Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Elasomeran (mRNA-1273)

Proprietary Product Name: Spikevax

Sponsor: Moderna Australia Pty Ltd

December 2021

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 medicines and medical devices.
- 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 (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

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

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Adverse reaction
BMI	Body mass index
bAb	Binding antibody
CDC	Centers for Disease Control and Prevention (United States of America)
CI	Confidence interval
CNS	Central nervous system
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases (United States of America)
DTaP	Diptheria, tetanus, and pertussis (vaccine)
ELISA	Enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization (United States of America)
FDA	Food and Drug Administration (United States of America)
GLSM	Geometric least squares mean
GM	Geometric mean

Abbreviation	Meaning
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
GMR	Geometric mean ratio
HIV	Human immunodeficiency virus
IA	Interim analysis
ID_{50}	Median infectious dose
Ig	Immunoglobulin
IM	Intramuscular
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
MAAE	Medically-attended adverse events
MERS	Middle East respiratory syndrome
mITT	Modified intent-to-treat
mRNA	Messenger ribonucleic acid
MSD	MesoScale Discovery
nAb	Neutralising antibody
NIH	National Institutes of Health (United States of America)
NIAID	National Institute of Allergy and Infectious Diseases (United States of America)
NIM	Noninferiority margin
PolyA	Polyadenylated
PP	Per-protocol
PsVNA	Pseudotyped virus neutralising assay
PT	Preferred Term
RMP	Risk management plan

Abbreviation	Meaning
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	Standard deviation
SMQ	Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query
Study P201	Study mRNA-1273-P201
Study P301	Study mRNA-1273-P301 (COVE)
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
US(A)	United States (of America)
UTR	Untranslated region
VE	Vaccine efficacy
VOC	Variant of concern
VOI	Variant of interest
VSV	Vesicular stomatitis virus
WT	Wild type
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Major variation (change of dose regimen and patient group)
Product name:	Spikevax
Active ingredient:	Elasomeran (mRNA-1273)
Decision:	Approved for provisional registration
Date of decision:	7 December 2021
Date of entry onto ARTG:	9 December 2021
ARTG number:	370599
, *Black Triangle Scheme:*[1]	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 60 Martin Place Sydney, NSW 2000
Dose form:	Suspension for injection
Strength:	0.2 mg/mL
Container:	Vial
Pack size:	10
Approved therapeutic use:	*Spikevax (elasomeran) COVID-19 vaccine has provisional approval for the indication below:* *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older.* *The use of this vaccine should be in accordance with official recommendations.* *The decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

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

Route of administration:	Intramuscular
Dosage:	Booster Dose Individuals 18 years of age and older Spikevax is administered intramuscularly as a single booster dose (0.25 mL; 50 micrograms) at least 6 months after completing a primary series. The decision when and for whom to implement a booster (third dose) of Spikevax should be made based on available vaccine safety and effectiveness data (see sections 4.4 Special warning and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Moderna Australia Pty Ltd (the sponsor) to make changes to the registration of Spikevax (elasomeran (mRNA-1273)) 0.2 mg/mL suspension for injection, including changes to the dosage regimen and the Product Information (PI)[2] as follows:

- Extension of dose regimen to include a booster dose:

  A booster dose (third dose) of Spikevax may be administered in adolescents and adults aged 12 years and older who received primary COVID-19 vaccination with Spikevax or another authorised or approved COVID-19 vaccine at least 6 months prior.

[2] The **Product Information (PI)** document provides health professionals with a summary of the scientific information relevant to the safe and effective use of a prescription medicine. The information in a product information document has been written by the pharmaceutical company responsible for the medicine and has been approved by the TGA. It provides objective information about the quality, safety and effectiveness of the medicine, as demonstrated in the data provided to the TGA by the pharmaceutical company.
This information is intended to assist doctors, pharmacists and other health professionals in prescribing and dispensing medicines. In addition, this information can be used by health professionals in their consultations with patients, so that the patient can be better informed about their medicines.

- Extension of patient group and altering the dose regimen for immunocompromised individuals aged at least 18 years and over:

  A third dose of Spikevax may be administered at least 28 days following the first two doses of Spikevax in individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Coronavirus disease 2019 (COVID-19) is an infectious disease with mainly respiratory symptoms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a zoonotic virus that first emerged as a human pathogen in December 2019 and has rapidly spread around the world by human-to-human transmission.

Following the initial outbreak of pneumonia of an unknown cause, by January 2020, it became clear that a novel Coronavirus (initially named 2019-nCoV by the World Health Organization (WHO), and later designated as being SARS-CoV-2 by the International Committee on the Taxonomy of Viruses) was the underly-19ng cause.[3] In early January 2020, the genetic sequence of SARS-CoV-2 became known to the WHO and the public, and the virus was categorised in the beta-coronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome coronavirus (MERS-CoV).

The virus causes a respiratory illness in people known as COVID-19, which is thought to spread primarily via respiratory droplets and aerosol transmission between people who are in close contact.[4] After an incubation period of around 5 days (range: 1 to 14), common clinical manifestations include fever, cough, dyspnoea and myalgia.[5,6]

The severity of COVID ranges from asymptomatic or mild presentations, to severe cases requiring intensive care/respiratory support and the fatality rate is currently about 2%.[7] Increasing age is a strong risk factor for morbidity and mortality associated with COVID-19 and comorbidities such as chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) have been found to be significantly associated with a worse prognosis.[8]

The COVID-19 outbreak was officially declared a pandemic by WHO on 11 March 2020.[9] Since its emergence, the SARS-CoV-2 virus has spread rapidly around the globe, affecting a growing number of countries. As of 8 December 2021, there have been over 265 million confirmed cases of COVID-19 globally, with over 5 million deaths reported to WHO.[10] In Australia, as of 8 December 2021, there have been over 220,000 confirmed COVID-19 cases and 2,065 deaths.[11]

[3] Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019, *N. Engl. J*. Med, 2020; 382(8): 727-733.
[4] CDC, 2020. (last viewed 8 November 2021)
[5] Li, Q., Guan, X, Wu, P., *et al*. Early Transmissions Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J* Med 2020; 382:1199-1207
[6] Huang, C., Wang, Y., Li, X., *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 2020; 395: 497-506.
[7] WHO dashboard https://covid19.who.int/
[8] Fang X, Li S, Yu H, *et al.* Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY).* 2020; 12 (13): 12493-503.
[9] World Health Organisation (WHO;2020) WHO Director-General Speeches: WHO Director-General's Opening Remarks at the Media Briefings on COVID-19- 11 March 2020. Accessed 28 October 2021. Available from the WHO website.
[10] World Health Organisation (WHO), Coronavirus Disease (COVID-19) Dashboard. Accessed 8 December 2021. Available from the WHO website.
[11] Australian Government, Department of Health (last updated 7 December 2021) Coronavirus (COVID-19) Case Numbers and Statistics. Accessed 8 December 2021.

In the current scenario, a critical component of the public health strategy in Australia to reduce COVID-19 related illnesses, hospitalisations, and deaths, and to help restore societal functioning, is immunisation with a safe and effective COVID-19 vaccine. At the time this submission was under consideration by the Therapeutic Goods Administration (TGA), there were 4 vaccines provisionally registered in Australia. [12]

These provisionally registered vaccines for prevention of COVID-19 include the Pfizer-BioNTech COVID-19 vaccine Comirnaty (BNT162b2 messenger ribonucleic acid (mRNA), also known as tozinameran);[13,14,15] COVID-19 Vaccine AstraZeneca (ChAdOx1-S);[16,17] COVID-19 Vaccine Janssen (Ad26.COV2.S), [18,19] and Spikevax (elasomeran) [20, 21,22]. Comirnaty, also commonly known as the Pfizer vaccine, has provisional approval as a booster dose in adults, and a third dose in severely immunocompromised individuals.

Spikevax (elasomeran) was the second messenger ribonucleic acid (mRNA) vaccine to receive provisional approval in Australia. mRNA vaccines use a synthetic genetic code called RNA to give cells instructions about how to make the coronavirus' unique spike protein. Once the human body has made the protein encoded by the mRNA vaccine, the body will recognise the spike protein as being foreign and will launch an immune response against it if exposed. The RNA from the vaccine does not change, or interact, with our own deoxyribonucleic acid (DNA) in any way.

At the time of this report, no COVID-19 vaccine is approved in Australia for booster vaccination of people aged under 18 years.

While over 85% of the Australian population aged 16 years and older are now doubly vaccinated, emerging data suggest a waning of immunity after around 6 to 12 months, and in addition there have been emergent variants (for example the Delta variant) with

Available at: Coronavirus (COVID-19) case numbers and statistics | Australian Government Department of Health

[12] 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.
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.

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

[14] 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

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

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

[17] 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.

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

[19] 7 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.

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

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

[22] 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.

increased transmissibility and ability to partially escape immunity.[23,24]Such waning of immunity over time may place vulnerable populations at a greater risk of infection or disease. In addition, international borders have reopened, providing another avenue for the virus or variants to enter the community and circulate. The extra protection against COVID-19 afforded by booster vaccination may help mitigate the ongoing effects of the pandemic.

Currently, Spikevax is provisionally approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older. In this submission the sponsor is seeking approval for extension of dose regimen to include a booster dose, extension of patient group and alteration in the dose regimen for immunocompromised individuals aged at least 18 years and over, and other updates to the safety and immunogenicity data in the PI for the existing Spikevax (elasomeran) vaccine in the Australian Register of Therapeutic Goods (ARTG).[25]

Regulatory status

The product received initial registration (provisional) on the Australian Register of Therapeutic Goods (ARTG) on 9 August 2021 for prevention of coronavirus disease (COVID-19) in individuals 18 years of age and older. A subsequent application resulted in the approval for use in individuals 12 years of age and older.

As of 3 September 2021, the approved indications for Spikevax were

> *Spikevax (elasomeran) COVID-19 vaccine has provisional approval for the indication below:*
>
> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*
>
> *The decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) on 12 August 2021 (use in immunocompromised patients) and 20 October 2021 (booster application); Switzerland on 26 October 2021 (for use in immunocompromised patients) and 26 November 2021 (for booster application); European Union (EU) on 5 October 2021 (for use in immunocompromised patients) and 29 October 2021 (for booster application); Canada on 12 November 2021 (for booster application); and in the United Kingdom on 1 December 2021 (for immunocompromised patients). A similar application was under consideration in Israel, submitted on 9 September 2021.

[23] Australian Government, Department of Health (last updated 24 November 2021) Coronavirus (COVID-19) Vaccination numbers and statistics. Accessed 24 November 2021.
Available at: Vaccination numbers and statistics | Australian Government Department of Health
[24] World Health Organisation (last updated 4 October 2021) Interim statement on booster doses for COVID-19 vaccination. Accessed 25 November 2021.
Available at: Interim statement on booster doses for COVID-19 vaccination (who.int)
[25] Therapeutic goods must be entered in the Australian Register of Therapeutic Goods (ARTG) before they can be lawfully supplied in or exported from Australia, unless exempt from being entered in the ARTG, or otherwise authorised by the TGA. For further information visit: Australian Register of Therapeutic Goods | Therapeutic Goods Administration (TGA)

Table 1: International regulatory status

Region	Regulatory status	Status of booster applications	Status of use in immunocompromised patients	Approved indications
United States of America	Emergency Use Authorization (US Food and Drug Administration (FDA))	Approved: 20 October 2021 (EUA Amendment) for selected patients Approved: 19 November 2021 (EUA Amendment) for all individuals aged 18 years or older. Submitted: 1 September 2021	Approved: 12 August 2021 (EUA Amendment)	*Moderna COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.*
Switzerland	Temporary Marketing Approval (SwissMedic)	Approved: 26 November 2021 Submitted: 7 September 2021	Approved: 26 October 2021 Submitted: 7 September 2021	*Spikevax is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older.* *The use of this vaccine should be in accordance with official recommendations.*
European Union	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA)	Approved: 29 October 2021 (Type II variation application) Submitted: 3 September 2021	Approved: 5 October 2021 (Type II variation application) Submitted: 3 September 2021	*Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.* *The use of this vaccine should be in accordance with official recommendations.*

Region	Regulatory status	Status of booster applications	Status of use in immunocompromised patients	Approved indications
Israel	Exceptional Use Authorisation (Ministry of Health; MOH)	Submitted: 9 September 2021	Not yet submitted	*COVID-19 Vaccine Moderna is indicated 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.*
Canada	Notice of Compliance (Health Canada)	Approved: 12 November 2021 Submitted: 5 October 2021	Approved: 12 Nov 2021 Submitted: 5 Oct 2021	*SPIKEVAX (elasomeran mRNA vaccine) is indicated for active immunization against coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 12 years of age and older.*
United Kingdom	Conditional Marketing Authorisation (Medicines and Healthcare products Regulatory Agency; MHRA)	Submitted: 29 October 2021	Approved: 01 December 2021 Submitted 8 October 2021	*Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.* *The use of this vaccine should be in accordance with official recommendations.*

Product Information

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

II. Registration timeline

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

Table 2: Timeline for Submission PM-2021-05131-1-2

Description	Date
Designation (Provisional)	Not applicable
Submission dossier accepted and first round evaluation commenced	8 November 2021
First round evaluation completed	2 December 2021
Sponsor provides responses on questions raised in first round evaluation	18 November 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	19 November 2021
Sponsor's pre-Advisory Committee response	24 November 2021
Advisory Committee meeting	1 December 2021
Registration decision (Outcome)	7 December 2021
Completion of administrative activities and registration on the ARTG	9 December 2021
Number of working days from submission dossier acceptance to registration decision*	22

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

Quality

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

A full quality evaluation for Spikevax (elasomeran) was conducted for an earlier submission.[26]

[26] AusPAR for Spikevax (elasomeran) new biological entity, published on 9 August 2021. Available at: Australian public assessment report for Elasomeran (tga.gov.au)

Nonclinical

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

A full nonclinical evaluation for Spikevax (elasomeran) was conducted for an earlier submission.

