Australian Government

Department of Health

Therapeutic Goods Administration

NONCLINICAL SUMMARY AND RECOMMENDATIONS

Submission Type:	New Vaccine		
Sponsor:	Adjutor Healthcare Pty Ltd on behalf of Moderna Australia Pty Ltd	**Tox File No.:**	E21-324111
Generic name:	**Elasomeran**	**TRIM Reference:**	D21-2803355
Trade name:	**SPIKEVAX®**		
Dose form & strength:	Suspension For Injection; Strength of 0.2 mg/mL (multidose vial; neat solution to deliver 100 µg/0.5 mL dose per injection)	**Date:**	15 July 2021 (Round 1) 29 July 2021 (Round 2)
Vaccine Type:	mRNA encapsulated in LNP		
Submission No.:	PM-2021-02994-1-2		

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

INTRODUCTION

This application is being evaluated for provisional registration of a new COVID-19 mRNA vaccine. This report contains a nonclinical summary and recommendation, and comments on the proposed Australian Product Information only. A comprehensive review of the nonclinical data can be found in the nonclinical evaluation report (D21-2850341) by SwissMedic. TGA evaluated studies provided in response to the 1st round evaluation report (see Appendix 1). Comments on Sponsor's response to Round 1 questions are included in Appendix 2.

EXECUTIVE SUMMARY AND RECOMMENDATIONS

- The mRNA-1273 vaccine is formulated in lipid nanoparticles (LNP) containing 2 new excipients. SARS-CoV-2 S-2P spike (S) protein was expressed in mammalian cells *in vitro* transfected with an unformulated preclinical mRNA encoding SARS-CoV-2 S-2P and in dendritic cells in mouse spleen and lymph nodes after an IM injection of mRNA-1273.
- mRNA-1273 was immunogenic in young and old mice, rats, hamsters and rhesus macaques. A prime/booster dosing regimen (3-4 weeks dosing interval) induced strong humoral and cellular immune responses. Antibodies (Abs) neutralised the wild-type SARS-CoV-2 virus strain isolated at the beginning of the pandemic. There was no data on activity against the new variants (e.g. alpha, beta, gamma, delta). In monkeys, Abs declined 2 weeks after the 2nd dose, raising long term immunity concerns.
- In short term protection studies, mRNA-1273 provided protection in in mice (young and aged), hamsters and monkeys challenged with SARS-CoV-2 or mouse-adapted SARS-CoV-2MA, 3-13 weeks after the 2nd dose. Immunisation reduced viral loads in both the upper (nasal turbinates) and lower airways (lungs) and reduced lung pathology. Long term immunity

was not assessed. Long term data will not be available as monkeys in the original study have been repurposed to evaluate protection by mRNA-1273 from a B.1.351 challenge.

