention published in February 2021. Available at www.fda.gov.
[47] WHO; Design of vaccine efficacy trials to be used during public health emergencies – points of consideration and key principles. Available at www.who.int.

- Elasomeran (drug development code: mRNA-1273) contains the mRNA encoding for the spike protein of SARS-CoV-2 of the ancestral strain;
- Imelasomeran (drug development code: mRNA-1273.529) contains the mRNA that encodes for the spike protein of the SARS-CoV-2 B.1.1.529 (Omicron) variant.

Spikevax Bivalent Original/Omicron is preservative-free and supplied frozen at -50°C to -15°C as a ready to use solution and once thawed the vaccine should not be re-frozen, with the following pack presentations:

- 10 x 2.5 mL multi-dose vials (0.1 mg/mL strength);
- 10 x 5 mL multi-dose vials (0.1 mg/mL strength).

There are no significant issues identified from the quality evaluation of the submitted data that would indicate the product should not be provisionally registered on the basis of quality, or safety-related issues arising from the quality of the product. The manufacturing quality information submitted by the sponsor support the provisional registration of Spikevax Bivalent Original/Omicron.

Nonclinical

Immunogenicity of elasomeran (mRNA-1273), imelasomeran (mRNA-1273.529) and elasomeran and imelasomeran combined (mRNA-1273.214) were determined in appropriate animal models. Protection studies were limited to primary immunisation with the monovalent (elasomeran) vaccine, and boosting with either the monovalent elasomeran, or imelasomeran vaccine; or the bivalent elasomeran and imelasomeran vaccine. The bivalent vaccine was not assessed in protection studies. SM-102 (a lipid component of lipid nanoparticles) metabolism was studied *in vitro* and in rats, but the rat study report is incomplete, and more information is requested from sponsor. The pivotal repeat dose toxicity study with elasomeran was conducted according to Good Laboratory Practices (GLP).

Nonclinical studies included immunogenicity of elasomeran and Omicron-matched vaccines (imelasomeran, or the bivalent vaccine combination) after primary immunisation (two doses) in mice, and immunogenicity and protection of booster doses with elasomeran, imelasomeran, or elasomeran and imelasomeran after primary immunisation with elasomeran in mice and non-human primates (NHPs). The mouse and NHP studies indicated that the bivalent combination and imelasomeran as primary series vaccination induces neutralising antibodies (NAbs) against Omicron subvariants (BA.1 and BA.2), but induces low NAb levels against the ancestral, Beta and Delta variants. However, boosting with the bivalent vaccine combination (after primary vaccination with elasomeran) demonstrated greater cross-variant neutralisation and cross-reactive B-cells in the draining lymph nodes against the ancestral (with D614G mutation) and Omicron BA.1 and BA.2 (sub)variants.

Protection by an imelasomeran booster dose against the Omicron BA.1 subvariant was demonstrated in mice and NHPs (no protection data for the bivalent vaccine). A booster dose of imelasomeran after primary immunisation with elasomeran reduced viral loads in upper and lower respiratory tracts, pro-inflammatory cytokines and lung pathology. There are no protection data for the bivalent vaccine. There are no nonclinical data on immune responses to Omicron variants of most concern (subvariants BA.4 and BA.5) or long-term protection against these variants.

The SM-102 (a component of lipid nanoparticles) was metabolised in rats by ester hydrolysis and β-oxidation and the metabolites were excreted via both the renal and hepatic routes, with the M3 (hydrolysis and β-oxidation) metabolite as the predominant metabolite in bile and the M1 (hydrolysis and N-dealkylation) metabolite and M3

metabolite as the main metabolites in urine. Unchanged SM-102 was excreted in bile, but not urine. Similar but fewer metabolites were formed *in vitro* in rat, monkey and human hepatocytes. The rat study report is incomplete and more information is requested from the sponsor.

In the repeat dose toxicity study in rats, treatment related findings were common to those observed with other surrogate mRNA-lipid nanoparticles vaccines developed using the same platform and notably can largely be attributed to the lipid nanoparticles of the vaccine and immune response. Treatment related findings mainly included: injection site inflammation (oedema, erythema); enlargement and some perturbations of haematology, coagulation and clinical chemistry parameters. The effects were either partially or fully reversible after two weeks of recovery.

The primary pharmacology studies indicated that the Spikevax Bivalent Original/Omicron as a booster induces greater cross-variant immunity against the ancestral (with D614G mutation) and Omicron (BA.1, and BA.2) subvariants, and a booster dose of the Omicron-targettingmRNA vaccine (imelasomeran) conferred protection against infection by the ancestral (with D614G) and Omicron BA.1 subvariant. There are no nonclinical data on immune responses to Omicron variants of most concern (Omicron subvariants BA.4 and BA.5) or long-term protection against these subvariants. There are no protection data from the Spikevax Bivalent Original/Omicron vaccine for the Omicron BA.4 and BA.5 subvariants.

A repeat dose toxicity study with the prototype elasomeran vaccine (Spikevax (monovalent)) in rats raised no safety issues. Findings were consistent with immune stimulation and inflammation responses.

There are no nonclinical objections to the provisional registration of the vaccine provided adequate immunogenicity is demonstrated in human studies.

Clinical

Pharmacology

The sponsor is using its mRNA-based platform, used to develop mRNA-1273 (elasomeran) and produce and modified, bivalent, lipid nanoparticles encapsulated, mRNA-based COVID-19 vaccines against SARS-CoV-2. In response to emerging SARS-CoV-2 variants and in accordance with the recommendations and guidance by global regulatory agencies, the sponsor developed modified, bivalent mRNA booster vaccine candidates (50 µg dose level) that retain the ancestral SARS-CoV-2 spike sequence (25 µg elasomeran) and include the spike sequence of an antigenically divergent variant (25 µg imelasomeran). After the emergence of the Omicron variant, the sponsor evaluated (a second booster dose of) Omicron BA.1 targeted bivalent vaccine at 50 µg which contains 25 µg of elasomeran and 25 µg of the Omicron spike mRNA sequence, imelasomeran. The product contains equal amount of two mRNA-1273 sequences: CX-024414 and CX-031302. CX-024414 encodes for the spike protein for SARS-CoV-2 ancestral strain, while CX-031302 encodes for the spike protein for SARS-CoV-2 Omicron (B.1.1.529) variant. This was evaluated as a second booster dose of elasomeran plus imelasomeran at 50 µg compared to a second booster dose of elasomeran at 50 µg.

After delivery, both vaccine mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers are formed (mixed protomers from the ancestral strain spike and the variant spike).

The inclusion of both the original and the variant spikes in the vaccine are intended to broaden immunity as significantly as possible. To that end, inclusion of the ancestral strain spike allows reactivation and boosting of memory immune cell populations, increasing immunity that was previously present. In addition, inclusion of the variant spike, which has novel functional epitopes present primarily on the receptor binding domain and the *N*-terminal domain, allows new naïve immune populations to be engaged and new memory responses to be elicited. This likely broadens immunity not only to the spike antigens delivered but likely also against a broader diversity of spike proteins.

Immunogenicity/efficacy

The following studies were included in the dossier to present information on immunogenicity:

- Study mRNA-1273-P205 is an ongoing open label Phase II/III study with multiple, sequentially enrolled cohorts to evaluate the immunogenicity and safety of variant-modified booster candidate vaccines.
- Study mRNA-1273-P205 Part G evaluated the safety, reactogenicity, and immunogenicity of 50 µg of mRNA 1273.214 (elasomeran plus imelasomeran) when administered as a second booster dose in adults who previously received 2 doses of 100 µg mRNA-1273 (elasomeran) as a primary series and a single booster dose of 50 µg mRNA-1273 (elasomeran).
- Study mRNA-1273-P205 Part F evaluated the safety, reactogenicity, and immunogenicity of 50 µg of mRNA 1273 (elasomeran) when administered as a second booster dose in adults who previously received 2 doses of 100 µg mRNA-1273 (elasomeran) as a primary series and a single booster dose of 50 µg mRNA-1273 (elasomeran).

The Part F (cohort 2) of Study mRNA-1273-P205 serves as the within-study, non-contemporaneous comparator group for Part G of Study mRNA-1273-P205 in the comparison between the two booster vaccines, the bivalent vaccine (elasomeran and imelasomeran) and the monovalent vaccine (elasomeran), when administered as second booster doses. The bivalent vaccine safety and immunogenicity data are summarised as the primary data in this submission.

The immunogenicity results of a related but different bivalent vaccine (a Beta-variant (as opposed to Omicron) containing bivalent booster vaccine (vaccine development code: mRNA-1273.211)) at 50 µg were presented in the clinical overview as supportive information. Study P205 Part A and Study P201 Part B are for an assessment of mRNA-1273.211 against mRNA-1273 (elasomeran).

Table 3: Overview of bioassays for the assessment of clinical endpoints

Assay Name	Methodology	Study Number(s)	Development Status (Performing Laboratory)[a]
SARS-CoV-2 Pseudotyped Virus Neutralization[b]	PsV neutralization	P205 (Part A), P201 (Part B), P205 (Part F and G), and P301 (Historical Control Primary Series)[c],	Validated (D614G, Beta, Omicron[a]) Fit-for-purpose (Delta[a]) (Duke University Medical Center)
MSD (VAC123)[d]	MSD multiplex	P205 (Part F and G)	Validated (PPD Vaccine Laboratories)

Abbreviations: MSD = Meso Scale Discovery; PsV = pseudotyped virus; PsVNA = pseudotyped virus neutralising antibodies; PPD = Pharmaceutical Product Development, Inc; SAR-CoV-2 = severe acute respiratory syndrome coronavirus that causes COVID-19.

a The Omicron assay has been validated and the validation report has been submitted to Center for Biological Evaluation and Research (US Food and Drug Administration). Given that the seroresponse rate (SRR) definition depends on the assay lower limits of quantification (LLOQ), and that the Delta assay is currently fit for purpose pending final validation, the SRR for Delta is not discussed in this report.

b These samples were run using PsVNA for ancestral SARS-CoV-2 as well as Beta, Delta and Omicron variants.

c Study P301 Part A PdVNA against Delta only available at Day 57.

d MSD VAC 123 assay simultaneously measures ancestral SARS-CoV-2 as well as Alpha, Beta, Gamma, Delta and Omicron variants.

The Omicron BA.4 and BA.5 sub-lineages were chosen for the development of a research grade pseudovirus neutralisation assay (undergoing validation process) using a spike pseudotyped virus designated Omicron BA.4/BA.5 given that the BA.4 and BA.5 sub-lineages have an identical spike sequence (Table 3). The assay was performed in a manner consistent with the BA.1 pseudovirus neutralisation assay. However, range, dilutional linearity, precision and limits of quantification have yet to be determined.

The major inclusion criteria were:

- Male or female of at least 18 years of age. Females had to be of nonchildbearing potential, allowing inclusion of those using of hormonal contraceptives such as oral contraceptive pills.
- Received a two dose primary series of Spikevax (elasomeran) followed by a 50 µg booster dose of Spikevax in at least three months prior to enrolment.

The major exclusion criteria were:

- Significant exposure to someone with SARS-CoV-2 infection or COVID-19 fourteen days prior to the screening visit.
- A known history of SARS-CoV-2 infection within three months prior to enrolment.
- Being acutely ill or febrile (temperature ≥ 38°C) less than 72 hours prior to or at the screening visit or Day 1.
- Currently having symptomatic acute or unstable chronic disease requiring medical or surgical care.
- Having a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus (HIV), or immune mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
- Receiving systemic immunosuppressants or immune-modifying drugs for > 14 days in total within six months prior to screening (for corticosteroids ≥ 10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.

- Having a documented history of myocarditis or pericarditis within two months prior to screening visit (Day 0).
- Having received or planned to receive any licensed vaccine ≤ 28 days prior to the injection (Day 1) or a licensed vaccine within 28 days before or after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.

Statistical Methods

Efficacy

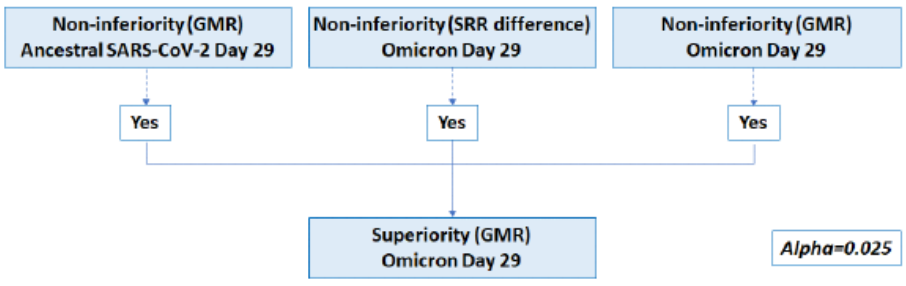
As for the comparison between Study P205 Part G and Study P205 Part F, pre-specified primary and key secondary immunogenicity objectives were to demonstrate the following 28 days after the bivalent vaccine combination at 50 µg second booster dose (Study P205 Part G) compared with monovalent vaccine (elasomeran) at 50 µg second booster dose (Study P205 Part F):

- Non-inferior neutralising antibody responses against the ancestral SARS-CoV-2 with D614G mutation.
- Superior neutralising antibody responses against the Omicron variant.