Clinical

The clinical dossier consisted of the clinical study report for the following studies:

- Study mRNA-1273-P201 Part A and Part B (here after abbreviated as Study P201 Parts A and B);
- Study DMID 21-0012; and
- Study mRNA-1273-P301 Part A (here after abbreviated as Study P301 (Part A)

Efficacy

The sponsor's approach to demonstrate efficacy of a third 'booster' dose of 50 µg was to provide immunobridging data comparing responses one month after a booster dose (that is, Dose 3) to those 28 days following the 2-dose primary vaccination course.

Elasomeran is referred to as mRNA-1273 in this AusPAR.

Table 3: Clinical studies supporting the development of mRNA-1273 50 µg booster

Study	2-Dose Primary Series	Booster Dose (Dose 3)	Interval Between Dose 2 and 3	N	Status
P201 B	50 µg – mRNA-1273	50 µg – mRNA-1273	≥6 months	173	Data available through Day 29 post-boost
	100 µg – mRNA-1273	50 µg – mRNA-1273	≥6 months	171	
DMID 21-0012	Group 1E: Janssen (1 dose only)	100 µg – mRNA-1273	12-20 weeks	53	Safety data available through Day 7; Immunogenicity data available through Day 15
	Group 2E: 100 µg – mRNA-1273	100 µg – mRNA-1273	12-20 weeks	51	Safety data available through Day 7; Immunogenicity data available through Day 15
	Group 3E: Pfizer 30 µg	100 µg – mRNA-1273	12-20 weeks	50	Safety data available through Day 7; Immunogenicity data available through Day 15

DMID = Division of Microbiology and Infectious Diseases.

The focus of this efficacy evaluation is the safety and immunogenicity data following a 50 µg booster dose of mRNA-1273 administered to adults previously immunised with an authorised 2-dose primary series of 100 µg of mRNA-1273 in Study P201 Part A.[27]

The primary immunogenicity analysis also included Study P201 Part B participants who received a 50 µg mRNA-1273 booster dose after an unauthorised 2-dose 50 µg mRNA-1273 primary series. For the purposes of this submission, only the assessments of serious adverse events (SAE) and adverse events (AE) of interest in this group were

[27]mRNA-1273 refers to the vaccine development name for the Moderna Spikevax (elasomeran) COVID-19 vaccine

considered relevant (for example, myocarditis, pericarditis, neurologic, neuro-inflammatory and thrombotic events).

Additional supportive safety data were provided from an ongoing Phase I/II open-label trial (Study DMID 21-0012) conducted by the Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases(NIAID), and National Institute of Health (NIH) all in the USA. In this study immunogenicity was evaluated only following a 100µg booster dose and no comparison with a 50 µg booster was performed. Participants included those primed with heterologous vaccines. .In addition, the neutralising antibody response was not easily comparable with the results obtained on the 50 µg booster dose in Study P201 due to the different dose and different interval between primary and booster doses.

Study design

Two parts (A and B) of ongoing Phase II Study P201 pertain to the safety and immunogenicity of mRNA-1273 vaccine administered to adults 18 years of age and older. The study took place at 10 sites in the USA and its territories.

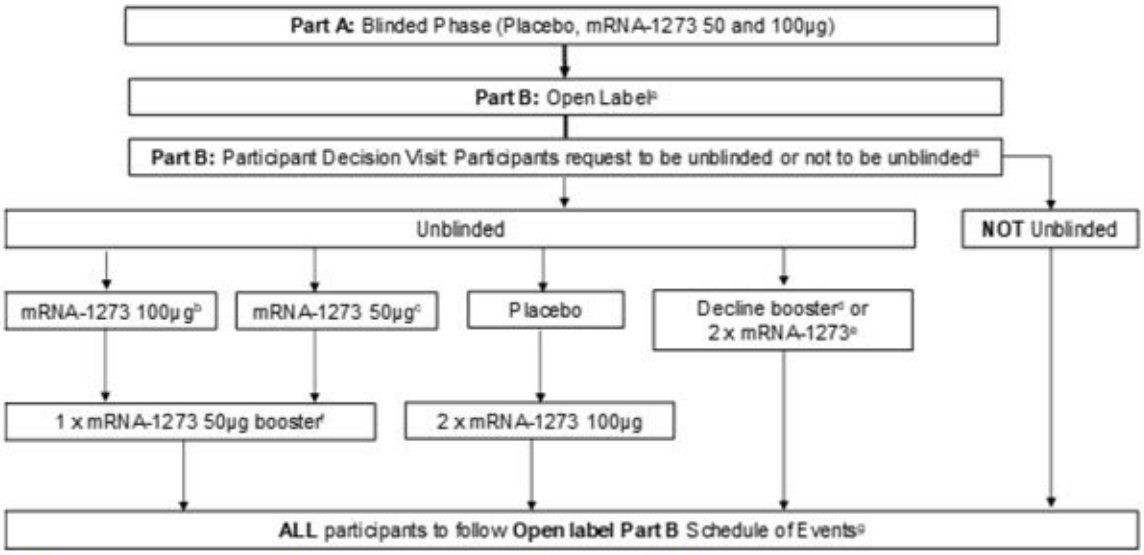
In Part A of the study participants in the 2 age cohorts received 50 µg, 100 µg of mRNA-1273, or placebo.

Table 4: Study P201 Part A Treatment cohorts, groups and investigational products

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Total			**600**

In Part B (Figure 1), the open-label interventional phase of the study, the safety and immunogenicity of a single 50 µg booster dose of mRNA-1273 was evaluated. In Part A of the study, participants who were randomised to receive the 50 µg or 100 µg mRNA-1273 vaccine were offered a single booster dose of mRNA-1273 (50 µg) at least 6 months after planned completion of the primary series. After booster dose administration in Part B (N=344), sera were collected on Days 1, 29, and 57 and at Month 6-7 to assess SARS-CoV-2 neutralising antibody titres (data are presently available to Day 29 only). Neutralising antibody titres (NAbs) titres were measured with an median infectious dose (ID_{50}) assay using a pseudovirus expressing the SARS-CoV-2 spike protein (Wild-type (WT) SARS-CoV-2); the pseudovirus neutralising assay (PsVNA) for the WT SARS-CoV-2 has been validated. Sera collected from all participants on Days 1 and 29 were also analysed using a pseudovirus neutralising antibody ID_{50} ($PsVNT_{50}$) assay for measuring antibodies against the SARS-CoV-2 B.1.617.2 variant virus (Delta variant). A pre-planned analysis for the booster dose at Day 29 was conducted (database lock date 10 June 2021).

Figure 1: Study P201 Part B Open label schema



[a] All participants will proceed to Part B, Open-Label Interventional Phase; begins with the Participant Decision Visit.
[b] Participants who received 2 injections of mRNA-1273 100 µg during Blinded Part A.
[c] Participants who received 2 injections of mRNA-1273 50 µg during Blinded Part A.
[d] Participants who received 2 injections of mRNA-1273 in Part A and decline booster injection in Part B.
[e] Participants who received placebo in Part A and decline 2 injections of mRNA-1273 in Part B.
[f] Participants who received 2 injections of mRNA-1273 (50 µg or 100 µg) in Part A will receive 1 booster injection of mRNA-1273 50 µg in Part B.

Objectives of the study (Part B) per study protocol

Primary immunogenicity objective

To evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 administered as 2 doses 28 days apart, as assessed by the level of specific binding antibodies (bAb).

Secondary immunogenicity objective

To evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 100 µg administered as 2 doses 28 days apart, as assessed by the titre of neutralising antibody (nAb).

Objectives per the statistical analysis plan

Against the WT SARS-CoV-2

Immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the WT SARS-CoV-2 was to be assessed by Study P201 Part B participants who received a single booster dose of 50 µg mRNA-1273. Immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the wild-type SARS-CoV-2 was to be assessed in Study P301 participants on mRNA-1273 100 µg, based on the same assays.

Against the variant virus strain (B.1.617.2)

Immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the variant virus stain (B.1.617.2) was assessed by Study P201 Part B participants who received a single booster dose of 50 µg mRNA-1273 based on the Duke assay against the variant virus stain (B.1.617.2, Delta). Immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the WT SARS-CoV-2 was assessed in Study P301 participants on mRNA-1273 100 µg, based on the Duke assay against the WT SARS-CoV-2. In addition, neutralising antibodies against the variant virus strain (B.1.617.2,

Delta) were measured at least 6 months after the completion of the 2 dose primary series of mRNA-1273 100 µg in StudyP301 participants.

Control group

Study P301 is an ongoing pivotal randomised, observer-blind, placebo-controlled study evaluating the safety, efficacy, and immunogenicity of a 2 dose primary series of 100 µg of mRNA-1273 in over 30,000 participants ≥ 18 years of age. Immunogenicity data from a random subset of Study P301 participants were used as the comparator group for immunobridging analyses to infer vaccine effectiveness of the booster dose. Data from Study P301 supported the provisional approval for the 2 dose primary series of the 100 µg dose of mRNA-1273. The final efficacy analysis of Part A of the Study (with median follow up of 5.3 months) demonstrated vaccine efficacy (VE) of 93.2% (95% confidence interval (CI): 91.0%, 94.8%, $p < 0.0001$), which was consistent with results of the interim and primary analyses.

Statistical analysis

Overall, the statistical methods are considered acceptable. Although selection bias and other sources cannot be completely ruled out, given the observed results between trials and the reported results within trial P201, this is not considered of high clinical relevance.

The analyses of non-inferiority were pre-specified, but the reporting of the immunogenicity objectives was a little unclear in the documentation. The statistical methods were only described in the SAP (not the protocol) which was drafted later (SAP Version 1.0: 04 June 2021; Version 2.0: 06 August 2021). This is acceptable in the context of the evolving nature of the pandemic situation and the requirement for adaptive trial designs, although it did make clinical evaluation difficult.

Booster dose co-primary immunogenicity endpoints against the wild type SARS-CoV-2

Co-primary Endpoint 1

Geometric mean of the neutralising antibody titres against the SARS-CoV-2 WT strain measured 28 days after a single 50 µg booster dose of mRNA-1273 in Study P201 Part B versus the corresponding responses measured 28 days after receipt of the second dose of the 50 or 100 µg mRNA-1273 2-dose primary series in Study P301. The pre-specified immunobridging success criteria required both a lower limit of the 95% confidence interval for the geometric mean titre (GMT) ratio (Study P201B/Study P301) ≥ 0.67 (1.5 fold immunobridging margin) and a GMT ratio point estimate ≥ 1.0.

Co-primary Endpoint 2

Seroresponse rate against the SARS-CoV-2 WT strain 28 days after a single 50 µg booster dose of mRNA-1273 in Study P201 Part B versus the corresponding responses 28 days after the second dose of the 50 or 100 µg mRNA-1273 2-dose primary series in Study P301. The pre-specified immunobridging criterion required a lower limit of the 95% confidence interval for the difference in seroresponse rates (Study P201B versus Study P301) ≥ 10%. Seroresponse was defined as ≥ 4 fold rise in neutralising antibody titres from baseline (pre-booster dose in Study P201 Part B and pre-dose 1 in Study P301), where baseline titres < lower limit of quantification (LLOQ) are set to LLOQ for the analysis.

Immune responses to a single booster dose of 50 µg mRNA-1273 would be considered successfully bridged (that is, non-inferior) to that of the 2 dose primary series of 100 µg of mRNA-1273 if each of the immunobridging criteria above were met.

Study disposition and baseline characteristics:

The safety and immunogenicity populations analysed in Studies P201 Parts A and B, and P301 are presented below in Table 5 and 6.

A total of 149 participants from the open-label phase of Study P201 Part B and 1,055 participants from a random sub-cohort of Study P301 were included in the per-protocol immunogenicity subset for the primary immunogenicity analyses. Reasons for exclusion from the Study P201 Part B per-protocol population included a major protocol violation involving incorrect dosing at the booster dose visit (receipt of a 100 µg booster dose instead of a 50 µg booster dose) and SARS-CoV-2 infection at baseline (which was an exclusion criterion for participation in Study P301); reasons for exclusion from the Study P301 per protocol population included human immunodeficiency virus (HIV) infection (an exclusion criterion for participation in Study P201) and error in the administration of the second primary series dose (not applicable to Study P201 Part B). Of note, one 100 µg primed booster dose participant who did not receive Dose 2 of the primary series was included in the per protocol population; participants were not required to receive both primary series doses to be included in the booster dose per protocol set. This participant received Dose 1 on 4 June 2020 and a 50 µg dose on 19 February 2021 (around 8 months after Dose 1).