- There was no evidence of vaccine enhanced respiratory disease (VA-ERD) with mRNA-1273 in the animal models. Instead, a robust induction of functional (neutralising) Abs and a balanced Th1-Th2 response was seen at optimal or suboptimal doses.
- A pharmacokinetic (bio)distribution study with a surrogate mRNA (CMV) vaccine from the same development platform showed mRNA was mainly localised at the injection site and also proximal/distal lymph nodes and spleen. Lower levels of mRNA were detected in plasma and in most other tissues analysed. mRNA is likely degraded in tissues with half-lives (t½) of 15-60 h.
- Repeat dose toxicity studies in rats with surrogate mRNA-LNP vaccines from the same development platform showed immune response-related findings including: injection site inflammation (swelling, oedema, erythema; skin thickening), enlargement and inflammation of draining lymph nodes, transient increases in cytokines associated with body temperature increases, decreased cellularity of spleen and some perturbations of haematology, coagulation and clinical chemistry parameters. Hepatocyte vacuolation and Kupffer cell hypertrophy (no serum transaminases increases) were observed, which were probably due to hepatocyte uptake of LNP lipids. All effects were either partially or fully reversible after 2 weeks of recovery. A non-GLP toxicity study in rats (with no necropsy or histology) with mRNA-1273 vaccine showed findings similar to those in repeat dose toxicity studies with surrogate mRNA vaccines.
- No genotoxicity studies were conducted for the vaccine, in line with relevant guidelines. The components of SPIKEVAX (mRNA and lipids) are not expected to be genotoxic.
- A developmental and reproductive toxicity (DART) study was conducted in female rats with mRNA-1273. Female rats were given a human clinical dose (100 µg; ≥140 times the human dose on a µg/kg basis) 28 and 14 days prior to mating and on days 1 and 13 of gestation. No effects on fertility, fetal development, fetal malformations or variations or postnatal (pre-weaning) development were observed. Exposure of fetuses and pups to vaccine-specific maternal antibodies was demonstrated in this study. The effect on male fertility has not been determined.
- There was no local tolerance study with mRNA-1273. However, the repeat dose toxicity studies with surrogate mRNA vaccines formulated in LNPs were well tolerated locally in rats.
- The LNP formulation contains 4 lipids (2 new excipients: SM-102 and PEG2000-DMG). Comprehensive kinetic data in rats for a lipid (SM-86) similar to SM-102 showed rapid elimination (by 24 h) via renal and biliary clearance after IV dosing. The new excipients were tested in LNP formulations in the 6 repeat dose, genotoxicity and reproductive toxicity studies. No findings (general toxicity, genotoxicity and reproductive toxicity) are attributable to the lipid excipients except for hepatocyte vacuolation, which was partially or completely reversible after 2 weeks of recovery.
- The nonclinical data package is considered adequate to support provisional approval of Spikevax®, administered as 2 IM injections (100 µg) 28 days apart, for the proposed indication.
- The Nonclinical Safety Specification of the RMP is commented on page 10.
- The draft Product Information should be amended as directed on pages 11-14.
- Comments on the Sponsor's response to Round 1 questions are included in Appendix 2.
- The sponsor is requested to address the following Round 2 Questions post-provisional approval.

Question 1

The following issue previously raised with the sponsor (Question 3 of the 1st round evaluation) remains unresolved. In answering TGA's request "Please provide bDNA assay qualification report for Study 5002121", the sponsor stated that there was no bDNA assay qualification report. Instead, 12 tables of quality control and calibration assay results were provided. The tables could not be located within Study 5002121, which was provided in the submission. If the above data were generated during separate method development activities, please provide any available data (inclusive of detailed methodology) to allow independent assessment and verification of assay accuracy, precision, etc.

Question 2

The sponsor was previously requested to provide the study report on SM-102 in PEG2000-DMG containing LNPs. In their response, the Sponsor indicated that the pharmacokinetic study was "unpublished data" and instead provided a brief summary.
Please provide more detailed information of the study (including methodology). Unpublished, draft or company internal data are acceptable if there are no audited/finalised reports.

Question 3

In response to a SwissMedic Nonclinical Evaluation Question, the sponsor stated:
"We have performed extensive characterisation of antigen expression in cells at the injection site, in the draining lymph nodes (dLN) and in systemic circulation. 1) We see the predominant site for expression to be in antigen presenting cells in the dLN, with plasmacytoid dendritic cells, conventional dendritic cells and subcapsular sinus macrophages the primary cells that express and display the encoded spike protein. In addition, we have evaluated the site of injection.
2) At the site of injection, we do see expression in tissue resident immune cells, again primarily antigen presenting cells. We have not observed expression to occur in muscle cells, but we have observed low levels of expression in adipocytes that may be present at the site of injection in some individuals. 3) Last, we have measured expression in circulating immune cell populations. While expression in these cells is generally lower than that observed in the dLN, we do see expression in antigen presenting cells that circulate and pool in the spleen. Expression in all these areas is transient, with levels of antigen generally peaking around 48 hours post injection, with a rapid clearance after >96 hours post injection we see little evidence of antigen remaining either in the dLN or in other tissues."

Please provide study reports supporting the above statements.

ASSESSMENT

Adjutor Healthcare Pty Ltd, on behalf of Moderna Australia Pty Ltd has applied for provisional registration of a new COVID-19 mRNA vaccine, elasomeran (SPIKEVAX®) expressing the full-length SARS-CoV-2 spike glycoprotein (S), in a SM-102 lipid nanoparticle (LNP) formulation [mRNA-1273], indicated for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 18 years of age and older. The proposed dosing regimen involved administering two doses of 100 μg of mRNA/0.5 mL per dose given 28 days apart intramuscularly (IM).