For the pre-specified primary objectives there were four corresponding clinical endpoints:

- non-inferiority of the antibody response of the second booster dose of 50 µg bivalent vaccine (elasomeran + imelasomeran) compared with the second booster dose of 50 µg mRNA-1273 based on the geometric mean ratio (GMR) against the Omicron variant;
- non-inferiority of the antibody response of the second dose of 50 µg bivalent vaccine (elasomeran + imelasomeran) compared to the second booster dose of 50 µg monovalent vaccine (elasomeran) against the Omicron variant based on the difference in seroresponse rates (SRR);
- non-inferiority of the antibody response of the second booster dose of 50µg bivalent vaccine (elasomeran + imelasomeran) compared to the second booster dose of 50 µg monovalent vaccine (elasomeran) based on GMR against the ancestral SARS-CoV-2 strain; and
- superiority of the antibody response of the second booster dose of 50 µg bivalent vaccine (elasomeran + imelasomeran) compared to the second booster dose of 50 µg monovalent vaccine (elasomeran) based on the GMR against the Omicron variant.

Figure 1: Study P205 Part G Statistical hypotheses testing strategy



Abbreviation: GMR = geometric mean ratio; SRR= seroresponse rate.

There was also a pre-specified key secondary, non-inferiority objective of the antibody response of the second booster dose of 50 µg bivalent vaccine (elasomeran + imelasomeran) compared to the second booster dose of 50 µg of elasomeran against the ancestral SARS-CoV-2 with D614G mutation based on the difference in SRR, to be tested if all primary endpoints were met.

The immunogenicity endpoints are tested 28 days after the booster dose (Day 29) and 90 days after the booster dose (Day 91) with an alpha of 0.025 (two sided) respectively at each one of the two time points (Figure 1). Non-inferiority is considered met when the lower bound of the 97.5% confidence interval (CI) of GMR is ≥ 0.67 and of SRR difference is > -10%. Superiority is considered met when the lower bound of the 97.5% CI of GMR is > 1 and for the difference in SRR > 0.

If non-inferiority is demonstrated for both the Omicron variant (based on GMR and SRR) and the ancestral SARS-CoV-2 strain with D614G mutation (based on GMR), the lower bound of 97.5% CI of GMR is compared to 1, and if greater than 1, then superiority against Omicron is demonstrated.

Superiority of the bivalent vaccine (elasomeran + imelasomeran) antibody response against the Omicron variant, compared to monovalent vaccine (elasomeran), is considered as demonstrated if superiority based on GMR is met at Days 29 or 91. The alpha was split with 2.5% assigned to Day 29 and 2.5% assigned to Day 91. The Day 29 interim analysis results are presented herein. The methods of analysis are considered acceptable.

An analysis of covariance (ANCOVA) model was performed to assess the difference in antibody responses between bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) groups, with antibody titres post-booster as a dependent variable, and a group variable (bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran)) as the fixed effect, adjusting for age groups (< 65, ≥ 65 years) and pre-booster antibody titres.

The geometric mean titres (GMT) (95% CI) estimated by the geometric least squares mean (GLSM) from the model for each group and the GMR (bivalent vaccine (elasomeran + imelasomeran) compared with monovalent vaccine (elasomeran)) estimated by the ratio of GLSM from the model (97.5% CIs) are provided. The 97.5% CI for GMR was used to assess the between group difference in antibody responses. The number and percentage of participants who achieved seroresponse is summarised with 95% CI calculated using the Clopper-Pearson method. The differences of SRR between bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) are calculated with 97.5% CI based on stratified Miettinen-Nurminen method.

Seroresponse is defined as a change from below the assay lower limits of quantification (LLOQ) to equal or above 4 times the LLOQ for those whose pre-Dose 1 baseline is less than LLOQ, or at least a 4-fold rise if pre-Dose 1 baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibody titre information, seroresponse is defined as equal to or greater than 4 times the LLOQ for those with negative SARS-CoV-2 status at pre-Dose 1 of the primary series (for these participants antibody titres are deemed less than LLOQ at pre-Dose 1 of the primary series).

A supportive analysis was also performed using the per-protocol set for immunogenicity (PPSI) (the population of participants with and without evidence of prior SARS-CoV-2 infection at pre-booster), also referred to as the supportive analysis set, using an ANCOVA model to assess the antibody responses, with antibody titres at Day 29 post-booster as the dependent variable and vaccine group variable as the fixed effect, adjusting for age groups (< 65, ≥ 65 years), pre-booster SARS-CoV-2 infection status, and pre-booster titres. The SRR difference between bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) was calculated with 97.5% CI based on stratified Miettinen-Nurminen method adjusted for the pre-booster SARS-CoV-2 infection status and age group.

A pre-planned subgroup analysis for the SARS-CoV-2 infection positive pre-booster participants was performed using an ANCOVA model to assess for neutralising antibody differences between the bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) groups based on GMRs with 95% CIs for the ancestral SARS-CoV-2

strain with D614G mutation and the Omicron variant. Lastly, a sensitivity analysis was performed excluding the participants with evidence of SARS-CoV-2-infection after the booster dose. All analyses were conducted using statistical analysis system version 9.4 or higher.

Safety

Safety and reactogenicity was assessed by clinical review of all relevant parameters including solicited adverse reactions (local and systemic), unsolicited treatment-emergent adverse events (AEs), treatment-related adverse events, severe adverse events, and serious adverse events (SAEs), medically-attended adverse events (MAAEs), adverse events of special interest (AESI), and adverse events leading to withdrawal from study participation.

Safety analyses was based on the safety set, except that the solicited safety set was used for analyses of solicited adverse reaction. The numbers and percentages of participants with any solicited local and systemic adverse reactions occurring within seven days post-booster were provided. Unsolicited AEs, SAEs, severe AEs, MAAEs, AESIs and AEs leading to study discontinuation were also summarised.

Clinical

Table 4: Study P205 Parts G and F; Participant disposition for second booster dose (full analysis set)

	P205 Part G	P205 Part F
	mRNA-1273.214 50 µg (N=437) n (%)	mRNA-1273 50 µg (N=377) n (%)
Number of participants		
Received injection	437	377
Completed study[a]	0	0
Discontinued from study	2 (0.5)	0
Reason for study discontinuation		
Withdrawal of consent by participant	2 (0.5)	0
Other	2 (0.5)	0

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

Percentages are based on the number of participants in the full analysis set

a Study completion is defined as a participant who completed 12 months of follow up after the injection.

In the Study P205 Part G booster dose group, 437 participants received the booster dose. Of these, 197 participants (45.1%) enrolled from Study mRNA-1273-P301 where they had received the primary series and the first booster dose of monovalent vaccine (elasomeran) and 240 of the 437 participants (54.9%) had received the primary series and the first booster dose under a FDA Emergency Use Authorization (EUA) in the USA. The median follow-up time from bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose injection was 43 days (range 22 to 51 days). Of the 437 participants who received the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose, two participants discontinued from the study (withdrawal of consent by participant) (see Table 4, above).

In the Study P205 Part F-cohort 2 booster dose group, 377 participants received the booster dose. Of these, 264 participants (70%) enrolled from Study mRNA-1273-P301 where they had received the primary series and the first booster dose of monovalent vaccine (elasomeran) and 113 of the 377 participants (30%) had received the primary series and the first booster dose under the EUA in the United States. The median follow up

time from monovalent vaccine (elasomeran) at 50 µg booster injection was 57 days (range 51 to 66 days). Of the 377 participants who received the monovalent vaccine (elasomeran) at 50 µg booster dose, all participants were still on study by the data cut-off date of 27 April 2022 (see Table 4, above).

Table 5: Study P205 Parts G and F; Number of participants in each analysis set for second booster dose (all enrolled set)

	P205 Part G mRNA-1273.214 50 µg (N=440) n (%)	P205 Part F mRNA-1273 50 µg (N=379) n (%)
All enrolled	440	379
Full analysis Set[a]	437 (99.3)	377 (99.5)
Per-protocol efficacy set	339 (77.0)	266 (70.2)
Per-protocol immunogenicity set[a]	428 (97.3)	367 (96.8)
Per-protocol immunogenicity SARS-CoV-2 negative set[a]	334 (75.9)	260 (68.6)
Safety Set	437	377
Solicited safety set[b]	437 (100)	351 (93.1)

Abbreviation: SARS-CoV-2 = severe acurte respiratory syndrome coronavirus-2

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

a Numbers are based on planned treatment group and percentages are based on the number of participants enrolled.

b Numbers are based on planned treatment group and percentages are based on the number of safety participants.

Table 6: Study P205 Parts G and F; Participant demographics and baseline characteristics for second booster dose (safety set)

	P205 Part G	P205 Part F
	mRNA-1273.214 50 µg (N=437)	mRNA-1273 50 µg (N=377)
Age (years), n	437	377
Mean (SD)	57.3 (14.60)	57.5 (15.31)
Median (mix, max)	60.0 (20, 88)	60.0 (20, 96)
Age subgroups		
≥ 18 and < 65 years	263 (60.2)	227 (60.2)
Mean (SD)	48.2 (11.26)	47.9 (11.49)
Median (mix, max)	49.0 (20, 64)	48.0 (20, 64)
≥ 65 years	174 (39.8)	150 (39.8)
Mean (SD)	71.1 (5.01)	72.1 (6.03)
Median (mix, max)	70.0 (65, 88)	70.0 (65, 96)
Gender, n (%)		
Male	179 (41.0)	186 (49.3)
Female	258 (59.0)	191 (50.7)
Race, n (%)		
White	381 (87.2)	322 (85.4)
Black or African American	31 (7.1)	29 (7.7)
Asian	14 (3.2)	16 (4.2)
American Indian or Alaska Native	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)
Multiracial	7 (1.6)	2 (0.5)
Other	3 (0.7)	2 (0.5)
Not reported	1 (0.2)	3 (0.8)
Unknown	0	1 (0.3)
Ethnicity, n (%)		
Hispanic or Latino	46 (10.5)	37 (9.8)
Not Hispanic or Latino	390 (89.2)	340 (90.2)
Not reported	1 (0.2)	0
Body mass index (kg/m^2), n	437	377
Mean (SD)	30.23 (7.074)	30.84 (7.525)
Median (mix, max)	28.97 (17.8, 71.8)	29.41 (18.4, 61.8)
Pre-booster RT-PCR results, n (%)		
Negative	434 (99.3)	367 (97.3)
Positive	2 (0.5)	2 (0.5)
Missing	1 (0.2)	8 (2.1)
Pre-booster Elecsys Anti-SARS-CoV-2 Results, n (%)		
Negative	341 (78.0)	276 (73.2)
Positive	95 (21.7)	100 (26.5)
Missing	1 (0.2)	1 (0.3)
Pre-booster SARS-CoV-2 Status, n (%) [a]		
Negative	340 (77.8)	267 (70.8)
Positive	96 (22.0)	101 (26.8)
Missing	1 (0.2)	9 (2.4)
Time between dose 2 of primary series to 1st booster dose (days), n	435	374
Mean (SD)	263.3 (61.33)	258.0 (56.89)
Median (mix, max)	245.0 (143, 457)	242.0 (170, 438)
Time between the 1st booster dose to 2nd booster dose (days), n	435	374
Mean (SD)	136.6 (34.92)	133.6 (21.47)
Median (mix, max)	136.0 (88, 408)	134.0 (90, 310)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain reactions; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

Percentages are based on the number of participants in the safety set.

a Per-booster/baseline SARS-CoV-2 status: positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys results at Day 1.

Overall, demographic and baseline characteristics were similar between the bivalent vaccine (elasomeran + imelasomeran) at 50 µg and monovalent vaccine (elasomeran) at 50 µg groups (see Table 6, above).