Table 5: Study P301 (primary series) and Study 201 Part B (booster dose, open-label phase) Immunogenicity analysis populations, participants ≥ 18 years of age

Population	Study P301 100 µg Primary Series N[a]=15,184 n (%)	Study P201B 50 µg Booster After 100 µg Primary Series N[b]=171 n (%)
Full Analysis Set (FAS)[c]	NA	156 (91.2)
Subjects excluded from FAS	NA	15 (8.8)
Reason for exclusion from FAS		
No baseline immunogenicity data	NA	12 (7.0)
No post-baseline immunogenicity data	NA	3 (1.8)
Subjects Selected for Random Subcohort (Baseline SARS-CoV-2 Negative)	1,080	NA
Per-Protocol Set (PPS)[d]	1,055 (97.7)	149 (95.5)
Subjects excluded from PPS	25 (2.3)	7 (4.5)
Reason for exclusion from PPS		
SARS-CoV-2 infection at baseline	0 (0.0)	6 (3.8)
Had other major protocol deviation	1 (<0.1)	1 (0.6)[e]
Human Immunodeficiency Virus Infection	18 (1.7)	0 (0.0)
Received dose 2 out of window for PPS	5 (0.5)	NA
Did not receive dose 2 per schedule	1 (<0.1)	NA

The FAS is not applicable to Study P301. A subset of P301 subjects were selected for immunogenicity sample testing.
a. N=number of subjects that received any dose of mRNA-1273 in P301 are included.
b. N=number of subjects vaccinated. Only subjects who received the booster injection in Part B of study P201 are included and summarized under the vaccination groups which they actually received in Part A.
c. All subjects who received any booster injection in Part B and had immunogenicity data available at both baseline (Part B Day 1) and at least 1 post-booster visit.
d. All subjects in the Full Analysis Set who did not have SARS-CoV-2 infection (positive reverse transcription polymerase chain reaction [RT-PCR] result or positive Elecsys result) at baseline (Part B Day 1), did not have a major protocol deviation that impacted immune response, had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for booster injection and Day 57 for Study P301). Denominator is the number of subjects in Full Analysis Set for P201 Part B and the number of subjects in the Random Subcohort with a negative baseline SARS-CoV-2 status in P301.
e. One participant was incorrectly dosed at the booster dose visit (a 100 µg mRNA-1273 booster dose was administered instead of a 50 µg mRNA booster dose). One participant in this same group received only the first primary series dose and missed the Day 29 primary series dose; this participant was included in the per-protocol population for the booster dose analysis.

The disposition of Study P201 Part A and Study P301 participants who received a 2 dose primary series of mRNA-1273 is presented below in Table 6 (Safety population), and the disposition of Study P201 Part B participants who received a mRNA-1273 booster dose is presented in Table 7 (Safety population). There were no notable differences between the disposition of participants in Studies P201A and P301 or between the disposition of participants in each study group within Study P201 Part B.

Table 6: Study P201 Part A and Study P301 (primary series) Disposition of participants ≥ 18 years of age, Safety populations

Disposition	Study P201A 50 µg Primary Series N=200 n (%)	Study P201A 100 µg Primary Series N=200 n (%)	Study P301 100 µg Primary Series N=15209 n (%)
Number of subjects randomized	200 (100)	200 (100)	15209 (100)
Received first injection	200 (100)	200 (100)	15180 (99.8)
Received second injection	195 (97.5)	198 (99.0)	14727 (96.8)
Discontinued study vaccine	5 (2.5)	2 (1.0)	453 (3.0)
Reason for study vaccine discontinuation (in Part A for Study P201 and/or P301)			
P201 AE (COVID-19 infection)	1 (0.5)	0 (0.0)	NA
P201 AE (other)	1 (0.5)	1 (0.5)	NA
P301 AE	NA	NA	47 (0.3)
P301 SAE	NA	NA	12 (<0.1)
Death	0 (0.0)	0 (0.0)	2 (<0.1)
Lost to follow up	2 (1.0)	0 (0.0)	76 (0.5)
Physician decision	0 (0.0)	0 (0.0)	21 (0.1)
Pregnancy	0 (0.0)	0 (0.0)	3 (<0.1)
Protocol deviation	0 (0.0)	0 (0.0)	37 (0.2)
P201 withdrawal of consent (COVID-19 non-infection related)	1 (0.5)	0 (0.0)	NA
P301 withdrawal of consent	NA	NA	78 (0.5)
P301 due to SARS-CoV-2	NA	NA	81 (0.5)
Other	0	1 (0.5)	94 (0.6)
Discontinued participation in study	12 (6.0)	15 (7.5)	440 (2.9)
Reason for discontinuation of study participation			
P301 adverse AE	NA	NA	4 (<0.1)
P301 SAE	NA	NA	5 (<0.1)
Death	0 (0.0)	0 (0.0)	16 (0.1)
Lost to follow-up	6 (3.0)	6 (3.0)	160 (1.1)
Physician decision	1 (0.5)	2 (1.0)	13 (<0.1)
Protocol deviation	3 (1.5)	3 (1.5)	46 (0.3)
P201 withdrawal of consent (COVID-19 non-infection related)	1 (0.5)	0 (0.0)	NA
P201 withdrawal of consent (other)	1 (0.5)	4 (2.0)	NA
P301 withdrawal of consent	NA	NA	155 (1.0)
Other	0 (0.0)	0 (0.0)	41 (0.3)
Completed Part A	188 (94.0)	185 (92.5)	NA

Abbreviations: AE= Adverse event; SAE=Serious adverse event; COVID-19 = coronavirus disease 2019; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Percentages are based on the number of safety subjects in Part A. Only subjects who received mRNA-1273 in Part A are included and are summarized under the vaccination groups which they actually received in Part A.
Safety Set in Part A included all randomized participants who received any mRNA-1273 primary series during Part A.

Table 7: Study P201 Part B Disposition of participants ≥18 years of age (by primary series dose), Safety populations

Disposition	Study P201B 50 µg Booster After 50 µg Primary Series N=200 n (%)	Study P201B 50 µg Booster After 100 µg Primary Series N=200 n (%)	Total N=400 n (%)
Completed Study P201 Part A	188 (94.0)	185 (92.5)	373 (93.3)
Consented to Study P201 Part B	188 (94.0)	185 (92.5)	373 (93.3)
Received Booster Injection[a]	173 (86.5)	171 (85.5)	344 (86.0)
Discontinued from Study in Part B	9 (4.5)	6 (3.0)	15 (3.8)
Reason for Discontinuation of Study in Part B			
Lost to follow up	3 (1.5)	2 (1.0)	5 (1.3)
Withdrawal of Consent (Other)	5 (2.5)	3 (1.5)	8 (2.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Completed Study P201 Part B[b]	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on the number of safety subjects in Part A. Only subjects who received mRNA-1273 in Part A are included and are summarized under the vaccination groups which they actually received in Part A

a. Includes one participant in the 100 µg-primed group that only received the 1st primary series dose and one participant in the 100 µg-primed group who received a third 100 µg dose instead of a 50 µg booster.

b. Study completion defined as a subject who completed 6 months of follow-up after the last injection received in Part B (Open-Label Phase).

Demographic and baseline characteristics of the safety population for Studies P201 (Parts A and B) and Study P301 and the per-protocol immunogenicity subsets for Study P201 Part B and Study P301 are shown in Tables 8 and 9, respectively. Compared to Study P301, participants in Study P201 Part A and Study P201 Part B were less racially and ethnically diverse. Study P201 Part A and Study P201 Part B participants also had a lower median body mass index (BMI), a lower rate of obesity (BMI ≥ 30 kg/m^2), and a lower percentage of males compared to Study P301 participants. Studies P201A, P201B and P301 had a similar median participant age and a similar proportion of participants ≥65 years of age. The noted differences in demographic characteristics between Study P201 Part B and Study P301 participants are considered unlikely to impact the clinical results from the safety and primary immunobridging analyses. The subgroup analyses of mRNA-1273 vaccine's safety and efficacy by sex, race and ethnicity in Study P301 supported consistency in vaccine efficacy estimates across subgroups.

Individuals with a history of chronic cardiovascular disease, chronic pulmonary disease, positive serology for human immunodeficiency virus (Type 1 or 2), diabetes, and history of hypertension were excluded from participating in Study P201 Parts A and B. In Study P301 however, 22.1% of participants were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection).

The noted differences in pre-existing medical conditions between Study P201 and Study P301 populations are considered unlikely to impact the conclusions of the primary analyses. Based on Study P301 subgroup efficacy analyses conducted under the original provisional approval;[28] there were no clear differences in vaccine efficacy estimates between Study P301 participants with a pre-existing condition (that is, chronic lung disease, significant cardiac disease, severe obesity (BMI ≥ 40 kg/m^2), diabetes, liver disease and HIV infection) and the overall Study P301 per protocol population.

[28] Spikevax (elasomeran) AusPAR https://www.tga.gov.au/auspar/auspar-elasomeran

Table 8: Study P201 Part B Demographic and baseline characteristics, (booster; by primary series dose) and comparator groups (primary series only), safety population

Characteristic	Study P301 100 µg Primary Series N=15,184	Study P201A Primary Series[a] Total N=200	Study P201B 50 µg Booster After 50 µg Primary Series N=173	Study P201B 50 µg Booster After 100 µg Primary Series N=171
Age[b] (Years)				
Median (Min, Max)	53.0 (18, 95)	54.5 (18, 87)	56.0 (18, 87)	55.0 (18, 87)
Age Group, n (%)				
≥18 and <65 years old	11415 (75.2)	157 (78.5)	127 (73.4)	133 (77.8)
≥65 years old	3769 (24.8)	43 (21.5)	46 (26.6)	38 (22.2)
Sex, n (%)				
Female	7266 (47.9)	124 (62.0)	124 (71.7)	104 (60.8)
Male	7918 (52.1)	76 (38.0)	49 (28.3)	67 (39.2)
Race, n (%)				
White	12034 (79.3)	188 (94.0)	164 (94.8)	164 (95.9)
Black or African American	1567 (10.3)	8 (4.0)	3 (1.7)	5 (2.9)
Asian	656 (4.3)	2 (1.0)	2 (1.2)	1 (0.6)
American Indian or Alaska Native	113 (0.7)	1 (0.5)	1 (0.6)	1 (0.6)
Native Hawaiian or Other Pacific Islander	36 (0.2)	0	1 (0.6)	0
Multiple	320 (2.1)	0	1 (0.6)	0
Other	299 (2.0)	1 (0.5)	1 (0.6)	0
Not Reported	97 (0.6)	0	0	0
Unknown	62 (0.4)	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	3122 (20.6)	16 (8.0)	10 (5.8)	10 (5.8)
Not Hispanic or Latino	11920 (78.5)	184 (92.0)	162 (93.6)	161 (94.2)
Not Reported	105 (0.7)	0	1 (0.6)	0
Unknown	37 (0.2)	0	0	0
Body Mass Index (kg/m^2)				
Median	28.13	25.24	26.12	25.59
Positive Baseline SARS-CoV-2 Status[c]	347 (2.3)	0	4 (2.3)	6 (3.5)
Comorbidities				
Obesity (≥30.0 kg/m^2)	5820 (38.3)	1 (0.5)[d]	17 (9.8)	17 (9.8)

a. Combined total of 50 µg mRNA-1273 primary series participants and 100 µg mRNA-1273 primary series participants.
b. For Study P201, age is defined at the time of screening for P201 Part A.
c. Participants who had immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 in Study P201 Part B or Day 1 in Study P301.
d. The difference in rates of obesity in study P201A vs P201B are explained by 14 subjects whose BMI changed from <30 kg/m^2 (i.e., 27.5 - 29.9) to ≥30 kg/m^2 (i.e., 30.1 - 32.3) during the time period between Part A and Part B of Study P201 and 2 subjects who appear to have an implausible weight or height recorded at P201B, leading to a BMI above 30 kg/m^2, but this could not be verified.

Table 9: Study P201 Part B (by primary series dose) and Study P301 comparator group (primary series only) Demographic and baseline characteristics, mRNA-1273 booster dose recipients, per-protocol immunogenicity subset

Characteristic	Study P301 100 µg Primary Series N=1055	Study P201B 50 µg Booster After 50 µg Primary Series N=146	Study P201B 50 µg Booster After 100 µg Primary Series N=149
Age (Years)			
n	1055	146	149
Mean (SD)	54.51 (15.329)	52.85 (15.334)	52.69 (15.058)
Median	57	57.00	56.00
Min, Max	18.0, 87.0	19.0, 87.0	18.0, 82.0
Age Group			
≥18 and <65 years old	700 (66.4)	107 (73.3)	112 (75.2)
≥65 years old	355 (33.6)	39 (26.7)	37 (24.8)
Sex, n (%)			
Male	560 (53.1)	44 (30.1)	59 (39.6)
Female	495 (46.9)	102 (69.9)	90 (60.4)
Race, n (%)			
White	767 (72.7)	139 (95.2)	142 (95.3)
Black or African American	188 (17.8)	2 (1.4)	5 (3.4)
Asian	26 (2.5)	2 (1.4)	1 (0.7)
American Indian or Alaska Native	17 (1.6)	1 (0.7)	1 (0.7)
Native Hawaiian or Other Pacific Islander	5 (0.5)	1 (0.7)	0
Multiple	15 (1.4)	1 (0.7)	0
Other	27 (2.6)	0	0
Not Reported	5 (0.5)	0	0
Unknown	5 (0.5)	0	0
Ethnicity, n (%)			
Hispanic or Latino	334 (31.7)	10 (6.8)	10 (6.7)
Not Hispanic or Latino	717 (68.0)	135 (92.5)	139 (93.3)
Not Reported	2 (0.2)	1 (0.7)	0
Unknown	2 (0.2)	0	0
Body Mass Index (kg/m^2)			
n	1050	143	147
Mean (SD)	30.96 (7.758)	25.84 (3.253)	25.47 (3.168)
Median	29.62	26.17	25.74
Min, Max	14.0, 79.2	18.3, 34.9	18.0, 32.7
Comorbidities			
Obesity (≥30.0 kg/m^2)	500 (47.2)	16 (11)	14 (9.4)

Percentages are based on the number of Per-Protocol Immunogenicity Subset subjects.
For Study P201, age is defined at the time of screening for P201 Part A.

Results

Among participants previously receiving 2 doses of 100 µg mRNA-1273, the 50 µg booster led to an increase in baseline titres, geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29). Among participants previously receiving 2 doses of 50 µg of mRNA-1273, the 50 µg booster led to a similar increase in titre GMT, with GMFR of 17.53 (95% CI: 14.94, 20.56), although the pre-booster GMT was slightly lower numerically. In both prime series groups combined, the GMFR is 15.06 at Day 29. Table 10 summarises serum nAb (PsVNA ID_{50}, WT) titres 28 days after the 50 µg booster in Study P201 Part B.