General Comments

The sponsor has conducted adequate studies on pharmacology and toxicity (GLP-compliant repeat dose studies and a developmental and reproductive toxicity [DART] study) with mRNA-1273 or other surrogate mRNA vaccines derived from the same development platform. Use of a single species (rats) is consistent with the relevant guidelines and demonstration of good immunogenicity supports the use of this species as an appropriate animal model for the toxicity studies. Biodistribution studies of mRNA from the same development platform were carried with other mRNA vaccines in a similar LNP formulation. An adequate battery of genotoxicity studies were conducted with 2 new LNP formulation ingredients alone (SM-102; PEG2000-DMG) and/or similar (surrogate) mRNA vaccines from the same development platform. Limited pharmacokinetic (ADME) data is presently available for the 2 new excipients.

The LNP comprises four lipid components: SM-102 (novel excipient), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and 1-monomethoxy-polyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG; novel excipient) at 2.15, 0.94, 0.55 and 0.23 mg/mL, respectively, with 0.20 mg/mL mRNA and pH 7.5. The modified mRNA (ie, introduction of two proline residues [K986P, V987P] in the S-protein sequence, S-2P) encodes the pre-fusion stabilised coronavirus spike protein (S) antigen.

Whilst no pharmacokinetics (ADME) were carried out for the novel excipients, some data is available for a close structural analogue, SM-86, the distribution of which is consistent with the distribution of mRNA from the administered LNPs. These lipids have also been tested in LNP formulations in 6 submitted repeat dose toxicity studies in rats and a single submitted reproductive developmental and reproductive toxicity rat study. Safety of the novel excipients was not assessed in a second species.

Pharmacology

mRNA-1273 is modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the S protein into the prefusion conformation. Additionally, mRNA-1273 is chemically modified (methylation of the pseudouridine base [base not found in the RNA of eukaryotic cells]).

Based on a submitted synopsis (complete study report to be provided when available), findings indicate substitution of uridine with 1-methyl pseudo uridine had no effect on mRNA degradation in one assay with mRNA expressing a fluorescent reporter protein and slightly increased the rate of mRNA degradation in another assay with a different fluorescent reporter mRNA. Thus, the limited findings suggest that mRNAs containing 1-methyl pseudo uridine may not have significant effects on the stability of mRNA in cells.

S antigen expression

Expression of the spike protein was determined *in vitro* in mammalian cells and *in vivo* in BALB/c mice using mAbs binding to the receptor binding domain (RBD) or the N-terminal domain (NTD) epitope. HEK293T cells transiently transfected with unformulated pre-clinical mRNA encoding SARS-CoV-2 S-2P showed SARS CoV-2 S-2P expression detected by both mAbs over 24 to 72 h.

Expression of the spike protein was also demonstrated in dendritic cells of spleen and draining lymph nodes of mice following a single IM injection of 2 or 10 μg mRNA-1273. Similar levels of the expressed spike protein were detected in dendritic cells of spleen at 24 and 72 h post dose, while the expression in lymph nodes peaked 48 h and then significantly decreased by 72 h. Whilst this study clearly detected increased antigen expression on the surface of cells by flow cytometry, further studies could have assessed whether membrane-bound S-2P protein could then be further proteolytically cleaved to form a soluble protein outside of cells.

Immunogenicity

Immunogenicity assessments (including binding and neutralising antibodies [NAb]) indicated protocols employing prime/boost IM immunisation with mRNA-1273 at 3-4 week intervals in nonclinical animal species induced a dose-dependent induction of both humoral and cellular immune responses. Animal models used in the immunogenicity studies included young and aged mice, hamsters and non-human primate (rhesus macaques).

Humoral response was characterised by significant S-protein binding of IgG antibodies specific for the ACE2-receptor-binding domain and for the S1-N-termimal domain. The boost immunisation led to a significant increase in binding antibodies and NAbs, in all animal models. Comparisons of activity of sera from vaccinated animals with human convalescent plasma showed convalescent plasma contained equal or less S protein binding and neutralising antibodies than sera from vaccinated animals. In older (aged) mice, a booster dose was necessary for the induction of neutralising antibodies. In NHPs, there were indications of a decline of binding IgG and neutralising antibodies two weeks after vaccination. Importantly, in all three species, a balanced expression levels of IgG2 and IgG1 indicated a vaccine-mediated Th1 response (ie, IgG2 levels at least as high as the IgG1 level). In a rat non-GLP toxicity study, a prime/boost immunisation elicited a substantial dose-dependent binding antibody response.