Immunogenicity

Table 7: Study P205 Parts G and F; Ancestral SARS-CoV-2 (with D614G) and Omicron neutralising antibody titres (ID_{50}) at 50 µg administered as second booster doses - per-protocol immunogenicity (SARS-CoV-2 negative set (primary analysis))

	Omicron Variant		Ancestral SARS-CoV-2	
Antibody: PsVNA nAb ID_{50} titers	P205 Part G mRNA-1273.214 50 µg (N=334)	P205 Part F mRNA-1273 50 µg (N=260)	P205 Part G mRNA-1273.214 50 µg (N=334)	P205 Part F mRNA-1273 50 µg (N=260)
Pre-booster, n	334	260	334	260
Observed GMT (95% CI)[a]	298.127 (258.753, 343.492)	332.023 (282.047, 390.854)	1266.743 (1120.190, 1432.469)	1520.998 (1352.766, 1710.151)
Day 29, n	334	260	334	260
Observed GMT (95% CI)[a]	2372.424 (2070.634, 2718.200)	1473.462 (1270.849, 1708.379)	5977.257 (5321.897, 6713.320)	5649.331 (5056.848, 6311.231))
Observed GMFR (95% CI)[a]	7.958 (7.181, 8.819)	4.438 (3.971, 4.960)	4.719 (4.358, 5.109)	3.714 (3.420, 4.034)
GLSM [Estimated GMT] (95% CI)[b]	2479.890 (2264.472, 2715.801)	1421.243 (1282.975, 1574.412)	6422.323 (5990.117, 6885.714)	5286.626 (4887.065, 5718.855)
GMR (97.5% CI)[b]	**1.745 (1.493, 2.040)**		**1.215 (1.078, 1.370)**	
Seroreponse, N1	333	258	334	260
Seroresponse rate, n (%)[c]	333 (100)	256 (99.2)	334 (100)	260 (100)
95% CI[d]	(98.9, 100.0)	(97.2, 99.9)	(98.9, 100.0)	(98.6, 100.0)
Difference in seroresponse rates (97.5%)[e]	**1.5 (-1.1, 4.0)**		**0**	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome 2.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

n = number of participants with non-missing data at the corresponding timepoint.

N1 = number of participants with non-missing data at pre-vaccination baseline and the corresponding timepoint.

a 95% CI is calculated based on the t-distribution of the log transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

b Based on ANCOVA modelling; the model includes adjustment for treatment group, pre-booster antibody titres, and age group.

c Seroresponse at participant level is defined as a change from below the LLOQ to equal or above 4 times LLOQ if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibodies titre information, seroresponse is defined as ≥ 4 times LLOQ for participants with negative SARS-CoV-2 status at their pre-Dose 1 of the primary series, and these titres are imputed as < LLOQ at pre-Dose 1 of primary series. For participants without SARS-CoV-2 status information at pre-Dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

d 95% CI is calculated using the Clopper-Pearson method.

e 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the

middles point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate of the CI cannot be calculated when the seroresponse rate in both groups are 100% absolute difference is reported.

The primary immunogenicity objective of Study P205 Part G was to compare the immunogenicity of bivalent vaccine (elasomeran + imelasomeran) 50 µg when administered as a second booster dose to the immunogenicity of monovalent vaccine (elasomeran) 50 µg as a second booster in Study P205 Part F2. In both parts, the second booster was given to adults who previously received three doses of monovalent vaccine (elasomeran) (two dose primary monovalent vaccine (elasomeran) 100 µg vaccine series and a booster dose of 50 µg elasomeran).

In the primary analysis set (per-protocol immunogenicity, SARS-CoV-2 negative set (PPSI-Neg set), the observed GMT (95% CI) for neutralising antibody against Omicron at pre-booster in Study P205 Part G were 298.1 (258.8, 343.5) and increased to 2372.4 (2070.6, 2718.2) at 28 days after the booster dose with bivalent vaccine (elasomeran + imelasomeran); the geometric mean fold rise (GMFR) (95% CI) for the GMTs at 28 days after the booster compared to pre-booster was 8 (7.2, 8.8). In comparison, the GMTs (95% CIs) at pre-booster in Study P205 Part F were 332 (282, 390.9) and increased to 1473.5 (1270.8, 1708.4) at 28 days after the booster dose with monovalent vaccine (elasomeran); the GMFR (95% CI) was 4.4 (4, 5).

The observed GMT (95% CI) against ancestral pre-booster were 1266.7 (1120.2, 1432.5) and increased to 5977.3 (5321.9, 6713.3) at 28 days after the booster dose for bivalent vaccine (elasomeran + imelasomeran) and GMFR (95% CI) for the GMTs at 28 days after the booster compared to pre-booster was 4.7 (4.4, 5.1). In comparison, the GMT (95% CIs) at pre-booster was 1521 (1352.8, 1710.2) compared to 5649.3 (5056.8, 6311.2) in the monovalent vaccine (elasomeran) group at 28 days after the booster dose and GMFR (95% CI) was 3.7 (3.4, 4).

The estimated/neutralising antibody GMTs (95% CI) against the Omicron variant were 2479.9 (2264.5, 2715.8) and 1421.2 (1283.0, 1574.4) 28 days following the bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) booster doses, respectively, and the GMR (97.5% CI) was 1.75 (1.49, 2.04) met the pre-specified superiority criterion (lower bound of CI > 1). Therefore, all primary immunogenicity endpoints were met based on the pre-specified testing sequence.

The Omicron variant SRRs (95% CI) were 100% (98.9, 100) and 99.2% (97.2, 99.9), 28 days after the bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) booster doses, respectively, and the SRR difference (97.5% CI) was 1.5% (-1.1, 4) meeting the non-inferiority criterion (lower bound of CI > -10%).

In the primary analysis set (PPSI-Neg), estimated neutralising antibody GMTs (95% CI) against the ancestral SARS-CoV-2 strain (with D614G mutation) adjusted for pre-booster titre and age group were 6422.3 (5990.1, 6885.7) and 5286.6 (4887.1, 5718.9) 28 days after the bivalent vaccine (elasomeran + imelasomeran), and monovalent vaccine (elasomeran) booster doses, respectively, and the GMR (97.5% CI) was 1.22 (1.08, 1.37), meeting the pre-specified criterion for non-inferiority (lower bound of CI ≥ 0.67).

In the over 65 years subgroup of the per-protocol immunogenicity, SARS-CoV-2 negative set, GMT ratios against Omicron BA.1 sub-variant and ancestral virus were in line with the primary analysis set.

The SRR (95% CI) against the ancestral SARS-CoV-2 strain (with D614G mutation) was 100% (98.9, 100 and 98.6, 100) 28 days after the bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) booster doses, respectively, with an SRR difference of zero. Therefore, the key secondary immunogenicity objective was also met.

A sensitivity analysis which excluded participants who had SARS-CoV-2 infection after the booster dose and up to Day 29 was also performed and the results were consistent with the primary analysis.

A supportive immunogenicity analysis was also performed taking into account all participants regardless of evidence of prior SARS-CoV-2 infection (per-protocol set for immunogenicity regardless of SARS-CoV-2 infection status at pre-booster baseline) and results were consistent with the primary immunogenicity analysis (see Table 8, below).

Table 8: Study P205 Parts G and F; Ancestral SARS-CoV-2 and Omicron neutralising antibody titres (ID_{50}) at 50 µg vaccine administered as second booster doses per-protocol immunogenicity set (participants with and without prior SARS-CoV-2 infection - supportive analysis)

	Omicron Variant		Ancestral SARS-CoV-2	
Antibody: PsVNA nAb ID_{50} titers	P205 Part G mRNA-1273.214 50 µg (N=428)	P205 Part F mRNA-1273 50 µg (N=367)	P205 Part G mRNA-1273.214 50 µg (N=428)	P205 Part F mRNA-1273 50 µg (N=367)
Pre-booster, n	428	367	428	367
Observed GMT (95% CI)[a]	432.051	511.984	1603.353	1944.781
	(372.466, 501.168)	(433.386, 604.836)	(1420.264, 1810.045)	(1725.353, 2192.116)
Day 29, n	428	367	428	367
Observed GMT (95% CI)[a]	3070.379	1932.785	6619.010	6047.489
	(2685.375, 3510.581)	(1681.186, 2222.037)	(5941.728, 7373.494)	(5465.873, 6690.994)
Observed GMFR (95% CI)[a]	7.107	3.775	4.128	3.110
	(6.484, 7.789)	(3.422, 4.165)	(3.840, 4.438)	(2.877, 3.361)
GLSM [Estimated GMT] (95% CI)[a]	3232.516 (2951.832, 3539.890)	1815.135 (1650.045, 1996.743)	6555.689 (6122.337, 7019.715)	5301.367 (4931.769, 5698.663)
GMR (97.5% CI)[a]	**1.781 (1.557, 2.037)**		**1.237 (1.117, 1.369)**	
Seroreponse, N1	380	342	383	347
Seroresponse rate, n (%)[c]	380 (100)	340 (99.4)	383 (100)	347 (100)
95% CI[d]	(99.0, 100.0)	(97.9, 99.9)	(99.0, 100.0)	(98.9, 100.0)
Difference in seroresponse rates (97.5%)[e]	**1.2 (-1.3, 3.7)**		**0 (- , -)**	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome 2.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

n = number of participants with non-missing data at the corresponding timepoint.

N1 = number of participants with non-missing data at pre-vaccination baseline and the corresponding timepoint.

a 95% CI is calculated based on the t-distribution of the log transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

b Based on ANCOVA modelling; the model includes adjustment for treatment group, baseline SARS-CoV-2 infection status, pre-booster antibody titres, and age group.

c Seroresponse at participant level is defined as a change from below the LLOQ to equal or above 4 times LLOQ if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibodies titre information, seroresponse is

defined as ≥ 4 times LLOQ for participants with negative SARS-CoV-2 status at their pre-Dose 1 of the primary series, and these titres are imputed as < LLOQ at pre-Dose 1 of primary series. For participants without SARS-CoV-2 status information at pre-Dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

d 95% CI is calculated using the Clopper-Pearson method.

e 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middles point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate of the CI cannot be calculated when the seroresponse rate in both groups are 100% absolute difference is reported.

In addition, a pre-planned subgroup immunogenicity analysis was also performed to assess the consistency of the immunogenicity results in participants with evidence of prior SARS-CoV-2 infection at pre-booster. Based on this subgroup analysis, results in participants with SARS-CoV-2 infection prior to the booster vaccination are consistent with the immunogenicity results of the primary analysis in that bivalent vaccine (elasomeran + imelasomeran) elicited higher neutralising antibody responses compared to monovalent vaccine (elasomeran). The GMR and SRR difference results are summarised in Table 9.

Table 9: Study P205 Parts G and F; Ancestral SARS-CoV-2 and Omicron neutralising antibody titres (ID_{50}) at 50 µg vaccine administered as second booster doses (per-protocol immunogenicity, SARS-CoV-2 positive set subgroup analysis)

	Omicron Variant		Ancestral SARS-CoV-2	
Antibody: PsVNA nAb ID_{50} titers	P205 Part G mRNA-1273.214 50 µg (N=94)	P205 Part F mRNA-1273 50 µg (N=98)	P205 Part G mRNA-1273.214 50 µg (N=94)	P205 Part F mRNA-1273 50 µg (N=98)
Pre-booster, n	94	98	94	98
Observed GMT (95% CI)[a]	1614.640 (1149.671, 2267.658)	1558.360 (1088.941, 2230.136)	3703.953 (2793.198, 4911.670)	3637.972 (2742.046, 4826.629)
Day 29, n	94	98	94	98
Observed GMT (95% CI)[a]	7676.226 (5618.245, 10488.050)	3885.596 (2877.774, 5246.367)	9509.727 (7345.948, 12310.856)	7003.503 (5592.574, 8770.390)
Observed GMFR (95% CI)[a]	4.754 (3.954, 5.716)	2.493 (2.058, 3.021)	2.567 (2.245, 2.936)	1.925 (1.649, 2.247)
GLSM [Estimated GMT] (95% CI)[b]	7669.159 (6470.661, 9089.642)	4041.480 (3375.056, 4839.493)	9891.516 (8732.181, 11204.771)	7776.531 (6813.034, 8876.285)
GMR (97.5% CI)[b]	**1.898 (1.499, 2.403)**		**1.272 (1.070, 1.512)**	
Seroreponse, N1	47	76	49	79
Seroresponse rate, n (%)[c]	47 (100)	76 (100)	49 (100)	79 (100)
95% CI[d]	(92.5, 100.0)	(95.3, 100.0)	(92.7, 100.0)	(95.4, 100.0)
Difference in seroresponse rates (97.5%)[e]	**0 (- , -)**		**0 (- , -)**	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold rise; GMR = geometric mean ratio; GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LLOQ = lower limit of quantification; nAb = neutralising antibodies; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome 2.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

n = number of participants with non-missing data at the corresponding timepoint.