Table 10: Study 201 Part B Summary of pseudovirus neutralising antibody 50% inhibitory dose titres after 50 µg booster injection (by prime series groups)

	mRNA-1273		
	50 µg Primary Series + 50 µg Booster N=146 n (%)	100 µg Primary Series + 50 µg Booster N=149 n (%)	50 µg Booster Total N=295 n (%)
Baseline (OL-Day 1; pre-booster), n[a]	145	149	294
GMT	104.658	150.224	125.696
95% CI[b]	88.282, 124.070	125.726, 179.495	111.011, 142.325
OL-Day 29, n[c]	146	149	295
GMT	1834.309	1951.735	1892.708
95% CI[b]	1600.233, 2102.623	1729.606, 2202.392	1728.800, 2072.157
N1	145	149	294
GMFR	17.53	12.99	15.06
95% CI[b]	14.94, 20.56	11.04, 15.29	13.43, 16.89

Abbreviations: nAb = neutralizing antibody. GMT = geometric mean titer; GMFR = geometric mean fold rise (post-baseline vs. baseline titers); CI = confidence interval; LLOQ = lower limit of quantification; OL = Open-Label; N1 = Number of subjects with nonmissing data at baseline and the corresponding visit; ULOQ = upper limit of quantification.

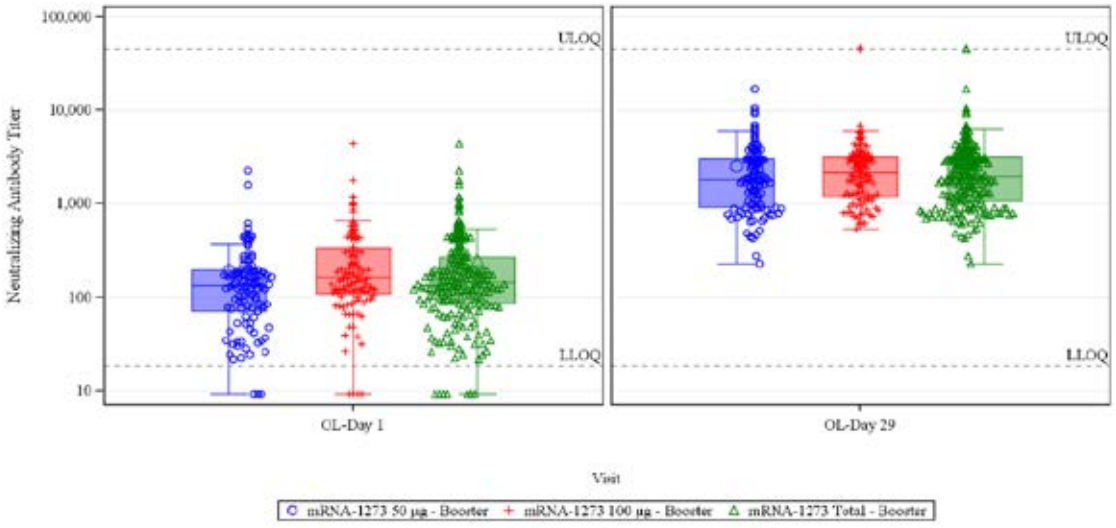
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values that are greater than the ULOQ are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with nonmissing data at baseline and the corresponding visit (N1).

[a] Number of subjects with nonmissing 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 GMT and GMFR, respectively, then back-transformed to the original scale for presentation.

[c] Number of subjects in the Per-Protocol Set with nonmissing data at the corresponding visit.

Figure 2: Study 201 Part B Box plot of pseudovirus neutralising antibody 50% inhibitory dose titres, Per-protocol set



Abbreviations: LLOQ = lower limit of quantification. ULOQ = upper limit of quantification. OL=Open-Label. LLOQ: 18.5, ULOQ: 45118

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

Subgroup analysis following stratification of the nAb response according to age groups and primary immunisation series is shown in Table 11. Generally, higher nAb responses (GMTs) are seen in the 18 to 55 years age group compared to the age group of the 55 years and older pre- and post-booster; however, a higher GMR is observed in subjects 55 years

and older. No further subgroup analysis stratified according to other age groups (18 years and older up to and including 64 year olds or older; and those who were65 years old and above) and primary series were provided with this submission.

Table 11: Study 201 Subgroup analysis stratified according to age group and priming group

	Age ≥ 18 to < 55 Years		Age ≥ 55 Years		Overall	
	50 µg Primary Series + 50 µg Booster N=63	100 µg Primary Series + 50 µg Booster N=68	50 µg Primary Series + 50 µg Booster N=83	100 µg Primary Series + 50 µg Booster N=81	≥18-<55 years N=131	≥55 years N=164
Baseline						
n	62	68	83	81	130	164
GMT	142.389	172.685	83.156	133.640	157.507	105.113
95% CI	110.899, 182.819	136.022, 219.231	65.582, 105.440	105.089, 169.947	132.519, 187.206	88.474, 124.882
28 Days after Booster						
n	63	68	83	81	131	164
GMT	2024.609	2001.294	1910.607	1699.914	2012.380	1803.469
95% CI	1709.910, 2397.227	1703.216, 2351.538	1629.225, 2240.586	1446.665, 1997.496	1792.123, 2259.707	1612.330, 2017.267
GMR	12.85	12.71	18.18	16.17	12.78	17.16
95% CI	10.86, 15.22	10.81, 14.93	15.50, 21.32	13.76, 19.00	11.38, 14.35	15.34, 19.19

Neutralising antibody response against the Delta variant pre and post Dose 3

The nAbs response of all participants in Study 201 Part B was determined by a validated assay using a pseudovirus based on the B.1.617.2 (Delta) variant. Serum samples were obtained from participants in Study P201 Part B (at least 6 months after receiving two primary doses of either 50 or 100 µg of mRNA-1273) pre-booster and on Day 29 post booster. Results of the Pseudovirus nAb assay against the Delta variant (B.1.617.2) are presented in Table 12.

Administration of the mRNA-1273 booster (50 µg) induced an 18 fold-rise in neutralising titres against the Delta variant compared to pre-booster levels in all participants combined (GMFR=18.97; 95% CI, 16.72, 21.53; overall group, n=295). In the overall Study P201 Part B group (previously primed with 2 doses of either 50 or 100 µg mRNA-1273, n=293), the pre-booster nAb GMT (for the Delta variant) was 42.27 (95% CI, 37.19, 48.04; n=293) and 28 days post-booster the GMT was 803.51 (95% CI, 731.42, 882.70; n=295). Over 90% of booster recipients in the overall group (92.2%; 95% CI, 88.5-95.0%; n=293) met the definition of a sero response for the Delta variant (using a four-fold increase from pre-booster baseline).

Administration of the 50 µg mRNA-1273 prototype booster resulted in substantial increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI, 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI, 14.38, 20.77). Numerically slightly lower GMTs pre and post Dose 3 were reported in the 50 µg priming group compared to the 100 µg priming group.

Table 12: Study 201 Part B Summary of pseudovirus neutralising antibody 50% inhibitory titres against new variant strain (B.1.617.2, Delta) per-protocol immunogenicity subset

Timepoint Statistic	P201 Part B 50 µg booster after 50 µg priming N=146	P201 Part B 50 µg booster after 100 µg priming N=149	P201 Part B Overall N=295
Pre-Booster			
n[1]	144	149	293
GMT	37.14	47.89	42.27
95% CI[2]	31.25, 44.15	39.68, 57.79	37.19, 48.04
Median	35.40	38.81	36.87
Min, Max	9.3, 818.3	9.3, 2730.5	9.3, 2730.5
28 Days After Boost Dose			
n[3]	146	149	295
GMT	779.48	827.77	803.51
95% CI[2]	670.05, 906.78	738.48, 927.86	731.42, 882.70
Median	819.12	792.27	801.12
Min, Max	43.5, 9720.8	124.2, 5587.5	43.5, 9720.8
GMFR	20.89	17.28	18.97
95% CI[2]	17.54, 24.87	14.38, 20.77	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	144	149	293
n (%)	137 (95.1)	133 (89.3)	270 (92.2)
95% CI[5]	90.2, 98.0	83.1, 93.7	88.5, 95.0

Abbreviations: CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and
the corresponding visit; nAb = Neutralizing antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification
(ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline
and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back
transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.

4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4×LLOQ, or a 4-times or higher ratio in
participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method. Source: P201 Part B: Table 7.4

Additional analyses of Delta variant nAb GMT by age group based on all subjects included in the per protocol set are provided in Table 11 and 12. nAb responses in older adults, defined either as ≥65 or ≥55 or years, are numerically similar to those observed in the younger groups (Table 13 and Table 14; 749.94 versus 822.98 and 758.68 versus 863.39, respectively). No analyses according to primary vaccination series and age group were submitted.

Table 13: Study 201 Summary of pseudovirus neutralising antibody 50% inhibitory titres against new variant strain (B.1.617.2); by age group (≥ 18 and < 65 years old versus ≥65 years old) per-protocol immunogenicity subset

Timepoint Statistic	P201 Part B 50 µg mRNA-1273 Booster		
	≥18 and <65 years N=219	≥ 65 years N=76	Overall N=295
Pre-Booster			
n[1]	218	75	293
GMT	47.20	30.67	42.27
95% CI[2]	40.64, 54.81	24.20, 38.88	37.19, 48.04
Median	39.57	28.39	36.87
Min, Max	9.3, 2730.5	9.3, 204.3	9.3, 2730.5
28 Days After Boost Dose			
n[3]	219	76	295
GMT	822.98	749.94	803.51
95% CI[2]	743.49, 910.97	600.87, 935.99	731.42, 882.70
Median	829.23	690.44	801.12
Min, Max	43.5, 5587.5	76.8, 9720.8	43.5, 9720.8
GMFR	17.38	24.45	18.97
95% CI[2]	14.98, 20.18	19.33, 30.92	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	218	75	293
n (%)	197 (90.4)	73 (97.3)	270 (92.2)
95% CI[5]	85.7, 93.9	90.7, 99.7	88.5, 95.0

CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and the corresponding visit; nAb = Neutralizing antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method. Source: P201 Part B: Table 7.5.

Table 14: Study 201 Summary of pseudovirus neutralising antibody 50% inhibitory concentration titres against new variant strain (B.1.617.2) by age group (≥ 18 and < 55 years old versus ≥ 55 years old) per-protocol immunogenicity subset

n[1]	130	163	293
GMT	52.68	35.46	42.27
95% CI[2]	43.07, 64.44	30.17, 41.67	37.19, 48.04
Median	43.51	33.61	36.87
Min, Max	9.3, 2730.5	9.3, 609.8	9.3, 2730.5
28 Days After Boost Dose			
n[3]	131	164	295
GMT	863.39	758.68	803.51
95% CI[2]	760.91, 979.66	662.07, 869.38	731.42, 882.70
Median	850.98	775.81	801.12
Min, Max	116.0, 4656.8	43.5, 9720.8	43.5, 9720.8
GMFR	16.31	21.40	18.97
95% CI[2]	13.28, 20.05	18.29, 25.03	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	130	163	293
n (%)	117 (90.0)	153 (93.9)	270 (92.2)
95% CI[5]	83.5, 94.6	89.0, 97.0	88.5, 95.0

CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and the corresponding visit; nAb = Neutralizing antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method. Source: P201 Part B: Table 7.6.

Non-inferiority analysis to compare the immunogenicity results in Study P201 post Dose 3 (booster) to the results in efficacy Study P301 post Dose 2 after the primary series

Geometric mean ratio as assessed by pseudovirus neutralising antibody 50% inhibitory titres

The primary analysis population for this coprimary endpoint (in Study P201 Part B) included all per protocol participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (that is, all participants combined regardless of whether they received 50 µg or 100 µg of mRNA-1273 in the primary series).

In comparison to the peak PsVNA ID_{50} titres in Study P301 Part A (Day 57, 28 days post Dose 2), where efficacy was demonstrated, the GMR (Study P201 Part B Day 29 versus Study P301 Day 57, against the original virus strain) was 1.71 (95% CI: 1.519, 1.929) (Table 15). The GMR estimate was 1.71 (above the prespecified threshold of 1.0), with the lower bound of the 95% CI greater than 0.67 (corresponding to noninferiority margin (NIM)=1.5). Hence, this GMR successfully met the prespecified NI criterion. A consistent trend to that observed from the analysis described above, with the 2 prime series groups combined, was also observed in the subgroup analysis (by prime series) (Table 16). The above suggests that the 50 µg booster increases nAb responses regardless of the dose (50 µg versus 100 µg) received in the primary series.

Table 15: Analysis of pseudovirus neutralising antibody 50% inhibitory concentration: mRNA-1273 post-Dose 3 (all subjects) compared with the Study P301 primary series peak titres (per-protocol (PP) immunogenicity set)

	P201 Part B 50 µg mRNA-1273 Booster	P301 mRNA-1273 100 µg Primary Series
	28 Days After Booster (P201 Part B) or Completion of Primary Series	
n	295	1053
GLSM	1767.936	1032.698
95% CI	(1586.445, 1970.189)	(974.207, 1094.701)
GMR (P201 Part B vs. P301; model-based)	1.712	
95% CI	(1.519, 1.929)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GLSM = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
n= number of subjects with nonmissing data at the corresponding timepoint

Table 16: Analysis of pseudovirus neutralising antibody 50% inhibitory concentration: mRNA-1273 post-booster compared with the Study P301 Primary series peak titres, by primary series groups (per-protocol (PP) immunogenicity set)

	P201 Part B 50 µg mRNA-1273 Booster After 50 µg Primary Series N=146	P301 mRNA-1273 100 µg Primary Series N=1055	P201 Part B 50 µg mRNA-1273 Booster After 100 µg Primary Series N=149	P301 mRNA-1273 100 µg Primary Series N=1055
28 Days after Booster (P201 Part B) or Completion of Primary Series				
n	146	1053	149	1053
GLSM	1716.185	1031.948	1802.426	1026.854
95% CI	(1469.496, 2004.286)	(971.974, 1095.622)	(1548.020, 2098.643)	(967.880, 1089.420)
GMR (P201 Part B vs. P301; model-based)	1.66		1.76	
95% CI	(1.412, 1.958)		(1.496, 2.060)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GLSM = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
Separate ANCOVA modes were used for P201 50 µg priming + 50 µg booster (group variables: P201 50 µg priming, and P301) and P201 100 µg priming + 50 µg booster (group variables: P201 100 µg priming, and P301).