N1 = number of participants with non-missing data at pre-vaccination baseline and the corresponding timepoint.

a 95% CI is calculated based on the t-distribution of the log transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

b Based on ANCOVA modelling; the model includes adjustment for treatment group, pre-booster antibody titres, and age group.

c Seroresponse at participant level is defined as a change from below the LLOQ to equal or above 4 times LLOQ if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibodies titre information, seroresponse is defined as ≥ 4 times LLOQ for participants with negative SARS-CoV-2 status at their pre-Dose 1 of the primary series, and these titres are imputed as < LLOQ at pre-Dose 1 of primary series. For participants without SARS-CoV-2 status information at pre-Dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

d 95% CI is calculated using the Clopper-Pearson method.

e 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middles point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate of the CI cannot be calculated when the seroresponse rate in both groups are 100% absolute difference is reported.

Seroresponse was defined relative to the pre-Dose 1 (primary series) baseline neutralising antibody titres. An alternative definition of seroresponse is 4-fold increase from pre-second booster baseline neutralising antibody titres these results were consistent with the GMT results:

Table 10: Study P205 Parts G and F; Summary of 4-fold increases from pre-second booster baseline to Day 29 by baseline SARS-CoV-2 status

PsVNA ID50	Omicron		Ancestral	
	Per protocol immunogenicity SARS-CoV-2 negative set			
	Part G	Part F2	Part G	Part F2)
	mRNA-1273.214 N=334	mRNA-1273 N=260	mRNA-1273.214 N=334	mRNA-1273 N=260
≥ 4-fold * increase from baseline to Day 29 n (%)	250 (74.9)	138 (53.1)	180 (53.9)	111 (42.7)
95% CI	(69.8, 79.4)	(46.8, 59.3)	(48.4, 59.3)	(36.6, 49.0)
	Per protocol immunogenicity SARS-CoV-2 positive set			
	Part G mRNA-1273.214 N=94	Part F2 mRNA-1273 N=98	Part G mRNA-1273.214 N=94	Part F2 mRNA-1273 N=98
≥ 4-fold * increase from baseline to Day 29 n (%)	51 (54.3)	29 (29.6)	23 (24.5)	17 (17.3)
95% CI	(43.7, 64.6)	(20.8, 39.7)	(16.2, 34.4)	(10.4, 26.3)

* ≥ 4-fold increase from Baseline at participant level is defined as a ≥ 4 times LLOQ for participants with baseline undetectable antibody level, or a 4 times or higher antibody level ratio in participants with pre-existing antibody levels.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

Exploratory immunogenicity analyses

An exploratory immunogenicity analysis to assess neutralisation against the Beta and Delta variants was performed based on the first 50 enrolled participants in each group (bivalent vaccine (elasomeran + imelasomeran) at 50 µg in Study P205 Part G and

monovalent vaccine (elasomeran) at 50 µg in Study P205 Part F). While the pre-booster titres for the Beta and Delta variants were lower for the bivalent vaccine (elasomeran + imelasomeran) compared to monovalent vaccine (elasomeran) in the group of participants without evidence of prior SARS-CoV-2 infection, the post-booster titres between the two vaccines are comparable (overlapping confidence intervals), and the GMFR was numerically higher in the bivalent vaccine (elasomeran + imelasomeran) group versus the monovalent vaccine (elasomeran) arm. The whole cohorts were able to be tested for multiple variants in the MSD assay because the multiplex nature of this assay allowed a higher throughput and more timely data availability.

These are exploratory analysis results (Beta and Delta variants) are to be interpreted with caution due to the small group of participants and differences in pre-booster titre in Beta and Delta variants between two treatment groups. This small dataset was intended to provide directional information.

Neutralising antibody titres for Omicron subvariants BA.4/BA.5

Table 11: Study P205 Parts G and F; Summary of neutralising antibody geometric mean titres for Omicron BA.4, BA.5 subvariant

	Omicron BA.4, BA.5 Variant					
	PPSI		PPSI - Neg		PPSI - Pos	
Antibody: PsVNA nAb ID_{50} titers	P205 Part G mRNA-1273.214 50 µg (N=428)	P205 Part F mRNA-1273 50 µg (N=367)	P205 Part G mRNA-1273.214 50 µg (N=334)	P205 Part F mRNA-1273 50 µg (N=260)	P205 Part G mRNA-1273.214 50 µg (N=94)	P205 Part F mRNA-1273 50 µg (N=98)
Pre-booster, n[a]	428	367	334	260	94	98
Observed GMT (95% CI)[a,b]	172.716 (147.449, 202.313)	209.307 (179.475, 244.097)	115.590 (98.507, 135.635)	139.683 (119.510, 163.260)	719.542 (531.639, 973.857)	609.123 (448.078, 828.051)
Day 29, n[a]	427	367	333	260	94	98
Observed GMT (95% CI)[a,b]	940.567 (826.319, 1070.611)	645.365 (570.113, 730.551)	727.427 (632.846, 836.143)	492.126 (431.053, 561.853)	2337.435 (1825.510, 2992.918)	1270.823 (987.277, 1635.804)
Observed GMFR (95% CI)[a,b]	5.444 (5.005, 5.922)	3.083 (2.842, 3.345)	6.299 (5.739, 6.913)	3.523 (3.212, 3.864)	3.249 (2.780, 3.795)	2.086 (1.795, 2.425)
GLSM [Estimated GMT] (95% CI)[b]	985.376 (914.769, 1061.434)	588.359 (544.078, 636.244)	776.447 (719.488, 837.915)	458.282 (420.621, 499.316)	2246.251 (1975.519, 2554.085)	1406.894 (1227.880, 1612.006
GMR (95% CI)[b]	**1.675 (1.521, 1.844)**		**1.694 (1.511, 1.900)**		**1.597 (1.336, 1.909)**	

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold rise (post-baseline/baseline titres); GMT = geometric mean titre; ID_{50} = 50% inhibitory dilution; LOD = limit of detection; mRNA = messenger RNA nAb = neutralising antibody; PPSI = per-protocol set for immunogenicity; PPSI-Neg = per-protocol set for immunogenicity-SARS-CoV-2 negative at Baseline; PPSI-Pos = per-protocol set for immunogenicity-SARS-CoV-2 positive at Baseline; PsVNA = pseudotyped virus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome 2.

Note: antibody values reported as below the lower limit of detection are replaced by 0.5 x LOD.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

N1 = number of participants with non-missing data at pre-vaccination baseline and the corresponding timepoint.

a Number of subjects with non-missing data at the timepoint (baseline or post-baseline).

b 95% CI is calculated based on the t-distribution of the log transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

This data was presented as an addendum to provide updated information on the neutralising antibody response against the Omicron subvariants BA.4, BA.5 elicited by the Omicron BA.1-containing bivalent vaccine (elasomeran + imelasomeran) at 50 µg (Study P205 Part G) and by monovalent vaccine (elasomeran) at 50 µg (Study P205 Part F) and to perform a GMR-based comparison of the antibody response between the two groups. The results in the ≥ 65 years subgroup are consistent with the overall results.

Table 11 above presents the summary of the observed neutralising antibody GMTs and GMFRs against the Omicron BA.4, BA.5 subvariants for Study P205 Part G and Study P205 Part F participants. All participants previously received two doses of monovalent vaccine (elasomeran) at 100 µg as the primary series vaccine followed by the booster dose of monovalent vaccine (elasomeran) at 50 µg dose as the first booster vaccine) in the; PPSI, PPSI-Neg and PPSI-Pos.

Summary of binding antibody geometric mean titres

An immunogenicity analysis was performed based on binding antibody data after the bivalent vaccine (elasomeran + imelasomeran) at 50 µg and monovalent vaccine (elasomeran) at 50 µg second booster doses (Day 29) from the full cohorts to evaluate the binding antibody response against multiple variants, including variants that are not contained in the bivalent vaccine (elasomeran + imelasomeran) booster vaccine (Alpha, Beats, Delta and Gamma variants).

The Day 29 GMR for bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose versus the monovalent vaccine (elasomeran) at 50 µg as booster dose for each VOC were as following:

- Ancestral strain SARS-CoV-2: 1.138 (95% CI: 1.068, 1.213).
- Alpha variant: 1.165 (95% CI: 1.093, 1.241).
- Beta variant: 1.142 (95% CI: 1.071, 1.217).
- Delta variant: 1.095 (95% CI: 1.031, 1.163).
- Gamma variant: 1.16 (95% CI: 1.087, 1.238).
- Omicron variant: 1.232 (95% CI: 1.149, 1.321).

An analysis with binding antibody immunogenicity was also performed with participants with no evidence of prior SARS-CoV-2 infection at pre-booster and the results were consistent with the analysis performed with all participants regardless of prior SARS-CoV-2 infection.

Clinical efficacy

SARS-CoV-2 incidence rates after the bivalent (elasomeran + imelasomeran) and monovalent (elasomeran) booster vaccines

The laboratory confirmed symptomatic (primary and secondary cases) and asymptomatic SARS-CoV-2 infections post-booster was analysed as exploratory endpoints.

Infections were counted starting 14 days after the booster doses (bivalent vaccine (elasomeran + imelasomeran) at 50 µg; monovalent vaccine (elasomeran) at 50 µg) through the follow up time of this interim analysis. Study P205 was not designed to evaluate booster vaccine effectiveness.

In the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose group, with a median of 43 days of follow up duration, 11 participants (3.2%) had SARS-CoV-2 infection starting at least 14 days after the 50 µg booster dose. Among the 11 participants with SARS-CoV-2 infection, four participants (1.2%) met the primary case definition of COVID-19 and five participants (1.5%) met the secondary case definition of COVID-19 (see Table 12). The remaining six participants (1.8%) had an asymptomatic infection. The exposure adjusted incidence rate for SARS-CoV-2 infection was 5.4 per 1000 person-weeks, 1.9 per 1000 person-weeks for the primary case definition of COVID- 19, 2.4 per 1000 person-weeks for the secondary case definition of COVID-19, and 2.9 per 1000 person-weeks for asymptomatic SARS-CoV-2 infection. Among participants in the bivalent vaccine (elasomeran + imelasomeran) at 50 µg group who met the primary and/or secondary case definition of COVID-19, onset day ranged from Day 7 to Day 36. No

participants with COVID-19 had an emergency room visit or hospitalisation due to the COVID-19 event.

Table 12: Study P205 Part A; Summary of COVID-19 Infections (per-protocol efficacy set)

	P205 Part A mRNA-1273.211 50 µg (N=296) n (%)
Primary case definition of COVID-19 (per Study P301) starting 14 days after injection, n[a]	22 (7.4)
Secondary case definition of COVID-19 (CDC criteria) starting 14 days after injection, n[b]	26 (8.8)
SARS-CoV-2 infection starting 14 days after injection, n	37 (12.5)
Asymptomatic SARS-CoV-2 infection starting 14 days after injection, n	11 (3.7)

Abbreviations: CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

This interim analysis includes Part A participants immunogenicity data up to Day 181 visit. The data cut-off date for safety an dSARS-CoV-2 infection is 2 February 2022.

a Primary case definition per Study P301 is positive post-baseline RT-PCR results and at least 2 of the following systemic symptoms: fever (≥ 38°C/≥ 100.4°F) chills, muscle and/or body aches (not related to exercise), headache, sore throat, new loss of taste/smell; or at least 1 of the following respiratory signs/symptoms: cough, shortness of breath and/or difficulty breathing, or clinical or radiographical evidence of pneumonia.

b Secondary case definition of COVID-19 is positive post-baseline RT-PCR result and at least 1 of the following systemic or respiratory symptoms fever: (≥ 38°C/≥ 100.4°F) chills, cough, shortness of breath and/or difficulty breathing, fatigue, muscle and/or body aches (not related to exercise), headache, new loss of taste/smell, sore throat, congestion, runny nose, nausea, vomiting or diarrhoea.

In the 50 µg elasomeran booster dose group, with a median of 57 days of follow up duration, five participants (1.9%) had SARS-CoV-2 infection starting at least 14 days after the 50 µg booster dose. Among the five participants with SARS-CoV-2 infection, one participant (0.4%) met both the primary case definition of COVID-19 and the secondary case definition of COVID-19 36 days after the booster dose. The remaining four participants had an asymptomatic infection. The exposure adjusted incidence rate for SARS-CoV-2 infection was 2.3 per 1000 person-weeks, 0.5 per 1000 person-weeks for both primary and secondary case definition of COVID-19, and 1.8 per 1000 person-weeks for asymptomatic SARS-CoV-2. No participants with COVID-19 had an emergency room visit or hospitalisation due to the COVID-19 event.