Seroresponse rates as assessed by pseudovirus neutralising antibody 50% inhibitory concentration titres

The calculated seroresponse rates (SRR) difference (for PsVNA ID_{50} titres) between Study P201 Part B Day 29 post booster and Study P301 Part A Day 57 was assessed. This analysis was performed using 2 definitions of SRR: (i) an assay-specific definition (3.3 fold rise) proposed by the sponsor, and (ii) a 4 fold rise definition as a more conservative approach. The primary analysis used the 4 fold definition (ii).

Using the assay-specific definition (3.3 fold rise), the calculated difference in SRR between Study P201 Part B Day 29 post-boost and Study P301 Part A Day 57 is -5.3% (95% CI: -8.8%, -2.9%) (Table 17). The lower bound of the 95% CI is -8.8%, meeting the prespecified success criterion of a NIM of 10%.

Using the 4 fold rise definition, the calculated difference in SRR between Study P201 Part B Day 29 post-boost and Study P301 Part A Day 57 is -8.2% (95% CI: -12.2%, -5.2%) (Table 17). The lower bound of the 95% CI is less than -10% (the prespecified NIM of 10%).

In general, the subgroup analysis (by prime series) and the SAP specified sensitivity analysis yielded similar results in confirming that the NIM of -10% was not met.

Table 17: Analysis of seroresponse rates by pseudovirus neutralising antibody 50% inhibitory concentration assay: mRNA-1273 post-booster compared with the Study P301 Primary series peak titres, by prime series groups (per-protocol (PP) immunogenicity set)

Statistic	SRR per Assay-Specific Definition [a]		SRR per 4-Fold Definition [b]	
	P201 Part B 50 µg mRNA-1273 Booster (N=295)	P301 mRNA-1273 100 µg Primary Series (N=1055)	P201 Part B 50 µg mRNA-1273 Booster (N=295)	P301 mRNA-1273 100 µg Primary Series (N=1055)
N1	294	1050	294	1050
Participants achieving seroresponse, n (seroresponse rate %)	275 /294 (93.5)	1038 /1050 (98.9)	265 (90.1)	1033 (98.4)
95% CI [c]	90.1, 96.1	98.0, 99.4	86.1, 93.3	97.4, 99.1
Difference in seroresponse rate (P201 Part B vs. P301) (%)	-5.3		-8.2	
95% CI [d]	-8.8, -2.9		-12.2, -5.2	

Abbreviations: CI = confidence interval; ID50 = 50% inhibitory dilution; LLOQ = lower limit of quantification.
N1 = Number of subjects with nonmissing data at both post-baseline timepoint of interest and baseline.
[a] Seroresponse specific to PsVNA ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
[b] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
[c] 95% CI is calculated using the Clopper-Pearson method.
[d] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Table 18: Analysis of seroresponse based on pseudovirus neutralising antibody titres by priming groups and 4 fold definition of the seroresponse (per-protocol immunogenicity subset) antibody: pseudovirus neutralising antibody 50% inhibitory titres

Statistic	P201 Part B 50 µg mRNA-1273 booster after 50 µg priming		P201 Part B 50 µg mRNA-1273 booster after 100 µg priming		Overall	
	P201 Part B 50 µg mRNA-1273 booster (N=146)	P301 mRNA-1273 100 µg primary series (N=1055)	P201 Part B 50 µg mRNA-1273 booster (N=129)	P301 mRNA-1273 100 µg primary series (N=1055)	P201 Part B 50 µg mRNA-1273 booster (N=275)	P301 mRNA-1273 100 µg primary series (N=1055)
N1	145	1050	129	1050	274	1050
Participants achieving seroresponse, n (Seroresponse Rate %) [1]	134 (92.4)	1033 (98.4)	113 (87.6)	1033 (98.4)	247 (90.1)	1033 (98.4)
95% CI [2]	86.8, 96.2	97.4, 99.1	80.6, 92.7	97.4, 99.1	86.0, 93.4	97.4, 99.1
Difference in seroresponse rate(P201 Part B vs. P301) (%)	-6.0		-10.8		-8.2	
95% CI [3]	-11.5, -2.5		-17.6, -6.1		-12.4, -5.1	

The upper limit of quantification (ULOQ) for selected P301 participants tested previously was different.
CI = Confidence interval.
N1 = Number of subjects with non-missing data at both post-baseline timepoint of interest and baseline.
Percentages are based on N1.
[1] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
[2] 95% CI is calculated using the Clopper-Pearson method.
[3] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

In summary, effectiveness of the booster dose against the WT SARS-CoV-2 is being inferred based on immunobridging to the 2 dose primary series, as assessed by SARS-CoV-2 neutralising antibody titres elicited by the vaccine. Immunobridging analyses against the WT SARS-CoV-2 met the pre-specified success criteria for the GMT ratio (Study P201 Part B/Study P301). The pre-specified success criterion for the difference in seroresponse rates after the booster dose compared to after Dose 2, was not met. The lower limit of the 95% CI for the difference in seroresponse rate (Study P201 Part B booster dose – Study P301 primary series) was <-10% (-16.7%). In post-hoc analyses, participants with lower pre-booster neutralising antibody titres were more likely to achieve a 4 fold rise in neutralising antibody titres after booster vaccination compared to participants with higher pre-booster neutralising antibody titres.

According to the SAP, both criteria on GMR and seroresponse needed to be demonstrated to conclude on non-inferiority of the booster dose in comparison to the primary vaccination series. No sequence of immunogenicity endpoints was defined in the SAP and the protocol considered the assessment of bAb levels as primary objective followed by the assessment of nAb levels. Non-inferiority was met for all assays based on the GMR. Non-inferiority was not formally met for the enzyme-linked immunosorbent (ELISA) assay and PsVNA ID_{50} in the 100 µg prime cohort, which is of primary interest. As especially the nAbs and the increase in antibody titres is considered of primary relevance for the assessment of the immunogenicity of the booster dose, the failure to prove non-inferiority in seroresponse after the booster dose in comparison to the primary vaccination series is not considered of critical importance. Possible explanation of lower SRR following a third dose can be explained by residual higher levels of nAbs pre booster in Study P201 and by the fact that the response rates following a booster dose were compared to peak levels after the primary series in Study P301. It should be noted that two different study populations were compared and the nAb levels reported in these populations post Dose 2 (GMT: Study P201 approximately with 1200 versus Study P301 with approxumately1000) differ.

Additionally, the sponsor proposes to infer effectiveness of the booster dose against the Delta variant from exploratory descriptive analyses of neutralising antibody titres against this variant evaluated among booster dose recipients from Study P201 Part B.

In conclusion, a booster dose of 50 µg dose administered 6 to 8 months after the primary vaccination series was shown to elevate the neutralising antibody responses significantly. The antibody levels determined 28 days post Dose 3 were higher when compared to peak antibody levels 28 days post Dose 2.

Safety

Safety analyses presented in this review are derived from:

- Summary of solicited adverse reactions (AR) and unsolicited AEs up to study Day 29 for Study P201 Part B. For Study P201 Part B, results are provided for recipients of (i) 100 µg Prime + 50 µg Boost and (ii) 50 µg Prime + 50 µg Boost; and (iii) the combined '50 + 100 µg' Prime + 50 µg Boost.
- Solicited ARs (post Dose 2) and unsolicited AEs for 28 days post any dose from Study P201 Part A (100 µg prime series group) and Study P301 Part A;
- Summaries of solicited AR and unsolicited AE (up to study Day 7) for the supportive study, DMID Study 21-0012.
- Updated listings of cumulative unsolicited AEs, SAEs, and medically-attended adverse events (MAAE) from participants who received a single booster dose in Study P201 Part B, generated from a live ongoing database (data subject to further cleaning; data snapshot date 16 August 2021).

Summary of solicited local adverse reactions

The following local ARs were evaluated in each study within 7 days after injection: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localised axillary swelling or tenderness ipsilateral to the injection arm.

The most common solicited AR after the 50 µg booster dose was pain (Table 19). Most solicited local ARs were Grade 1 to Grade 2 in severity. Pain was the most commonly reported Grade 3 local AR in Study P201 Part B. No Grade 4 solicited local ARs were reported in either primary series group in Study P201. Local ARs were transient, and most resolved by Day 4. The frequency and severity of solicited local ARs was numerically comparable between age cohorts (18 to < 55; ≥ 55 years of age).

The frequencies of reported solicited local ARs were comparable between booster doses both primarily vaccinated with 50 µg or 100 µg of Spikevax and comparable to the safety profile of primary vaccination schedules in Study P201 Part A as well as to the safety profile of the primary vaccination schedule in the pivotal Study P301. No safety data were provided for children aged 12 to 17 years. The frequencies of reported solicited local reactions were comparable between both age strata (18 to < 55; ≥ 55 years of age).

Summary of solicited systemic adverse reactions

The following systemic ARs were evaluated in each study: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, fever, and chills.

Rash was a solicited systemic AR in Study P201 only; therefore, no comparison between Study P201 and Study P301 can be made (Table 20).

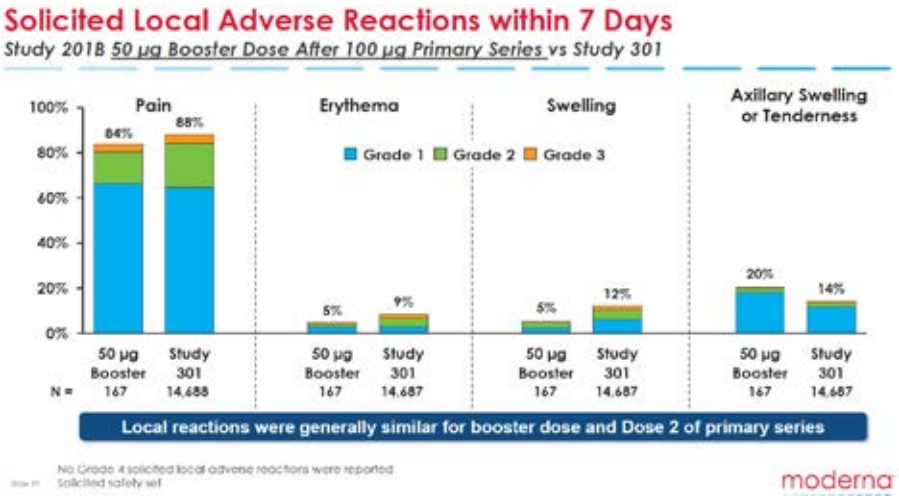
The frequencies of reported solicited systemic ARs were comparable for booster doses given to subjects after primary vaccination with either 50 µg or 100 µg of Spikevax and comparable to the safety profiles of primary vaccination schedules in Study P201 Part A as well as to the safety profile of the primary vaccination schedule in the pivotal Study P301. Reported frequencies of solicited systemic reactions were comparable between both age strata. The sponsor has applied for a booster indication for adolescents and adults aged 12 years and above. No data of solicited systemic ARs were provided by the sponsor for the age group of adolescents aged 12 to 17 years after a booster dose. Both age strata (18 to < 55; ≥ 55 years of age) took medication in comparable amounts to prevent pain around 8% and to prevent fever around 45%.

Table 19: Studies 201 and 301 Solicited local adverse reactions

	mRNA-1273				
	P201 50 µg Prime + 50 µg Booster N=163 n(%)	P201 100 µg Prime + 50 µg Booster N=167 n (%)	P201 Part B 50 µg Booster Total (N=330) n (%)	P201 Part A 100 µg N=198 n (%)	P301 100 µg N= 14691 n (%)
Pain, N1	162	167	329	198	14688
Any	144 (88.9)	140 (83.8)	284 (86.3)	169 (85.4)	12964 (88.3)
Grade 1	111 (68.5)	111 (66.5)	222 (67.5)	140 (70.7)	9508 (64.7)
Grade 2	26 (16.0)	23 (13.8)	49 (14.9)	28 (14.1)	2850 (19.4)
Grade 3	7 (4.3)	6 (3.6)	13 (4.0)	1 (0.5)	606 (4.1)
Erythema (Redness), N1	162	167	329	198	14687
Any	10 (6.2)	8 (4.8)	18 (5.5)	15 (7.6)	1274 (8.7)
Grade 1	4 (2.5)	5 (3.0)	9 (2.7)	7 (3.5)	456 (3.1)
Grade 2	4 (2.5)	2 (1.2)	6 (1.8)	3 (1.5)	531 (3.6)
Grade 3	2 (1.2)	1 (0.6)	3 (0.9)	5 (2.5)	287 (2.0)
Swelling (Hardness), N1	162	167	329	198	14687
Any	12 (7.4)	9 (5.4)	21 (6.4)	21 (10.6)	1807 (12.3)
Grade 1	4 (2.5)	4 (2.4)	8 (2.4)	14 (7.1)	900 (6.1)
Grade 2	7 (4.3)	4 (2.4)	11 (3.3)	6 (3.0)	652 (4.4)
Grade 3	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.5)	255 (1.7)
Lymphadenopathy, N1	162	167	329	198	14687
Any	35 (21.6)	34 (20.4)	69 (21.0)	20 (10.1)	2092 (14.2)
Grade 1	22 (13.6)	30 (18.0)	52 (15.8)	17 (8.6)	1735 (11.8)
Grade 2	13 (8.0)	3 (1.8)	16 (4.9)	3 (1.5)	289 (2.0)
Grade 3	0	1 (0.6)	1 (0.3)	0	68 (0.5)

N1 = Number of exposed subjects who submitted any data for the event.
Percentages are based on the number of exposed subjects who submitted any data for the event (N1).