Bivalent vaccine booster, mRNA-1273.211

The sponsor has also investigated the safety, reactogenicity and immunogenicity of mRNA-1273.211, another different bivalent vaccine containing equal amounts, 25 µg of the ancestral SARS-CoV-2 strain and Beta variant spike protein sequences (in contrast to the Omicron variant in this submission's vaccine).

Participants in Study P 205 Part A received mRNA-1273.211, a bivalent vaccine as a first booster dose to participants who had received two 100 µg doses of monovalent vaccine (elasomeran) as primary series. The analyses are based on an external comparison with data from Study P201 Part B. The same assay (Duke pseudovirus neutralisation assay) was used for Study P205 Part A and Study P201 Part B.

Neutralising antibody titres against ancestral SARS-CoV-2, and the Beta, Delta, and Omicron variants were overall numerically higher in participants who received the mRNA-1273.211 at 50 µg booster dose compared to participants who received the monovalent vaccine (elasomeran) at a 50 µg booster dose.

The data show that at the Day 181 timepoint, the neutralising immune response to the bivalent vaccine mRNA-1273.211 wanes but does not return to Baseline, for all tested variants. In addition, based on an external comparison, the apparent benefit of the related bivalent Beta variant targeting vaccine (mRNA-1273.211) over the monovalent vaccine (elasomeran) also persists for all tested variants.

These data suggest some persistence of the neutralising antibodies induced by a bivalent mRNA vaccine against ancestral and variant strains. These data also provide some supportive evidence to extrapolate the bivalent vaccine (elasomeran + imelasomeran) to the first booster setting.

Safety

These sections present reactogenicity and safety data for the bivalent vaccine (mRNA-1273.214, elasomeran + imelasomeran) 50 µg given as a second booster (Study P205 Part G; N = 437) alongside comparative data for 50 µg monovalent vaccine (elasomeran) given as a second booster (Study P205 Part F cohort 2; N = 377).

Specifically, median intervals before the booster doses (Study P205 Parts G and F) and median durations of follow-up after the booster doses are as follows:

- 50 µg bivalent vaccine (elasomeran + imelasomeran) (Study P205 Part G) second booster dose: Administered a median of 136 days after a first booster dose of monovalent vaccine (elasomeran) at 50 µg; median follow up duration was 43 days (range 22 to 51 days).
- 50 µg monovalent vaccine (elasomeran) (Study P205 Part F) second booster dose: Administered a median of 134 days after a first booster dose of monovalent vaccine (elasomeran) at 50 µg; median follow up duration was 57 days (range 51 to 66 days).

The safety assessments for Study P205 Part G and F were as follows:

- Solicited local and systemic adverse reactions during the seven day follow up period after vaccination.
- Unsolicited adverse events (AEs) during the 28 day follow up period after vaccination. This includes any AE reported by the participant that is not specified as a solicited adverse reaction in the protocol or is specified as a solicited adverse reaction but starts outside the protocol-defined period for reporting solicited adverse reaction s (that is seven days after vaccination).
- Serious adverse events (SAEs), medically attended adverse events (MAAEs), AEs leading to withdrawal and adverse events of special interest (AESI) throughout the studies until the data cut-off (27 April 2022).

Solicited adverse reactions

For reactogenicity assessments, participants recorded solicited local and systemic adverse reactions in the eDiary on the day of vaccination and during the seven days after vaccination (that is the day of injection and six subsequent days). Solicited local adverse reactions assessed were injection site pain, injection site erythema, injection site swelling/induration, and axillary swelling or tenderness ipsilateral to the side of the injection. Solicited systemic adverse reactions assessed were headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever (oral temperature).

Severity grading of solicited adverse reactions occurred automatically based on participant entry into the eDiary according to the grading scales modified from the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine

clinical trials.[48] Any solicited adverse reaction that was ongoing beyond Day 7 was to be reported in the eDiary until it resolved.

Solicited local adverse reactions

In the 50 µg booster dose bivalent vaccine (elasomeran + imelasomeran) group (Study P205 Part G), most participants had at least one solicited local adverse reaction (347 out of 437 (79.4%)). The most common solicited local adverse reaction after the mRNA-1273.214 at 50 µg booster dose was pain (338 out of 437 participants (77.3%)), followed by axillary swelling or tenderness (76 out of 437 participants (17.4%)). The majority of solicited local adverse reactions were Grade 1 (291 out of 437 participants (66.6%)). Fifteen participants (15 out of 437 (3.4%)) had a Grade 3 local adverse reaction and the most commonly reported was erythema (9 out of 437 participants (2.1%)). There were no Grade 4 local adverse reaction. Local adverse reactions were transient; the median duration was two days (range 1 to 10 days).

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F), most participants had at least one solicited local adverse reaction (279 out of 351 (79.5%)). Pain was the most common solicited local adverse reaction after the monovalent vaccine (elasomeran) at 50 µg booster dose (269 out of 351 participants (76.6%)), followed by axillary swelling or tenderness (54 out of 351 participants (15.4%)). The majority of solicited local adverse reactions were Grade 1 (239 out of 351 [68.1%]). Twelve participants (12 out of 359 (3.4%)) had a Grade 3 local adverse reaction and the most commonly reported was swelling (5 out of 351 participants (1.4%)). No Grade 4 solicited local adverse reactions were reported. Local adverse reactions were transient; the median duration was two days (range 1 to 22 days).

Solicited systemic reactions

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group (Study P205 Part G), most participants had at least one solicited systemic adverse reaction (307 out of 437 (70.3%)). The most common systemic adverse reaction after the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose was fatigue (240 out of 437 participants (54.9%)), followed by headache (192 out of 437 participants (43.9%)), myalgia (173 out of 437 participants (39.6%)), and arthralgia (136 out of 437 participants (31.1%)). The majority of solicited systemic adverse reactions were Grade 1 (167 out of 437 (38.2%)) followed by Grade 2 (116 out of 437 (26.5%)). Twenty four participants (24 out of 437 participants (5.5%)) had a Grade 3 systemic adverse reaction and the most commonly reported was fatigue (15 out of 437 participants (3.4%)). No Grade 4 solicited systemic adverse reactions were reported. The median duration of systemic adverse reactions was two days (range 1 to 21 days).

In the monovalent vaccine (elasomeran) 50 µg booster dose group (Study P 205 Part F), most participants had at least one solicited systemic adverse reaction (232 out of 351 [66.1%]). The most common systemic adverse reaction after the 50 µg monovalent vaccine (elasomeran) booster dose was fatigue (180 out of 350 participants (51.4%)), followed by headache (144 out of 350 participants (41.1%)), myalgia (135 out of 350 participants (38.6%)), and arthralgia (111 out of 350 participants (31.7%)). The majority of solicited systemic adverse reactions were Grade 1 (124 out of 351 (35.3%)) followed by Grade 2 (92 out of 351 (26.2%)). Sixteen participants (16 out of 351 (4.6%)) had a Grade 3 systemic adverse events and the most commonly reported was myalgia (13 out of 350 participants (3.7%)). No Grade 4 solicited systemic adverse reactions were reported. The median duration of systemic adverse reactions was two days (range 1 to 13 days).

[48] Guidance for industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials published in September 2007. Available at https://www.fda.gov

The most noticeable difference was seen for erythema (6.9% in Study P205 Part G versus 3.7% in Study P205 Part F). Aside from this, the frequency of systemic adverse events in Study P205 Part G and P205 Part F were similar.

Solicited adverse reactions by pre-booster SARS-CoV-2 Status

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part G) solicited safety set, 96 out of 437 participants (22%) had a positive pre-booster SARS-CoV-2 status and 340 out of 437 participants (77.8%) had a negative pre-booster SARS-CoV-2 status (one participant had missing status). Overall, the frequency of solicited local adverse reactions was similar among participants with a positive pre-booster SARS-CoV-2 status 74 out of 96 (77.1%)) and participants with a negative pre-booster SARS-CoV-2 status (272 out of 340 (80%)). The frequency of solicited systemic adverse reactions was similar among participants with positive pre-booster SARS-CoV-2 status (63 out of 96 (65.6%)) and participants with negative pre-booster SARS-CoV-2 status (244 out of 340 (71.8%)). The frequency of Grade 3 solicited local adverse reactions was similar among participants with positive pre-booster SARS-CoV-2 status (1 out of 96 (1%)) and participants with negative pre-booster SARS-CoV-2 status (14 out of 340 (4.1%)). Grade 3 systemic adverse reactions were similar in participants with positive pre-booster SARS-CoV-2 status (5 out of 96 (5.2%)) and participants with negative pre-booster SARS-CoV-2 status (19 out of 340 (5.6%)).

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F) solicited safety set, 92 out of 351 participants (26.2%) had positive pre-booster SARS-CoV-2 status and 250 out of 351 participants (71.2%) had a negative pre-booster SARS-CoV-2 status (nine participants had missing status). The frequency of solicited local adverse reactions was similar among participants with a positive pre-booster SARS-CoV-2 status (73 out of 92 (79.3%)) and participants with a negative pre-booster SARS-CoV-2 status (200 out of 250 (80%)). The frequency of solicited systemic adverse reactions was similar among participants with positive pre-booster SARS-CoV-2 status (57 out of 92 (62%)) and participants with negative pre-booster SARS-CoV-2 status (171 out of 250 (68.4%)). Grade 3 local adverse reactions had a similar frequency among participants with positive pre-booster SARS-CoV-2 status (3 out of 92 (3.3%)) and participants with a negative pre-booster SARS-CoV-2 status (9 out of 250 (3.6%)). Grade 3 systemic adverse reactions were similar in participants with positive pre-booster SARS-CoV-2 status (1 out of 92 (1.1%)) and participants with negative pre-booster SARS-CoV-2 status (15 out of 250 (6%)).

Overall, there were no safety concerns or differences identified in solicited adverse events based on pre-booster SARS-CoV-2 status.

Unsolicited adverse events

Unsolicited treatment-emergent adverse events (TEAE) were systematically collected from Day 1 through Day 29 (28 day follow up) after the booster dose. Adverse events leading to discontinuation from study participation, SAEs, MAAE, adverse events of special interest, and pregnancies were collected from Day 1 through the entire study period or until the last day of study participation. SAEs, MAAE, adverse events of special interest, and pregnancies presented are as of the data cut-off for each study part.

The incidence of unsolicited TEAEs in Study P205 Part G was similar for all types of events (TEAEs, SAEs, MAAEs, AEs considered by the investigator to be related to vaccination) to Study P205 Part F.

Safety events in Study P205 Part G

There were no fatal events and 2 out of 437 participants (0.5%) had SAEs; both SAEs were considered by the investigator to be unrelated to study vaccination (prostate cancer and traumatic fracture. At least one MAAE was reported for 43 out of 437 participants (9.8%),

of whom two participants (0.5%) had an MAAE that was considered by the investigator to be related to study vaccination (fatigue and dermatitis). No participants had TEAEs leading to study discontinuation.

Unsolicited TEAEs within 28 days after the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose (Study P205 Part G), regardless of relationship to study vaccination as assessed by investigators, were reported for 81 out of 437 participants (18.5%). Of those, 25 out of 437 participants (5.7%) had a TEAE that was assessed by the investigator as related to study vaccination, and the majority of these were consistent with reactogenicity: fatigue (9 out of 437 [2.1%]), arthralgia (6 out of 437 (1.4%)), and headache (6 out of 437 (1.4%)) were the most frequently reported TEAEs considered by investigators to be related to vaccination, and all other treatment related TEAEs were reported in less than 1% of participants. One participant experienced a severe TEAE that was considered related to vaccination: a 41 year old female had non-serious severe fatigue that began on Day 1 and continued until Day 14; the event was not medically attended.

The most commonly reported unsolicited TEAEs within 28 days after the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose (Study P 205 Part G) regardless of causality were fatigue (11 out of 437 (2.5%)); headache and arthralgia (7 out of 437 (1.6%) each); and myalgia, COVID-19, and upper respiratory tract infection (5 out of 437 (1.1%) each). All other unsolicited TEAEs in the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose group were reported in less than 1% of participants.

Up to the data cutoff date (27 April 2022), one additional SAE occurred in the bivalent vaccine (elasomeran + imelasomeran) at 50 µg booster dose group (nephrolithiasis; considered unrelated to vaccination by the investigator. As of the data cut-off, there were no fatal events or study discontinuations due to AEs.

Safety events in Study P205 Part F cohort 2

There were no fatal events and 1 out of 377 participants (0.3%) had an SAE; the SAE was assessed by the investigator as unrelated to study vaccination (spinal osteoarthritis. At least one MAAE was reported for 52 out of 377 participants (13.8%), of whom 2 out of 377 participants (0.5%) had an MAAE that was considered by the investigator to be related to study vaccination (hypertension and urticaria. No participants had TEAEs leading to study discontinuation (see Table 13).

Unsolicited TEAEs within 28 days after the 50 µg monovalent vaccine (elasomeran) booster dose (Study P205 Part F), regardless of relationship to study vaccination as reported by investigators, were reported in 78 out of 377 participants (20.7%). Of those, 22 out of 377 participants (5.8%) had a TEAE that was assessed by the investigator as related to study vaccination, and the majority of these were consistent with reactogenicity events: fatigue (11 out of 377 (2.9%)), arthralgia 6 out of 377 (1.6%)), and myalgia (6 out of 377 (1.6%)) were the most frequently reported TEAEs considered by investigators to be related to vaccination, and all other treatment related TEAEs were reported in less than 1% of participants (see Table 13). Two participants experienced severe TEAEs that were considered related to vaccination and were not medically attended: a 31 year old male with history of chronic fatigue had non-serious severe fatigue that began on Day 2 and resolved on Day 8 and occurred concurrently with an unsolicited AE of moderate asthma (verbatim: asthma exacerbation) that was assessed by the investigator as not related to vaccination; and a 42 year old male had non-serious severe myalgia that began on Day 7 and resolved on Day 8.

The most commonly reported unsolicited TEAEs within 28 days after the 50 µg monovalent vaccine (elasomeran) booster dose (Study P205 Part F) regardless of causality were fatigue (12 out of 377 (3.2%)), upper respiratory tract infection (9 out of 377 (2.4%)), coronavirus infection (that is coronaviruses other than SARS-CoV-2) (8 out of 377 (2.1%)), arthralgia (7 out of 377 (1.9%)), myalgia (6 out of 377 (1.6%)), and headache

(4 out of 377 (1.1%)). All other unsolicited TEAEs in the 50 µg monovalent vaccine (elasomeran) booster dose group were reported in less than 1% of participants.

As of the data cutoff, there were no fatal events or study discontinuations due to AEs. One additional MAAE was considered related to vaccination by the investigator occurred in the mRNA-1273 at 50 µg booster dose group (back pain).

Table 13: Study P205 Parts G and F; Summary of unsolicited treatment emergent adverse events up to 28 Days after second booster dose (safety set)

	P205 Part G mRNA-1273.214 50 µg (N=437) n (%)	P205 Part F mRNA-1273 50 µg (N=377) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination		
All	81 (18.5)	78 (20.7)
Serious	2 (0.5)	1 (0.3)
Fatal	0	0
Medically-attended	43 (9.8)	52 (13.8)
Leading to study discontinuation	0	0
Grade 3 or higher	4 (0.9)	3 (0.8)
At least 1 non-serious event [a]	79 (18.1)	78 (20.7)
Grade 3 or higher	3 (0.7)	2 (0.5)
Unsolicited TEAEs related to study vaccination		
All	25 (5.7)	22 (5.8)
Serious	0	0
Fatal	0	0
Medically-attended	2 (0.5)	2 (0.5)
Leading study discontinuation	0	0
Grade 3 or higher	1 (0.2)	2 (0.5)
At least 1 non-serious event [a]	25 (5.7)	22 (5.8)
Grade 3 or higher	1 (0.2)	2 (0.5)

Abbreviation: TEAE = treatmen emergent adverse event.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsen in intensity or frequency after exposure. Percentages are based on the number of participants in the safety set.

a Participants with at least one non-serious TEAE regardless of reporting any serious adverse event or not.

Unsolicited adverse events by pre-booster SARS-CoV-2 status

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part G) safety set, 96 out of 437 participants (22%) had a positive pre-booster SARS-CoV-2 status, and 340 out of 437 participants (77.8%) had a negative pre-booster SARS-CoV-2 status (one participant with missing status) (see Table 14). The incidence of all unsolicited TEAEs regardless of relationship to study vaccine was similar in participants with positive pre-booster SARS-CoV-2 status (13 out of 96 (13.5%)) and participants with negative pre-booster SARS-CoV-2 status (68 out of 340 (20%)). There were no safety concerns or differences identified in SAEs, MAAEs, and severe TEAEs based on pre-booster status. The incidence of SAEs, MAAEs, and Grade 3 or higher TEAEs was similar among bivalent vaccine (elasomeran + imelasomeran) participants with positive pre-booster SARS-CoV-2 status and participants with negative pre-booster SARS-CoV-2 status.

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F) safety set, 101 out of 377 participants (26.8%) had positive pre-booster SARS-CoV-2

status and 267 out of 377 participants (70.8%) had a negative pre-booster SARS-CoV-2 status (nine participants with missing status) (see Table 14). The incidence of all unsolicited TEAES regardless of relationship to study vaccine was similar in participants with positive pre-booster SARS-CoV-2 status (17 out of 101 (16.8%)) to incidence in participants with negative pre-booster SARS-CoV-2 status (59 out of 267 (22.1%)). There were no safety concerns or differences identified in SAEs, MAAEs, and severe TEAEs based on pre-booster status.

The incidence of unsolicited TEAEs related to study vaccine was similar among participants with positive pre-booster SARS-CoV-2 status and participants with negative pre-booster SARS-CoV-2 status, in the bivalent vaccine (elasomeran + imelasomeran) and monovalent vaccine (elasomeran) groups respectively.

Table 14: Study P205 Parts G and F; Summary of unsolicited treatment emergent adverse events up to the data cut-off date, second booster dose (safety set)

	Part G mRNA-1273.214 50 ug (N=437) n(%)	Part F Cohort 2 mRNA-1273 50 ug (N=377) n(%)
Unsolicited TEAEs Regardless of Relationship to Study Vaccination		
All	98 (22.4)	111 (29.4)
Serious	3 (0.7)	1 (0.3)
Fatal	0	0
Medically-Attended	58 (13.3)	85 (22.5)
Leading to Discontinuation from Participation in the Study	0	0
Grade 3 or Higher	5 (1.1)	3 (0.8)
Non-serious [1]	95 (21.7)	110 (29.2)
Grade 3 or Higher	3 (0.7)	2 (0.5)
At Least 1 Non-serious Event [2]	95 (21.7)	111 (29.4)
Grade 3 or Higher	3 (0.7)	2 (0.5)
Unsolicited TEAEs Related to Study Vaccination		
All	25 (5.7)	23 (6.1)
Serious	0	0
Fatal	0	0
Medically-Attended	2 (0.5)	3 (0.8)
Leading to Discontinuation from Participation in the Study	0	0
Grade 3 or Higher	1 (0.2)	2 (0.5)
Non-serious [1]	25 (5.7)	23 (6.1)
Grade 3 or Higher	1 (0.2)	2 (0.5)
At Least 1 Non-serious Event [2]	25 (5.7)	23 (6.1)
Grade 3 or Higher	1 (0.2)	2 (0.5)

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

A treatment emergent adverse event (TEAE) is defined as any event not present before exposure to study vaccination or any event already present that worsen in intensity or frequency after exposure. Percentages are based on the number of subjects in the safety set. [1] Subjects without any SAE and with any non-serious TEAE. [2] Subjects with at least one non-serious TEAR regardless of reporting any SAE or not.

Table 15: Study P205 Parts G and F; Participant incidence of serious treatment emergent adverse events by System Organ Class and Preferred Term up to the data cut-off date, second booster dose

	P205 Part G	P205 Part F
System Organ Class Preferred Term	mRNA-1273.214 50 µg (N=437) n (%)	mRNA-1273 50 µg (N=377) n (%)
Number of participants reporting unsolicited AEs	3 (0.7)	1 (0.3)
Number of unsolicited AEs	3	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.2)	0
Prostate cancer	1 (0.2)	0
Musculoskeletal and connective tissue disorders	0	1 (0.3)
Spinal osteoarthritis	0	1 (0.3)
Renal and urinary disorders	1 (0.2)	0
Nephrolithiasis	1 (0.2)	0
Injury, poisoning and procedural complications	1 (0.2)	0
Traumatic fracture	1 (0.2)	0

Abbreviations: MedDRA = Medicial Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

Part G cohort: mRNA-1273-214, bivalent vaccine (elasomeran + imelasomeran).

Part F cohort: mRNA-1273, monovalent vaccine (elasomeran).

A treatment emergent adverse event (TEAE) is defined as any event not present before exposure to study vaccination or any event already present that worsen in intensity or frequency after exposure. Percentages are based on the number of subjects in the safety set. MedDRA version 23.0.

Medically attended adverse events

A medically attended adverse event (MAAE) in Study P205 Parts G and F comprised an adverse event that leads to an unscheduled visit to a health care professional. Per protocol, this included visits to a study site for unscheduled assessments (for example, abnormal laboratory follow up, COVID-19) and/or visits to health care professionals external to the study site (for example, urgent care, primary care physician). All confirmed COVID-19 cases were to be recorded as MAAEs.

Medically attended adverse events in Study P205 Parts G and F (cohort 2)

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group (Study P205 Part G) within 28 days after the booster dose, 43 out of 437 participants (9.8%) had 52 MAAEs. Two MAAEs that were also SAEs were reported in two participants (traumatic fracture and prostate cancer; The most commonly reported MAAEs, and the only Preferred Terms reported for more than one participant, were COVID-19 (5 out of 437 (1.1%)) and upper respiratory tract infection (5 out of 437 (1.1%) followed by coronavirus infection (non-COVID) (3 out of 437 (0.7%)), procedural pain (3 out of 437 (0.7%)), and fatigue (2 out of 437 (0.5%)).

Two non-serious MAAEs in two participants were assessed as related to vaccination by the investigator (self-limiting reactogenicity event of moderate fatigue and mild dermatitis which resolved on study Day 19).

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) group (Study P205 Part G) up to the data cut-off date, 58 out of 437 participants (13.3%) had 74 MAAEs inclusive of the 52 MAAEs reported within 28 days after the booster dose. One MAAE was also reported as an SAE (nephrolithiasis;). COVID-19 (8 out of 437 (1.8%)) was the most commonly reported MAAE, followed by upper respiratory tract infection (6 out of 437 (1.4%)) and coronavirus infection (non-COVID) (4 out of 437 (0.9%)). No MAAEs with an onset beyond 28 days after vaccination were assessed by the investigator as related to vaccination.

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F) within 28 days after the booster dose, 52 out of 377 participants (13.8%) had 56 MAAEs. One MAAE was also an SAE (spinal osteoarthritis). Upper respiratory tract infection (9 out of 377 (2.4%)) was the most commonly reported followed by coronavirus infection (8 out of 377 (2.1%)), urinary tract infection (3 out of 377 (0.8%)), hypertension (3 out of 377 (0.8%)), rhinovirus infection (2 out of 377 (0.5%)), and urticaria (2 out of 377 (0.5%)). The remaining MAAE preferred terms were reported in one participant only. Two non-serious MAAEs in two participants were assessed as related to vaccination by the investigator,

- A 55 year old female with no relevant medical history had mild hypertension (verbatim: high blood pressure without diagnosis of hypertension) starting on study Day 13. The event worsened, and a moderate MAAE of hypertension, no longer assessed as related to vaccination, was reported with onset on Day 30. Treatment included amlodipine and the event was ongoing at the time of the data cutoff.
- Mild urticaria which resolved four days later.

In the 50 µg monovalent vaccine (elasomeran) group (Study P205 Part F) up to the data cut-off date, 85 out of 377 participants (22.5%) had 104 MAAEs inclusive of the 56 MAAEs reported within 28 days after the booster dose. Upper respiratory tract infection (15 out of 377 (4%)) was the most commonly reported MAAE, followed by coronavirus infection (9 out of 377 (2.4%)). One of the MAAEs with onset beyond 28 days from the booster dose was assessed as related to vaccination by the investigator,

- A 55 year old female with a medical history of chronic back pain had mild back pain (verbatim: worsening of chronic back pain) starting on study Day 33. At the time of the data cutoff, the event was ongoing.

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) group (Study P205 Part G) up to the data cut-off date, 58 out of 437 participants (13.3%) had 74 MAAEs up to the data cut-off. COVID-19 (8 out of 437 (1.8%)) was the most commonly reported MAAE, followed by upper respiratory tract infection (6 out of 437 (1.4%)) and coronavirus infection (non-COVID) (4 out of 437 (0.9%)). Two non-serious MAAEs in two participants were assessed as related to vaccination by the Investigator: moderate fatigue (Day 2); mild dermatitis (Day 7).