Figure 3: Solicited local adverse reactions within 7 Days



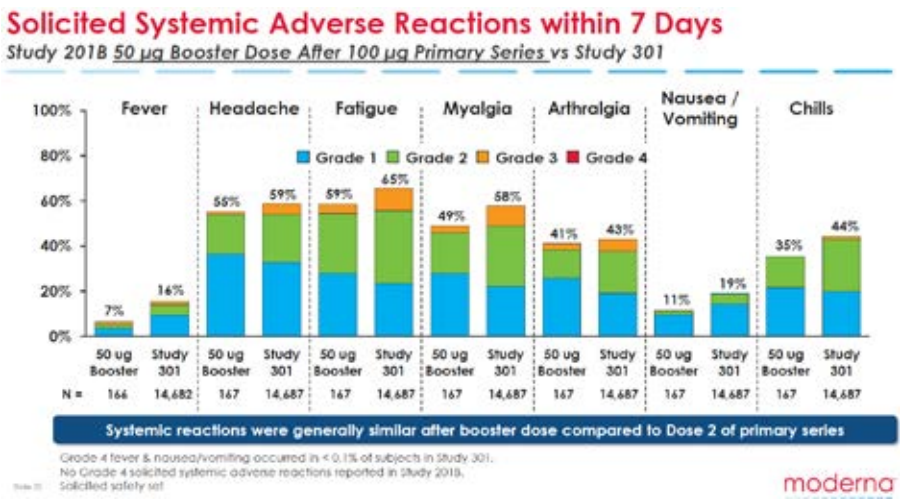
US CDC Advisory Committee on Immunization Practices (ACIP) October 2021.

Table 20: Solicited systemic adverse reactions

	mRNA-1273				
	50 µg Prime + 50 µg Booster (N=163) n (%)	100 µg Prime + 50 µg Booster N=167 n (%)	P201 Part B 50 µg Booster Total (N=330) n (%)	P201 Part A 100 µg N=198 n (%)	P301 100 µg N=14691 n (%)
Fever, N1	162	166	328	198	14682
Any	13 (8.0)	11 (6.6)	24 (7.3)	26 (13.1)	2276 (15.5)
Grade 1	12 (7.4)	6 (3.6)	18 (5.5)	19 (9.6)	1363 (9.3)
Grade 2	1 (0.6)	3 (1.8)	4 (1.2)	3 (1.5)	697 (4.7)
Grade 3	0	2 (1.2)	2 (0.6)	4 (2.0)	203 (1.4)
Grade 4	0	0	0	0	13 (<0.1)
Headache, N1	162	167	329	198	14687
Any	97 (59.9)	92 (55.1)	189 (57.4)	104 (52.5)	8637 (58.8)
Grade 1	57 (35.2)	61 (36.5)	118 (35.9)	56 (28.3)	4815 (32.8)
Grade 2	34 (21.0)	29 (17.4)	63 (19.1)	39 (19.7)	3156 (21.5)
Grade 3	6 (3.7)	2 (1.2)	8 (2.4)	9 (4.5)	666 (4.5)
Fatigue, N1	162	167	329	198	14687
Any	103 (63.6)	98 (58.7)	201 (61.1)	128 (64.6)	9607 (65.4)
Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	44 (22.2)	3431 (23.4)
Grade 2	50 (30.9)	44 (26.3)	94 (28.6)	66 (33.3)	4743 (32.3)
Grade 3	13 (8.0)	7 (4.2)	20 (6.1)	18 (9.1)	1433 (9.8)
Myalgia, N1	162	167	329	198	14687
Any	86 (53.1)	82 (49.1)	168 (51.1)	104 (52.5)	8529 (58.1)
Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	35 (17.7)	3242 (22.1)
Grade 2	37 (22.8)	30 (18.0)	67 (20.4)	54 (27.3)	3966 (27.0)
Grade 3	9 (5.6)	5 (3.0)	14 (4.3)	15 (7.6)	1321 (9.0)
Arthralgia, N1	162	167	329	198	14687
Any	66 (40.7)	69 (41.3)	135 (41.0)	77 (38.9)	6303 (42.9)
Grade 1	35 (21.6)	43 (25.7)	78 (23.7)	32 (16.2)	2809 (19.1)
Grade 2	23 (14.2)	21 (12.6)	44 (13.4)	37 (18.7)	2719 (18.5)
Grade 3	8 (4.9)	5 (3.0)	13 (4.0)	8 (4.0)	775 (5.3)
Nausea/Vomiting, N1	162	167	329	198	14687
Any	29 (17.9)	19 (11.4)	48 (14.6)	41 (20.7)	2794 (19.0)
Grade 1	25 (15.4)	16 (9.6)	41 (12.5)	25 (12.6)	2094 (14.3)
Grade 2	4 (2.5)	3 (1.8)	7 (2.1)	16 (8.1)	678 (4.6)
Grade 3	0	0	0	0	21 (0.1)
Grade 4	0	0	0	0	1 (<0.1)
Chills, N1	162	167	329	198	14687
Any	62 (38.3)	59 (35.3)	121 (36.8)	78 (39.4)	6500 (44.3)
Grade 1	32 (19.8)	36 (21.6)	68 (20.7)	30 (15.2)	2907 (19.8)
Grade 2	28 (17.3)	23 (13.8)	51 (15.5)	47 (23.7)	3402 (23.2)
Grade 3	2 (1.2)	0	2 (0.6)	1 (0.5)	191 (1.3)

N1 = Number of exposed subjects who submitted any data for the event. NR = not reported.
Percentages are based on the number of exposed subjects who submitted any data for the event (N1).

Figure 4: Studies 201B and Study 301 Solicited systemic adverse reactions within 7 Days



US CDC Advisory Committee on Immunization Practices (ACIP) October 2021

Unsolicited adverse reactions

In Study P201 Part B, unsolicited treatment-emergent adverse events (TEAEs) were systematically collected during the 28 day time window after the booster dose.

Table 21: Studies P201 and P301 Summary of unsolicited treatment-emergent adverse events up to 28 days after the booster in Study P201 Part B or up to 28 days after any injection in Study P201 Part A and Study P301, Safety set

	mRNA-1273				
	50 µg Prime + 50 µg Booster N=173 n (%)	**100 µg Prime + 50 µg Booster N=171 n (%)**	**P201 Part B 50 µg Booster Total (N=344) n (%)**	**P201 Part A 100 µg N=200 n (%)**	**P301 mRNA-1273 (N=15184) n (%)**
Unsolicited TEAEs regardless of relationship to study vaccination					
All	17 (9.8)	22 (12.9)	39 (11.3)	56 (28.0)	4752 (31.3)
Serious	0	0	0	0	98 (0.6)
Fatal	0	0	0	0	2 (<0.1)
Medically-attended	8 (4.6)	12 (7.0)	20 (5.8)	17 (8.5)	1819 (12.0)
Leading to study discontinuation	0	0	0	0	9 (<0.1)
Severe	0	0	0	5 (2.5)	258 (1.7)
Unsolicited TEAEs related to study vaccination					
All	6 (3.5)	7 (4.1)	13 (3.8)	27 (13.5)	2067 (13.6)
Serious	0	0	0	0	8 (<0.1)
Fatal	0	0	0	0	0
Medically-attended	0	2 (1.2)	2 (0.6)	5 (2.5)	198 (1.3)
Leading to study discontinuation	0	0	0	0	1 (<0.1)
Severe	0	0	0	2 (1.0)	83 (0.5)

TEAE = treatment-emergent adverse event.

Table 22: Study P201 Part B Incidence of unsolicited treatment emergent adverse events by Preferred Term up to 28 days after booster, Safety set

Preferred Term	50 µg Prime + 50 µg Booster N=173 n (%)	100 µg Prime + 50 µg Booster N=171 n (%)	P201 Part B 50 µg Booster Total (N=344) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	17 (9.8)	22 (12.9)	39 (11.3)
Number of Unsolicited Adverse Events	19	27	46
Headache	1 (0.6)	4 (2.3)	5 (1.5)
COVID-19	1 (0.6)	3 (1.8)	4 (1.2)
Fatigue	0	4 (2.3)	4 (1.2)
Arthralgia	1 (0.6)	1 (0.6)	2 (0.6)
Lymphadenopathy	2 (1.2)	0	2 (0.6)
Oropharyngeal pain	1 (0.6)	1 (0.6)	2 (0.6)
Tooth abscess	2 (1.2)	0	2 (0.6)
Abdominal pain	0	1 (0.6)	1 (0.3)
Allergy to arthropod bite	0	1 (0.6)	1 (0.3)
Anxiety	0	1 (0.6)	1 (0.3)
Chills	1 (0.6)	0	1 (0.3)
Dermatitis exfoliative	1 (0.6)	0	1 (0.3)
Dizziness	0	1 (0.6)	1 (0.3)
Facial paralysis	1 (0.6)	0	1 (0.3)
Gastrooesophageal reflux disease	0	1 (0.6)	1 (0.3)
Glycosylated haemoglobin increased	0	1 (0.6)	1 (0.3)
Humerus fracture	0	1 (0.6)	1 (0.3)
Hypertension	1 (0.6)	0	1 (0.3)
Influenza	0	1 (0.6)	1 (0.3)
Injection site erythema	0	1 (0.6)	1 (0.3)
Myalgia	0	1 (0.6)	1 (0.3)
Osteopenia	1 (0.6)	0	1 (0.3)
Pruritus	1 (0.6)	0	1 (0.3)
Rash	0	1 (0.6)	1 (0.3)
Skin laceration	1 (0.6)	0	1 (0.3)
Suspected COVID-19	1 (0.6)	0	1 (0.3)
Tooth fracture	1 (0.6)	0	1 (0.3)
Urinary tract infection	0	1 (0.6)	1 (0.3)
Vertigo	1 (0.6)	0	1 (0.3)
Vitamin D deficiency	0	1 (0.6)	1 (0.3)
Vomiting	1 (0.6)	0	1 (0.3)
Wheezing	0	1 (0.6)	1 (0.3)

Source: P201 Part B: Table 14.3.1.9.3.1.
n/N = number; TEAE = treatment-emergent adverse event.

Preferred Term	50 µg Prime + 50 µg Booster N=173 n (%)	100 µg Prime + 50 µg Booster N=171 n (%)	P201 Part B 50 µg Booster Total (N=344) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	17 (9.8)	22 (12.9)	39 (11.3)
Number of Unsolicited Adverse Events	19	27	46
Headache	1 (0.6)	4 (2.3)	5 (1.5)
COVID-19	1 (0.6)	3 (1.8)	4 (1.2)
Fatigue	0	4 (2.3)	4 (1.2)
Arthralgia	1 (0.6)	1 (0.6)	2 (0.6)
Lymphadenopathy	2 (1.2)	0	2 (0.6)
Oropharyngeal pain	1 (0.6)	1 (0.6)	2 (0.6)
Tooth abscess	2 (1.2)	0	2 (0.6)
Abdominal pain	0	1 (0.6)	1 (0.3)

Medically attended TEAEs seem to be slightly more frequent in the 100 µg priming cohort than in 50 µg cohort (n = 12 versus 8). However, since events like influenza, allergy to arthropod bite, vitamin D deficiency and anxiety were counted, this difference seems coincidental and it may be concluded that no difference has been observed between 100 and 50 µg cohorts if medically attended TEAEs are considered in general.

Unsolicited medically attended TEAEs up to 28 days were more frequent in subjects above 55 years old in 100 μg cohort (9 %) than in 50 μg cohort (4.3%). This effect was not observed in subjects younger than 55 years old.

Deaths

No deaths were reported in Study P201 Part A or among Study P201 Part B booster participants.

Serious adverse events

There were no SAEs reported within the 28 day time window post-booster in Study P201 Part B or within the 28 day time window post any injection in Study P201 Part A.

The review of cumulative SAEs among Study P201 Part B participants who received a booster in the live clinical database as of 16 August 2021 shows 5 SAEs, in 4 participants (2 in each of the 50 μg and 100 μg priming groups) were reported, and all were considered by the investigator to be not related to mRNA-1273.

Adverse events leading to discontinuation

There was no study discontinuation due to an adverse event in Study P201 Part B.

Adverse events of clinical interest

Ad hoc analyses of AEs of clinical interest were performed in Study P201 Part B up to Day 29 by searching the database using Standardised Medical Dictionary for Regulatory Activities Queries (SMQs) for the following events of interest: angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, haematopoietic cytopenia, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis.

In addition, given the newly identified risk of myocarditis/pericarditis, the sponsor searched the live clinical database up to 16 August 2021 for reported cases of myocarditis and pericarditis and individual symptoms or abnormalities that may be associated with these events (that is, TEAEs of angina pectoris, chest pain, dyspnoea, palpitations, and syncope) as well as electrocardiogram (ECG) with ST-elevation or PR-depression, troponin elevation, pericardial rub on examination, and echocardiographic abnormalities.

The results of this analysis showed that no participants had AEs of interest in the SMQs of vasculitis, peripheral neuropathy, demyelination, convulsions, CNS haemorrhage and cerebrovascular conditions, embolic and thrombotic events, thrombophlebitis, haematopoietic cytopenias, or cardiomyopathy (Study P201 Part B).