In the 50 µg monovalent vaccine (elasomeran) group (Study P205 Part F) up to the data cut-off date, 85 out of 377 participants (22.5%) had 104 MAAEs up to the data cut-off. Upper respiratory tract infection (15 out of 377 (4%)) was the most commonly reported MAAE, followed by coronavirus infection (9 out of 377 (2.4%)). Three non-serious MAAEs in three participants were assessed as related to vaccination by the investigator: mild hypertension (Day 13); mild urticaria (Day 18); mild back pain (Day 33).

Adverse events leading to discontinuation from Study P205 Parts G and F

No participants in either the bivalent vaccine (elasomeran + imelasomeran) group or the monovalent vaccine (elasomeran) group discontinued due to a TEAE.

Adverse events of special interest

Investigator assessed adverse events of special interests in Study P205 Parts G and F

Investigators were asked to report all suspected cases of probable and confirmed myocarditis, pericarditis, or myopericarditis as an AESI even if they did not meet the CDC case definition criteria.

No participants in the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group (Study P205 Part G) had an investigator assessed AESI up to the data cutoff date

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F), one out of 377 participants (0.3%) had an investigator assessed AESI.

- A 71 year old African American male had a moderate non-serious irregular heart rate (verbatim: unspecified irregular heartbeat) on Day 17 after the mRNA1273 [monovalent vaccine (elasomeran)] at 50 µg booster dose. Medical history included hypertension, Type II diabetes mellitus, hyperlipidaemia, osteoarthritis, prostate cancer, and seasonal allergy. At the time of the data cutoff, the event had not resolved, and no diagnosis was available as evaluation was ongoing. The investigator assessed the event as not related to study vaccination.

Adverse events of special interests based on standardised MedDRA queries in Study P205 Parts G and F

The standardised MedDRA queries (SMQ) analyses of AEs within 28 days of the booster dose did not identify any safety concerns after vaccination with 50 µg bivalent vaccine (elasomeran + imelasomeran) (Study P205 Part G) or 50 µg monovalent vaccine (elasomeran) (Study P205 Part F) when administered as a second booster dose.

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group (Study P205 Part G) within 28 days after vaccination, no events were captured in the SMQs (narrow and broad scope) for ischemic heart disease, cardiac failure, cardiomyopathy, embolic and thrombotic events, central nervous system vascular disorders, hearing and vestibular disorders, convulsions, demyelination, haematopoietic cytopenias, peripheral neuropathy, thrombophlebitis, or vasculitis.

Cases with Preferred Terms (PT) identified by SMQs were medically reviewed and no safety concerns were identified.

- Cardiac arrhythmia SMQ:
  - Tachycardia (one out of 437 participants (0.2%)): A 53 year old female with a medical history of obesity had a nonserious MAAE of moderate tachycardia on study Day 7 that resolved on the same day without treatment. The event was assessed by the investigator as unrelated to vaccination and of unknown aetiology. The participant had a nonserious MAAE of moderate cough beginning on study Day 3 and a nonserious MAAE of moderate symptomatic COVID-19 beginning on study Day 5.
- Hypersensitivity SMQ:
  - Dermatitis (one out of 437): mild, resolved on study Day 19, assessed as related to vaccination by the investigator.
  - Urticaria (one out of 437): mild, resolved on Day 34, assessed as related to vaccination.
  - Contact dermatitis (one out of 437): mild due to poison ivy, resolved by Day 18, assessed as unrelated to vaccination.
  - Macular rash (one out of 437) resolved on the same day, assessed as unrelated to vaccination.
- Arthritis SMQ:
  - Rheumatoid arthritis (1 out of 437). The event was ongoing as of the data cutoff and was assessed by the investigator as unrelated to vaccination.

In the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group (Study P205 Part G) up to the data cut-off, no new events were reported that were captured in SMQs.

In the 50 µg monovalent vaccine (elasomeran) group (Study P205 Part F) within 28 days after vaccination, no events were captured for the SMQs (narrow and broad scope) for ischemic heart disease, cardiomyopathy, embolic and thrombotic events, central nervous system vascular disorders, convulsions, demyelination, haematopoietic cytopenias, thrombophlebitis, and vasculitis.

Cases considered of interest following medical review are presented below:

- Cardiac arrhythmia SMQ:
  - Irregular heart rate (1 out of 377 participants (0.3%)) was reported as an investigator assessed AESI and considered unrelated to vaccination.
- Cardiac failure SMQ:
  - Peripheral oedema (1 out of 377): mild, history of hypertension myocardial infarction resolved on Day 28, assessed as unrelated to vaccination.
- Hypersensitivity SMQ:
  - Urticaria (2 out of 377 participants (0.5%); also reported under the angioedema SMQ):
  - Mild urticaria and seasonal allergies assessed as unrelated to vaccination.
  - Asthma (1 out of 377): moderate asthma assessed as unrelated to vaccination.
  - Contact dermatitis (2 out of 377 participants (0.5%)): attributed to poison ivy assessed as unrelated to vaccination.
  - Eczema (1/out of 377): history of eczema assessed as unrelated to vaccination.
- Peripheral neuropathy SMQ:
  - Muscular weakness (1 out of 377) in 85 year old White male resolved on study Day 25 assessed as unrelated to vaccination.
- Some additional events were reported that were captured in SMQs but were assessed as unrelated to vaccination: Cardiac failure (1 out of 377), Arthritis (1 out of 377), Anaemia (1 out of 377) and Hypoesthesia (1 out of 377).

Myocarditis and pericarditis events enhanced assessment using custom MedDRA query

The custom MedDRA query analysis did not identify any cases fulfilling the CDC working case definition for probable or confirmed cases of acute myocarditis or acute pericarditis in Study P205 Parts G and F booster dose groups.

Pregnancy

No pregnancies were reported in the 50 µg bivalent vaccine (elasomeran + imelasomeran) booster dose group or in the 50 µg monovalent vaccine (elasomeran) booster dose group up to the data cut-off.

Deaths

No deaths were reported in either the 50 µg bivalent vaccine (elasomeran + imelasomeran booster dose group or the 50 µg monovalent vaccine (elasomeran) booster dose group.

Other serious adverse events

In Study P205 Part G, there were three participants (0.7%) who had one SAE each at the time of the data cut-off.

In the bivalent vaccine (elasomeran + imelasomeran) 50 µg booster dose group (Study P205 Part G), two participants (0.5%) had one SAE each within 28 days of the booster dose and both SAEs were assessed as not related to vaccination by the investigator.

In the 50 µg bivalent vaccine (elasomeran + imelasomeran booster dose group (Study P205 Part G), one participant had an SAE beyond 28 days after the booster dose that was assessed by the investigator as not related to vaccination.

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F), one participant (0.3%) had an SAE within 28 days of the booster dose and the SAE was assessed as not related to vaccination by the investigator.

In the 50 µg monovalent vaccine (elasomeran) booster dose group (Study P205 Part F), no participants had an SAE beyond 28 days from the booster dose at the time of the data cut-off date (27 April 2022).

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 4.2 (date 28 June 2022; data lock point (DLP) 27 April 2022) and Australia specific annex (ASA) version 1.0 (date 8 July 2022) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 16 Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 16: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myocarditis	ü*	ü†	ü	–
	Pericarditis	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	üµ	ü	–
	Long-term safety	ü	ü†	–	–
	Use in immunocompromised subjects	ü	ü†	ü	–
	Interaction with other vaccines	ü	ü†	ü	–
	Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive	ü	ü†	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)				
	Use in subjects with autoimmune or inflammatory disorders	ü	ü†	ü	–

*Follow-up questionnaires

†Clinical studies

µ Observational cohort database study

The summary of safety concerns is acceptable. The advice from the clinical evaluator, the Delegate and the ACV has been considered when making this decision.

The pharmacovigilance plan is acceptable. In response to RMP evaluator's recommendation, the sponsor agreed to provide monthly summary safety reports for the first 6 months post registration, and thereafter at intervals specified by the TGA.

Only routine risk minimisation measures have been proposed. The introduction of the bivalent vaccine is not expected to require additional risk minimisation measures as part of the RMP.

Risk-benefit analysis

Delegate's considerations

Immunogenicity/Efficacy

The Omicron variant (emergence in November 2021) and current subvariants (BA.2, BA.2.12.1, BA.4, and BA.5) are the most antigenically divergent variants to date with antibody escape site mutations and increased transmissibility, and their circulation was associated with unprecedented rates of infection globally. In response, the sponsor has developed a variant modified Omicron BA.1 containing bivalent mRNA vaccine. Spikevax bivalent (elasomeran + imelasomeran) COVID-19 vaccine is a 50 µg formulation that retains the ancestral SARS-CoV-2 spike sequence (25 µg) and also encodes for the Omicron spike sequence (25 µg).

The clinical evaluation of immunogenicity was based on the pivotal studies (Study P205 Part G and Study P205 Part F cohort 2). In the Study P205 Part G versus Part F analysis, the primary immunogenicity objective (pre-specified) was to compare the immunogenicity of 50 µg bivalent vaccine (elasomeran + imelasomeran) and 50 µg monovalent vaccine (elasomeran) as a second booster. The co-primary endpoints were GMT and seroresponse rates (SRR) for serum neutralising antibody (NAb) titres against the SARS-CoV-2 ancestral strain and Omicron (BA.1)(sub)variant. The primary efficacy analysis set was the PPSI-Neg set. Although not randomised this comparison of the two cohorts is considered acceptable considering similar inclusion criterion, overall

demographic and baseline characteristics was similar, timing of enrolment almost similar with specific primary endpoint. The statistical methods are considered acceptable.

The results are available for a data cutoff date of 27 April 2022 which corresponds to the interim analysis at Day 29. Overall, demographic and baseline characteristics were similar between the 50 µg bivalent vaccine (elasomeran + imelasomeran) and 50 µg monovalent vaccine (elasomeran) groups.

In Study P205 Part G, all primary and key secondary immunogenicity objectives were met. 50 µg bivalent vaccine (elasomeran + imelasomeran) elicited a superior neutralising antibody response against the Omicron BA.1 subtype, and a non-inferior antibody response against the ancestral SARS-CoV-2 strain (with D614G mutation) 28 days after booster dose administration as compared to a 50 µg booster dose of monovalent vaccine (elasomeran). The GMR (97.5% CI) for primary analysis population (participants with no prior infection) against the Omicron variant was 1.75 (1.49, 2.04), meeting the prespecified superiority criterion (lower bound of CI > 1). The GMR (97.5% CI) against the ancestral SARS-CoV-2 strain (with D614G mutation) was 1.22 (1.08, 1.37), meeting the prespecified criterion for non-inferiority (lower bound of CI ≥ 0.67). The Omicron neutralising antibody responses were higher in participants both with and without prior evidence of SARS-CoV-2 infection in the entire study population (GMR (97.5% CI) 1.79 (1.56, 2.04). The sponsor has confirmed that Day 91 data for bivalent vaccine (elasomeran + imelasomeran) group will be provided when available. Although there is no immune correlate of protection, the difference in neutralising antibodies against Omicron would be expected to translate into a clinical benefit of the bivalent vaccine compared to the original vaccine.

Study P205 was not designed to evaluate booster vaccine effectiveness and the sponsor has stated that they will actively monitor real world effectiveness data including future variants with additional antibody escape mutations, following the use of Spikevax bivalent vaccine (elasomeran + imelasomeran) if approved.

The seroresponse was calculated relative to baseline titres pre-Dose 1 of the primary series. With an alternative definition of seroresponse which is being ≥ 4-fold increase relative to baseline titres pre-second booster, SRRs were consistent with the GMT results.

In addition, a subgroup analysis in participants with evidence of SARS-CoV-2 infection at Baseline showed that the bivalent vaccine (elasomeran + imelasomeran) demonstrated higher immunogenicity against the Omicron (B.1.1.529) variant and ancestral SARS-CoV-2 (with D614G mutation) strain with the Day 29 GMR of 1.898 (97.5% CI: 1.499, 2.403) and 1.272 (97.5% CI: 1.070, 1.512), respectively.

Additionally, in the exploratory immunogenicity analysis, 50 µg bivalent vaccine (elasomeran + imelasomeran) elicited higher neutralising antibody response against the Omicron BA.4 and BA.5 subvariants; the Spikevax bivalent vaccine (elasomeran + imelasomeran) also elicited higher binding antibody responses against multiple variants not contained in the vaccine, including the Alpha, Beta, Gamma, and Delta variants.