Within the 28 day time window post-booster in Study P201 Part B, no cases of myocarditis or pericarditis have been reported. No TEAEs were identified for the relevant clinical symptoms and abnormalities: chest pain, palpitations, dyspnoea, syncope, troponin elevation, ECG with ST-elevation or PR-depression, pericardiac rub, or echocardiographic findings.

In the live clinical database up to 16 August 2021 among Study P201 Part B participants who received a booster, review of SAEs and MAAEs as well as reported unsolicited AEs shows no myocarditis events. One SAE of pericarditis and AE of angina pectoris was reported in a person over 85 years old; onset was 89 days after the booster for both events in the 50 μg prime group. The case was assessed as unrelated to mRNA-1273.

Two participants in the 50 μg prime group had adverse events mapping to relevant clinical symptoms for the evaluation of myocarditis or pericarditis; however, in both cases, the events occurred in participants > 65 years old, beyond 7 days following the booster, and were not associated with other reported myocarditis/pericarditis symptoms as described above. The first case is a nonserious Grade 2 dyspnoea on exertion in a person over 65

year of age, 78 days after the booster, which resolved 112 days after the booster dose. The second participant is a person over 70 years of age with nonserious premature ventricular contractions, assessed as unrelated by the investigator to mRNA-1273, which started 92 days after the booster and were ongoing as of 16 August 2021.

Pregnancies

There were no pregnancies reported following on-study testing in Study P201 Part B within the 28 day time window post-booster in Study P201 Part B or within the 28 day time window post any injection in Study P201 Part A.

Study DMID 21-0012 safety results

From the data available within the data snapshot, the number and proportion of participants reporting severe local solicited events/symptoms (out of the total 154 enrolled in all 3 groups) is as follows: 0 (0%) reported severe erythema/redness, 1 (0.6%) severe induration/swelling and 1 (0.6%) severe pain and/or tenderness. Most of the events were mild or moderate. There were no notable clinical differences between groups. Subjects reported with a higher frequency solicited local ARs after priming with Janssen-vaccine and boost with Spikevax compared to both other groups where priming and boost were administered mRNA-vaccines. Only induration was reported with a lower frequency in the Janssen group compared to the Comirnaty and Spikevax groups.

From the data available up to the data snapshot, the number and proportion of participants reporting severe systemic solicited events/symptoms (out of the total 154 participants enrolled in all 3 groups) are as follows: 5 (3.2%) reported chills, 7 (4.5%) malaise and/or fatigue, 3 (1.9%) myalgia, 2 (1.3%) headache, 1 (0.6%) nausea, 1 (0.6%) arthralgia, and 2 (1.3%) fever (Table 5).

No potentially life-threatening systemic solicited events/symptoms have been reported (Study DMID 21-0012 Day 7 Safety Report). Other than fever, participants in the mRNA priming series groups (Dosed Moderna, Boost Moderna and Dosed Pfizer/BioNTech, Boost Moderna) tended to report more solicited systemic AEs post vaccination compared with participants in the Dosed Janssen, Boost Moderna group.

Most participants experienced mild or moderate AEs. The most common AE related to study vaccine was lymphadenopathy.

No deaths, SAEs or pregnancies have been reported.

Use in immunocompromised patients

The sponsor also seeks to extend the patient group and alter the dose regimen for immunocompromised patients, by including a recommendation for administration of a third dose administered at least 28 days following the first two doses of this vaccine in individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Primary evidence to support the dose regimen change is derived from independent sub study of the observational cohort study 'The PREVent-COVID' study**Error! Bookmark not defined.**. It is a randomised, double-blind, placebo-controlled trial of 120 solid organ transplant recipients who were randomised in a 1:1 ratio to receive either a third 100 μg dose of mRNA-1273 (two months after Dose 2) or placebo. The description of statistical analyses in the protocol or SAP remains vague in many places and is not to the standard of pivotal trials usually submitted to the TGA. However, the conducted analyses seem acceptable for this application.

As Elecsys anti-SARS-CoV-2 S enzyme immunoassay was not employed in the clinical evaluation of the pivotal study for approval of Spikevax, the study results do not allow the drawing of any conclusions on the vaccine efficacy of a third dose of Spikevax in patients under immune suppression. However, no internationally recognised immunological surrogate of protection is yet established. Published data by Riester *et al*, 2021[29] on independent performance evaluation of the Elecsys anti-SARS-CoV-2 S enzyme immunoassay indicate a high sensitivity (97.92%; 95% CI: 95.21–99.32) and specificity (99.95%; 95% CI: 99.87–99.99) for the detection of anti-spike antibodies. Note that the anti-receptor-binding domain (anti-RBD) assay used for the primary endpoint did not assess neutralising capacity.

The study met its primary immunogenicity endpoint, with the analysis of anti-RBD antibodies one month after Dose 3 showing that the relative risk of being above the 100 U threshold in the mRNA-1273 group as compared with the placebo group was 3.1 (95% CI: 1.7, 5.8; P<0.001). Secondary endpoints were supportive of the immunogenicity of Dose 3 but were not controlled for multiplicity.

The groups were not balanced with respect to time since transplantation. An influence on the outcome cannot be ruled out.

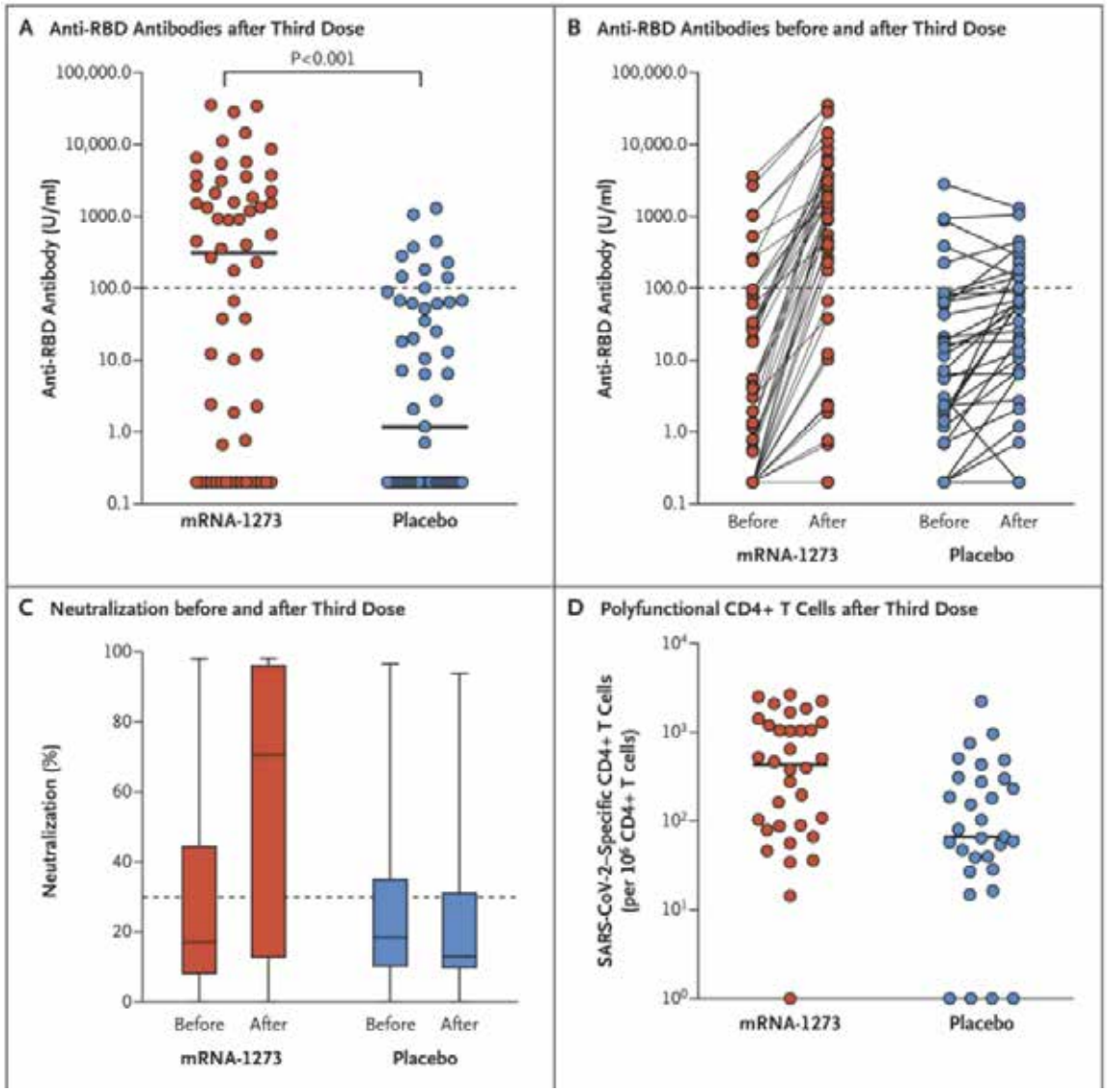
No confirmatory clinical efficacy data were available (there was one case of COVID-19 in a patient in the placebo group). No data are available on persistence of the immune response beyond Month 4.

Note that the third mRNA-1273 dose in this study was administered two months following Dose 2, while the proposed dosing interval in the PI is '*at least 28 days following the first two doses*'. Data were not available with a 28 day dosing interval between Dose 2 and 3.

No new safety signals were identified during the study. Local and systemic reactogenicity events were more frequently reported with Dose 3 than placebo but were mostly Grade 1.

[29]Riester, E ,Majchrzak, M, Mühlbacher A et al (2021). Multicentre Performance Evaluation of the Elecsys Anti-SARS-CoV-2 Immunoassay as an Aid in Determining Previous Exposure to SARS-CoV-2 Infect Dis Ther 2021 Dec;10(4):2381-2397.Epub 2021 Aug 9.

Figure 5: Immune responses in transplant recipients who received third dose mRNA-1273 or placebo



Solid horizontal lines = median values; dotted horizontal lines = pre-specified thresholds

Source: Hall et al., Figure 1[Error! Bookmark not defined.].

Risk management plan

- The most recently evaluated EU-risk management plan (RMP) was version 2.1 (date 15 July 2021; data lock point (DLP) 31 May 2021) and Australia specific annex (ASA) 0.3 (date 5 August 2021). In support of the current submission, the sponsor has provided EU-RMP version 2.3 (date 28 October 2021; DLP 30 June 2021) and ASA version 1.1 (date 5 November 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 23.[30]Table 23: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Anaphylaxis	ü*	ü†	ü	–
	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	ü†	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 pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	ü	ü†	ü	–

[30] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

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

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in subjects with autoimmune or inflammatory disorders	ü	ü†	ü	–

*Follow-up questionnaires. †Clinical studies

- This summary of safety concerns is the same as the summary that was evaluated and considered acceptable for the previous submission for Spikevax (elasomeran).[31] The changes proposed by the current submission do not warrant changes to the summary of safety concerns from an RMP perspective.
- The pharmacovigilance plan was found to be acceptable during the previous evaluation and continues to be acceptable for the current submission. The acceptability of the clinical study plan submitted as part of the provisional approval pathway will be assessed by the clinical evaluator or Delegate.
- Only routine risk minimisation measures are currently in place. This approach was deemed acceptable during the previous evaluation. The changes proposed by the current submission do not warrant additional risk minimisation measures as part of the RMP.

Risk-benefit analysis

Delegate's considerations

Recent evidence has raised concerns over the declining neutralising antibody titres or reduced effectiveness against symptomatic disease, which may significantly decrease the effectiveness against severe disease. In addition, emergence of the highly transmissible Delta variant of SARS-CoV-2 has resulted in a new wave of COVID-19 cases in many parts of the world, including the recent wave in Australia. It has led to considerations for administration of booster doses to individuals who received primary series of vaccines to enhance immunity, and thus sustain protection from COVID-19.

While currently authorised COVID-19 vaccines in Australia afford protection against severe COVID-19 and death, there are emerging data, primarily from observational studies, that suggest there is a decline in clinical efficacy (or efficacy versus the Delta variant) over time. An independent review of these data has not been conducted by the TGA.

The clinical data submitted in this application come from an ongoing Study P201 (Part A and B) and Study P301, which is also the source of clinical data supporting the original approval of the 2 dose primary series for use in individuals 12 years of age and older. The results for a 50 µg booster dose of Spikevax (mRNA-1273/elasomeran) given at approximately 6 to 8 months after Dose 2 show that higher neutralising titres are obtained after the booster dose compared to the second dose.

For the primary endpoints, there is statistically significant evidence of non-inferiority between geometric mean neutralising titres (as measured by geometric mean ratios) to the WT SARS-CoV-2 at 28 days post-Dose 3 (that is, following the booster) and one month

[31] AusPAR for Spikevax (elasomeran) new biological entity, published on 4 September 2021. Available at: Australian Public Assessment Report for Elasomeran (tga.gov.au)

post Dose 2 (that is, following the primary 2 dose vaccination course). While 87.9% (95% CI 81.6, 92.7) of 100 μg primed booster dose participants achieved at least a 4 fold rise in neutralising antibody titres, the difference in seroresponse rates (among 100 μg-primed participants) did not meet the pre-specified immunobridging success criterion. The lower limit of the 95% confidence interval for the difference in seroresponse rate (booster dose – primary series) was <-10% (-16.7% in those primed with 100 μg). Possible explanation of lower SRR following a third dose can be explained by residual higher levels of nAbs pre booster in Study P201 and by the fact that the response rates following a booster dose were compared to peak levels after the primary series in Study P301.