The sponsor has provided supportive Day 181 data for a different bivalent COVID-19 vaccine (mRNA-1273.211), a bivalent vaccine containing equal amounts of the ancestral SARS-CoV-2 and Beta variant spike protein sequences, from Part A1 of Study P205. These data suggest some persistence of the neutralising antibodies induced by a bivalent mRNA vaccine against ancestral and variant strains. These data also provide some supportive evidence to extrapolate Spikevax bivalent vaccine (elasomeran + imelasomeran) as evaluated in this submission, to the first booster setting.

Safety

Safety data was obtained from Study P205 Parts G and F, with a median follow up duration of 43 days (range 22 to 51 days) for Study P205 Part G and 57 days (range 51 to 66 days)

for Study P205 Part F. This involved collection of solicited local and systemic adverse events (AEs) during 7-day follow up period after vaccination, as well as unsolicited AEs during 28 day follow up period after vaccination. Serious adverse events, medically-attended adverse events and adverse events with special interest were also collected until the data cutoff.

The reactogenicity profile of 50 µg bivalent vaccine (elasomeran + imelasomeran) appeared similar to that of 50 µg monovalent vaccine (elasomeran) when administered as a second booster dose (median of 133 days after a first booster dose of 50 µg monovalent vaccine (elasomeran)). The reactogenicity profile of 50 µg bivalent vaccine (elasomeran + imelasomeran) was similar for participants with and without prior SARS-CoV-2 infection who received bivalent vaccine.

Reactogenicity outcomes for the Spikevax bivalent vaccine (elasomeran + imelasomeran) were comparable to those for the solicited safety set of Study P201 Part B which included 330 participants who received a 50 µg first booster of the Spikevax monovalent vaccine (elasomeran) after their Spikevax monovalent (elasomeran) primary series of vaccination. The sponsor claims that this would suggest that at the 50 µg dose, the reactogenicity profile of the Spikevax bivalent vaccine (elasomeran + imelasomeran) when used as a second booster should be similar to the reactogenicity profile of the Spikevax monovalent vaccine (elasomeran) when used as a first or second booster, in individuals who received Spikevax monovalent vaccine (elasomeran) as the primary series.

The solicited local and systemic AE profiles were similar between Study P205 Parts G and F. The most common solicited local AE was pain (77% in Study P205 Part G), followed by axillary swelling or tenderness (17% in Study P205 Part G). The most common systemic AE was fatigue (55% in Study P205 Part G), followed by headache, myalgia, and arthralgia. The majority of solicited local and systemic AEs were Grade 1 followed by Grade 2. The median duration of local and systemic AEs was 2 days, and no Grade 4 local AE was reported in both parts of Study P205.

Approximately 20% of participants experienced at least one TEAE. Those that were considered by the investigator to be related to vaccination (Study P205 Part G, 5.7%) were generally consistent with reactogenicity (lymphadenopathy, arthralgia, myalgia, fatigue, and injection site reactions). The incidence of serious AEs and severe treatment-emergent AEs was low, and no serious AEs were considered by the investigator to be related to vaccination.

The sponsor confirms that review of potential adverse events of special interest using SMQs (including cardiomyopathy, cardiac arrhythmia, and hypersensitivity) did not identify any new safety concerns. One event of tachycardia (in a 53 year old female) and one event of irregular heart rate (in a 71 year old male) ware not considered by the investigator to be related to vaccination.

No cases of myocarditis or pericarditis were reported in the Spikevax bivalent vaccine (elasomeran + imelasomeran) participants, nor in the sponsor's alternate investigational bivalent vaccine (mRNA-1273.211) participants enrolled in Study P205. The sponsor confirmed that an enhanced safety analysis has been performed to capture any unrecognised myocarditis or pericarditis events by searching the safety dataset for adverse events compatible with signs, symptoms, laboratory investigations, and procedural findings that might indicate potential events. The myocarditis and pericarditis risk appeared to be consistent with the known safety profile of mRNA-1273 based vaccines and the sponsor has confirmed that the monitoring will continue in clinical studies, pharmacovigilance, and post authorisation safety study.

No new safety concerns have been identified in studies of modified mRNA-1273 bivalent vaccine (elasomeran + imelasomeran) at 50 µg given as a second booster dose (N = 437,

median of 136 days after a first booster dose of 50 µg of the Spikevax monovalent vaccine (elasomeran), with a median follow up of 43 days).

The sponsor believes that, in principle, the use of Spikevax Bivalent Original/Omicron COVID-19 vaccine as a booster regardless of the dose number, is supported by the data generated as a second booster and can be safely used as a first booster as there is no scientific reason, based on either safety or efficacy to believe that the immunogenicity and safety results would be qualitatively different in other booster settings. The sponsor states that safety and the reactogenicity profile for Spikevax Bivalent Original/Omicron COVID-19 vaccine is similar with that of Spikevax booster in the clinical study, Study P205. Additionally, the safety of the sponsor's alternate investigational bivalent vaccine, mRNA 1273.211, was evaluated as a third dose (first booster dose) in the Study P205 study as well. The safety data from mRNA 1273.211 at 50 µg also are similar to that of Spikevax booster at 50 µg. The proposed dose recommendations for Spikevax Bivalent Original/Omicron COVID-19 vaccine (elasomeran + imelasomeran) allows for its use as a booster (at least three months) after completion of a primary series and any number of boosters, and for heterologous boosting. This is also is in line with current Spikevax (monovalent, elasomeran) vaccine that already has provisional registration. This is considered acceptable.

Proposed action

A second booster dose of Spikevax bivalent Omicron BA.1-containing vaccine (elasomeran + imelasomeran) at 50 µg compared to a second booster dose of the (original) Spikevax monovalent vaccine at 50 µg showed that the bivalent vaccine (elasomeran + imelasomeran) elicited a superior neutralising antibody response against Omicron BA.1 strain and a non-inferior antibody response against the ancestral SARS-CoV-2. Additionally, in the exploratory immunogenicity analysis, 50 µg bivalent vaccine (elasomeran + imelasomeran) elicited higher neutralising antibody response against the Omicron BA.4 and BA.5 subvariants. The bivalent vaccine also elicited higher binding antibody responses against multiple variants not contained in the vaccine, including the Alpha, Beta, Gamma, and Delta variants, thereby achieving broader immunity.

Based on a clinical safety database of 437 participants with median follow up of six weeks, the safety and reactogenicity profiles of Spikevax bivalent vaccine (elasomeran + imelasomeran) as a 50 µg second booster appears similar to that of Spikevax monovalent (elasomeran) vaccine as a 50 µg second booster. No new safety concerns are raised.

The overall benefit risk balance of Spikevax Bivalent Original/Omicron COVID-19 vaccine in this submission as a booster dose in individuals 18 years of age and older appears favourable for its Provisional;[19] registration.

The final decision will be made following the ACV discussion.

Advisory Committee considerations

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. ***Please advise on the proposed indication. Considering this vaccine is only for booster dosing the indication should clearly state so, such as: Spikevax Bivalent***

Original/Omicron (elasomeran/imelasomeran) COVID-19 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 and older….

The ACV advised that the proposed provisional indication is appropriate based on submitted data comparing neutralising antibodies following the Spikevax Bivalent Original/Omicron bivalent booster compared to after the Spikevax (original) booster. The ACV noted that there are no data available on vaccine efficacy or effectiveness at this stage.

The ACV was supportive of the inclusion of the wording 'As a booster dose' within the indication as this is consistent with the provided data.

An indication for use as a booster dose would be consistent with the recent approval in the United Kingdom (by the Medicines and Healthcare Products Regulatory Agency) and the data available in this submission, and ACV noted that the sponsor has accepted this wording in the pre-ACV response. The ACV noted that very few people have not been exposed to SARS-CoV-2, whether by vaccination or infection. However, there are no data for the use of Spikevax Bivalent Original/Omicron as a primary series (noting that the dose studied for the primary series of Spikevax (original) (100 µg) is twice the mRNA content of this vaccine).

Data provided by the sponsor from the mRNA 1273.211 (alternate Beta variant bivalent) vaccine study supports the assertion that bivalent boosters can be used as first or subsequent boosters.

The ACV noted that the safety data are limited, with a relatively small numbers of participants, and limited duration of follow up (mean 43 days and 57 days) involved in the clinical study. However the available data suggest that the safety profile of Spikevax Bivalent Original/Omicron appears similar to that of the Spikevax (original) booster.

2. Please comment on the proposed 'Dose Recommendations'.

The ACV was supportive of the dose recommendation stating:

> *'Spikevax Bivalent Original/Omicron may be given at least 3 months following a primary series and/or previous booster dose with Spikevax or another authorised/approved COVID-19 vaccine, in accordance with official recommendations.'*

The ACV requested that 'in accordance with official recommendations' be included within the dose recommendations.

The ACV was supportive of Spikevax bivalent being given at least 3 months after a primary series and/or previous booster dose with Spikevax or another authorised/approved COVID-19 vaccine. While the data are limited to fourth doses in those who have previously received [the same sponsor] Moderna primary and booster doses, it is likely that these data can be generalised to those who have received other vaccine types, and for first or subsequent boosters.

3. Other advice

The ACV noted that data on efficacy/immunogenicity and adverse events in individual aged less than 18 years is not relevant to Spikevax Bivalent Original/Omicron and need not be included in the product information.

Conclusion

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

Spikevax Bivalent Original/Omicron (elasomeran/imelasomeran) COVID-19 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 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.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Spikevax Bivalent Original/Omicron COVID-19 Vaccine (elasomeran and imelasomeran) 0.1 mg/mL, suspension for injection, multidose vial, indicated for:

*Spikevax Bivalent Original/Omicron (elasomeran/imelasomeran) COVID-19 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.

Specific conditions of registration applying to these goods

- Spikevax Bivalent Original/Omicron COVID-19 Vaccine (elasomeran/imelasomeran) is to be included in the Black Triangle Scheme. The PI and [Consumer Medicine Information] CMI for Spikevax Bivalent Original/Omicron COVID-19 Vaccine must include the black triangle symbol and mandatory accompanying text for the product's entire period of provisional registration.
- The Spikevax Bivalent Original/Omicron COVID-19 Vaccine EU-Risk Management Plan (version 4.2, dated 28 June 2022; DLP 27 April 2022), with Australia-Specific Annex (version 1.0, date 8 July 2022), included with submission PM-2022-02203-1, and any subsequent revisions, as agreed with the TGA 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 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report 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 summary safety 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 Conditions

- Spikevax Bivalent Original/Omicron COVID-19 Vaccine:
  - Submit the interim and final analysis of the pivotal studies P205 Part G and P205 Part F (cohort 2) and their CSR (Clinical Study Report) when available.
  - Submit data on booster vaccine effectiveness of mRNA-1273.214 when available.
  - Omicron BA.4/BA.5 neutralization assay validation report should be submitted when available.
- Existing conditions for Spikevax (original) remain.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Quality Conditions

- GMP clearance for listed manufacturers: All relevant manufacturing sites require approved and current GMP Clearances prior to Australian supply. A commitment is required from the sponsor that they maintain the validity of all manufacturer GMP Clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP Clearance approval is upheld.
- Batch Release Testing and Compliance

  It is a condition of registration that all independent batches of Spikevax Bivalent Original/Omicron (elasomeran and imelasomeran) 0.1 mg/mL suspension for injection vial imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

  For each independent batch of the product imported into Australia, the sponsor must supply the following:

  - A completed Request for Release Form, available from vaccines@health.gov.au.
  - Complete summary protocols for manufacture and QC, including all steps in production in the agreed format.
  - At least 10 (ten) vials (samples) of each manufacturing batch of Spikevax Bivalent Original/Omicron (elasomeran and imelasomeran) 0.1 mg/mL suspension for injection vial with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted) representative of all batches of product seeking distribution in Australia.
  - At least 5 (five) vials (samples) of any further consignments of a manufacturing batch of Spikevax Bivalent Original/Omicron (elasomeran and imelasomeran) 0.1 mg/mL suspension for injection vial with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted). Further

consignments cover batches previously supplied to TGA for the purposes of batch release testing but are seeking to be supplied again.

- 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 be provided.
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Sponsors must provide all requested samples and data in sufficient time (at least 5 business days) prior to any distribution date to allow the TGA to perform testing and review. Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

Samples and data should be forwarded to the Biotherapeutics Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing.

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 (1) 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.

Quality Commitments

- Post-approval stability protocol and stability commitment: The manufacturer has provided commitment to continue the ongoing stability studies presented in the stability studies protocol. Additionally, 1 batch of DP per year for all relevant products will be placed on long-term stability program and on accelerated stability testing where significant changes are made to the manufacturing process. The manufacturer has committed to communicate any out of specifications stability test results to the TGA.

Attachment 1. Product Information

The PI for Spikevax Bivalent Original/Omicron approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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