In *post hoc* analyses, participants with lower pre-booster nAbs titres were more likely to achieve a 4 fold rise in nAbs titres after booster vaccination compared to participants with higher pre-booster nAbs titres. Effectiveness of the booster dose against the Delta variant is inferred from exploratory descriptive analyses of ID_{50} titres against this variant evaluated among booster dose recipients from Study P201 Part B.

Stratification according to age and primary vaccination dose reveals that lower antibody levels are elicited 28 days after booster in the age group ≥ 55 years compared to 18 to 55 years (GMT 100 μg: 1670 versus 2001) but that the increase in nAb levels from pre Dose 3 to post Dose 3 is higher for the older age cohort (GMR: 16.17 versus 12.85). This demonstrates that the older age group might still benefit from a booster dose due to more pronounced waning and good ability to booster the nAb response. Data on persistence of the antibody response following a third dose of 50 μg are missing to evaluate the durability of the lower booster dose.

There were also no data generated from participants < 18 years of age.

As to the appropriateness of 50 μg booster dose, as part of initial dose ranging of mRNA-1273 (Study P201 Part A), both 50 and 100 μg were evaluated. Both dosages induced substantial neutralising antibody. While the 100 μg dosage was advanced to the pivotal trial (Study P301), it was postulated that a 50 μg booster dose would be effective in briskly activating recall responses. The trend toward lower reactogenicity observed for the 50 μg dose in Study P201 Part A also supported this selection. Finally, there is precedence for a booster dose to be lower than the priming vaccine dose. For example, Tdap (tetanus, diphtheria, pertussis) vaccine, the booster for the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine, has a reduced dose of the diphtheria and pertussis vaccines and is intended to boost the immunity that wanes after primary vaccination. The rationale to recommend the lower 50 μg dose for boosting seems to be supported also by the fact that this dose has had numerically better safety in the elderly compared to 100 μg.

To date, the reactogenicity and safety profile of the booster seems to be consistent with that observed following the primary series in Study P301, which included more than 30,000 study participants, and Study P201 Part A. No new unexpected safety concerns have been identified from a booster dose. Slight imbalances however, in unsolicited AEs have been noted related to the priming dose. The submitted data is also limited in terms of the numbers of vaccinees included in the study and the duration of follow up does therefore not allow any firm conclusions regarding the pattern and incidence of uncommon or rare AEs/SAEs.

Additional results from the ongoing Phase I DMID 21-0012 study, which has enrolled 154 participants who received heterologous prime series and a subsequent booster dose of 100 μg of mRNA-1273 further seem to support a similar reactogenicity and safety profile within the 7 days following the administration of the booster dose.

In the post-authorisation period, a total of 301,035,380 doses have been distributed worldwide. Rare cases of anaphylaxis, myocarditis, and pericarditis events have been reported during the post-authorisation period from healthcare professionals and

spontaneously reported from patients. The risk of these events after a booster dose cannot be determined due to the sample size that can be achieved prior to an approval.

The sponsor has committed to the European Medicines Agency to amend Study P301 (known as the COVE trial, the pivotal efficacy and safety study) to administer the booster dose, after which participants will continue to be followed for breakthrough disease. The sponsor would also amend Study P901, the effectiveness study that is currently ongoing to follow effectiveness after the booster dose, which will also contribute extensive information on future protection against variant of concern (VOC).

Immunogenicity of Spikevax in immunocompromised (IC) patients was assessed in a randomised, placebo-controlled trial conducted in Canada and the study results were published by Hall et al., (2021).**Error! Bookmark not defined.** In this study, 243 IC patients were enrolled and of those 120 randomised to receive either a third dose of Spikevax or placebo, respectively, within 2 months. No control arm of healthy individuals was included. The trial was not planned with the usual standards of pivotal trials but was conducted and analysed seemingly in an acceptable manner. Although no correlate of protection is yet established, the immunogenicity data reported by Hall et al.,**Error! Bookmark not defined.** suggest that a third dose of Spikevax is able to elicit a pronounced antibody response in a substantial number of IC patients at risk for severe COVID-19. IC patients having received a third dose of Spikevax were compared to IC patients treated with placebo. Prior to the third dose, 11.7% in the vaccine group and 8.8% in the placebo group had anti-RBD-antibody titres ≥ 100 U/mL, an antibody response considered by the investigators as seropositive. The median anti-RBD titre reported for both groups was low with 0.37 U/mL (IQR: 0.2-27.64) for the Spikevax group and 0.44 U/mL (IQR: 0.2-18.19) for the placebo group. Following administration of a third dose of Spikevax a significant rise in antibodies was observed with 55% of the IC patients showing at least an antibody titre of 100 U/mL with a calculated absolute mean anti-RBD titre of 3145 U/mL (median: 313.8 U/mL, interquartile range (IQR): 0.2-2191). In the placebo group only 17.5% of IC patients had antibodies ≥100 U/mL and a GMC of 86 U/mL (median: 1.19 U/mL, IQR: 0.2-63.4) was reported.

Overall, the data submitted in this submission has shown that a 50 µg booster dose of Spikevax (mRNA-1273/elasomeran) given 6 months after the primary vaccination series restored waning neutralising titres against WT SARS-CoV-2 to significantly higher levels than seen following the primary vaccination course.

However, as there is no serological correlate of protection, the clinical relevance of restoring the waning titres is unknown. Therefore, while the immunogenicity and reactogenicity of a third dose have been appropriately characterised, the utility of a third dose has not been fully established. In addition, the risk of more rare and serious side effects such as myocarditis remains uncharacterised. Hence, the decision to implement a 50 µg booster dose of Spikevax (mRNA-1273/elasomeran) needs to be taken based on emerging epidemiological vaccine efficacy or effectiveness data in different age groups and given differing comorbidities, including immunosuppression.

The potential benefit in terms of increased duration of protection, and possibly increased protection against variants of concern has not been clearly demonstrated. However, in the view of the waning immune titres observed following the primary vaccination, it is likely that a 50 µg booster dose of Spikevax (mRNA-1273/elasomeran) in individuals aged 18 years and older will provide longer term protection based on experience with other vaccines, and the immunogenicity data available. Duration of the antibody responses following a 50 µg booster dose and the level of long-term protection are currently not known.

Proposed action

In summary, the benefit risk profile of a 50 μg booster dose of Spikevax (mRNA-1273) in individuals aged 18 years and older appears positive, provided its implementation is guided by vaccine effectiveness data and considering limited safety data.

Advisory Committee considerations[32]

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

Specific advice to the Delegate

1. Does the ACV agree that the immunogenicity and safety data support the administration of a 50 μg booster dose for adults aged 18 years and older?

The ACV advised that the current data support the administration of a 50 μg booster dose for adults aged 18 years and older.

The ACV commented that the submitted dataset is relatively limited and relies on immunobridging studies as a surrogate for efficacy.

The safety data provided by the sponsor were reassuring. The ACV noted higher reactogenicity observed with Spikevax compared to Comirnaty in US surveillance data. A higher rate of lymphadenopathy was observed in clinical trials of Spikevax than in the corresponding trials with Comirnaty. While an independent study suggested higher rates of reactogenicity with Spikevax boosters compared with Comirnaty boosters, particularly following Comirnaty primary courses, this study did not use the selected (half) dose and the booster was administered between 12-20 weeks, shorter than the proposed booster interval.

The ACV noted that the observed rate of myocarditis seen with Spikevax primary vaccination is higher in younger males than with Comirnaty in different surveillance systems. In this context, the ACV advised that close monitoring for myocarditis following a Spikevax booster will be important, in particular for young males and when using Spikevax as a booster following a Comirnaty primary course. As these data are rapidly accumulating, communications and guidance will need to be updated accordingly.

The ACV noted that the booster dose (50 μg) is half the dose of the primary doses (100 μg). The ACV strongly emphasised the importance of having clear communication regarding the different doses for the primary course (including third doses in immunocompromised individuals) compared with the booster dose in the labelling, prescribing software, product information and clinical guidance to avoid confusion.

[32] The Advisory Committee on Vaccines (ACV) provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-market monitoring and safe use in national immunisation programs.
The Committee is established under Regulation 39F of the Therapeutic Goods Regulations 1990 and the members are appointed by the Minister for Health.
The ACV was established in January 2017, following consolidation of previous functions of the Advisory Committee on the Safety of Vaccines (ACSOV) and the pre-market functions for vaccines of the Advisory Committee on Prescription Medicines (ACPM).
Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues.

2. Advice on the booster dosing wording in the PI.

a. Booster Dose

Individuals 18 years of age and older

Spikevax is administered intramuscularly as a single dose (0.25 mL) at least 6 months after completing a primary series.

b. Interchangeability

Primary series

The interchangeability of Spikevax with other COVID-19 vaccines to complete the vaccination course has not been established.

Individuals who have received one dose of Spikevax (0.5 mL, 100 micrograms) should receive the second dose of Spikevax (0.5 mL, 100 micrograms) to complete the vaccination course.

Booster dose

A single booster dose of Spikevax (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorised or approved COVID-19 vaccine.

The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorised for a booster dose of Spikevax.

The ACV recommended the following underlined modifications to the proposed PI wording for clarity and to align with other COVID-19 mRNA vaccines:

Booster Dose

Individuals 18 years of age and older

Spikevax is administered intramuscularly as a single booster dose (0.25 mL; 50 micrograms) at least 6 months after completing a primary series.

The decision when and for whom to implement a booster (third dose) of Spikevax should be made based on available vaccine safety and effectiveness data (see sections 4.4 Special warning and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations.

Interchangeability

Primary series

The interchangeability of Spikevax with other COVID-19 vaccines to complete the vaccination course has not been established.

Individuals who have received one dose of Spikevax (0.5 mL, 100 micrograms) should receive the second dose of Spikevax (0.5 mL, 100 micrograms) to complete the vaccination course.

Booster dose

A single booster dose of Spikevax (0.25 mL; 50 micrograms) may be administered as a homologous (same brand) booster dose following completion of primary vaccination with Spikevax or as a heterologous booster dose following completion of primary vaccination with another authorised or approved COVID-19 vaccine.

~~The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorised for a booster dose of Spikevax.~~

3. Does the ACV agree that data provided support the PI changes in relation to a third dose for immunocompromised patients at least 28 days after the primary series?

Immunocompromised individuals

A third dose of Spikevax (0.5 mL) administered at least 28 days following the first two doses of this vaccine is authorised for administration to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

The ACV advised that the proposed wording in the PI regarding a third primary dose for immunocompromised patients is appropriate and reflects the evidence from the clinical trial in individuals who have undergone solid organ transplant. The ACV noted that the dose interval between the second and third primary doses was 2 months and noted the limited data in younger immunocompromised individuals. The generalisability of this trial to other individuals at a similar level of immunocompromise is felt to be appropriate.

The ACV advised that '100 µg' should be added after '0.5 mL' to clearly highlight the different doses between the booster and the primary series.

Conclusion

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

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Spikevax (elasomeran) 0.2 mg/mL, suspension for injection, vial, indicated for the following extension of indications:

The provisionally approved full indication for the new Spikevax medicine, which is unchanged from that for the existing Spikevax medicine is:

Spikevax (elasomeran) COVID-19 Vaccine has provisional approval for the indication below:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

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

Specific conditions of registration applying to these goods

- Spikevax (elasomeran) COVID-19 vaccine is to be included in the Black Triangle Scheme. The PI and CMI for Spikevax must include the Black triangle symbol and mandatory accompanying text for the entire period of provisional registration.
- The Spikevax European Union (EU)-Risk Management Plan (RMP) (version 2.3, date 28 October 2021; DLP 30 June 2021), with Australian Specific Annex (version 1.1, 5 November 2021), included with submission PM-2021-05131-1-2, 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).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this 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.

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

- Clinical

  Existing Conditions for adolescent data

  The following reports/data will have to be submitted before a definitive authorisation can be considered:

  – Submit safety data for all adolescents 12 to 17 years of age in Study P203, 6 months post Dose 2, when the data become available.

  – Submit clinical study report of Study P203 (interim and final), including data up to 24 months after Dose 2 in adolescents 12 to17 years of age, when the data become available.

  – Submit safety data in relation to follow-up at 6 months post Dose 2 for all original Spikevax recipients and at 6 months post Dose 4 for original placebo recipients subsequently vaccinated with Spikevax, when the analysis is available.

  Existing Conditions for adult data

  The following reports/data will have to be submitted before a definitive authorisation can be considered:

  – Submit safety analysis at 6 months post Dose 2 from Study Phase 1 and, 2 Study when the analysis is available.

  – Submit the clinical study report for Study P301 (Phase 3) and Study P201 (Phase 2) when ready. Please also submit the final report for these studies with 24 months follow up duration when it became available.

  – Submit the immunogenicity data for Study 301.

- When available, the sponsor to please provide:

  – Further data relating to vaccine efficacy against asymptomatic disease, efficacy against SARS-CoV-2 transmission, vaccine efficacy in immunocompromised subjects, efficacy in subjects with autoimmune conditions, efficacy against variants of concern, pregnant women, lactating mothers, and information relating to post-market safety and effectiveness studies should be provided to the TGA to update the Product information.

  – Please also provide Real world post market global/local efficacy data, when available.

- 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.

  Further guidance for sponsors is available on the TGA website.

- Quality

  Batch release testing and compliance

  Batch release testing and compliance with the certified product details conditions of provisional registration for Spikevax

  – It is a condition of registration that all independent batches of Spikevax elasomeran COVID-19 VACCINE 0.2 mg/mL suspension for injection vial imported into Australia are not released for supply by or on behalf of the sponsor 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 elasomeran 0.2 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 elasomeran 0.2 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.

  – The 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 address for courier delivery is:

  Certified Product Details

  An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for

biological prescription medicines and Vaccines can be obtained from the TGA website https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescriptionmedicines]. 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.

- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

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

Therapeutic Goods Administration

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