No long-term efficacy data was submitted (eg, 3-6 months post-vaccination with respect to sustained levels of neutralising antibodies in animals after vaccination). Also, based on experience with other Covid-19 vaccines, it is likely the level of protecting antibody titres diminish over time. When neutralising antibody levels diminish, there may also be a higher risk of ERD or other forms of antibody-dependent enhancement of disease.

Cellular immune responses were induced by mRNA-1273 in mice at 1 μg mRNA-1273 (Th1 response with CD4+ and CD8+ cells expressing INFγ, IL-2 and TNF-α). In contrast, doses considered suboptimal (with respect to protection from viral challenge) induced a Th2 skewed response in CD4+ cells indicated by expression of IL-4, IL-5 and IL-13. The T cell response was not assessed in hamsters. Similarly, in NHPs, there was a dose-dependent increase in the Th1 response in CD4+ cells with no clear evidence of a Th2 response; a low CD8 T-cell response was detected after mRNA-1273 vaccination of NHPs.

Protection against infection

Challenge (protection) studies were carried out in the above nonclinical animal species. Animals were challenged 3-13 weeks after the 2nd vaccine dose.

- Mice **-** a mouse-adapted (MA) SARS-CoV-2 MA virus with the S protein genetically modified to interact with the mouse ACE2 protein (as SARS-CoV-2 recognises human, not mouse ACE2) was given intranasally and elicited respiratory disease (associated with weight loss and lung haemorrhage) and viral replication in the respiratory tract. mRNA-1273 dosed mice were protected (dose-dependently) at ≥1 μg, whilst untreated mice started to recover after 4 days. Histopathological assessment indicated the vaccine reduced lung inflammation and pneumocyte hyperplasia, and reduced SARS-CoV-2 MA virus load (RNA and/or infectious virus) in lung and nasal turbinates. Suboptimal doses (ie, <1 μg), did not elicit ERD.
- Older mice (1 year old) **-** challenged with the mouse-adapted SARS-CoV-2 MA virus results in more severe disease cf. young mice. mRNA-1273 at 1 μg IM (prime + boost) provided protection and a suboptimal dose of 0.1 μg (only partial protection) did not induce any signs of ERD.
- Hamsters - mRNA-1273 (1-25 μg) prime/boost immunisation protected animals following an intranasal challenge of wild-type SARS-CoV-2. Viral load decreased from day 2 post-challenge (no weight loss) and lung histology assessment showed reduced inflammation. A prime-only dose of 25 μg of mRNA-1273 provided partial protection.
- Rhesus macaques – only a high prime/boost dose of 100 μg mRNA-1273 was effective in decreasing viral load in both bronchoalveolar lavage fluid (BAL) and nasal turbinates (NS). However, viral replication was not completely inhibited in either the lower or upper respiratory tract. Following 7-8 days post challenge, lungs were harvested for histology. Control animals showed moderate to severe inflammation (inflammatory cell infiltrates occasionally in alveolar air spaces, moderately thickened alveolar capillary septa , and moderate and diffuse type II pneumocyte hyperplasia) and multiple pneumocytes were present in the lung sections from controls which were positive for both SARS-CoV-2 viral RNA and antigen. However, no significant inflammation was observed in the lungs of animals immunised with 100 μg of mRNA-1273. Vaccine-associated immunopathologic changes were not seen. The lower dose 10 μg prime/boost mRNA-1273 also reduced lung inflammation but not viral replication.

Overall, mRNA-1273 induced both humoral (including NAb) and cellular immunity in animal models and protected mice, hamsters and NHPs against SARS-CoV-2 challenge 3-13 after the boost dose. Also, there was no evidence of vaccine associated ERD in mice, hamsters, and NHPs immunised with optimal (protective) and suboptimal (subprotective) doses of mRNA-1273. Animal studies were of short term. However, long term immunogenicity with mRNA-1273 immunisation and protection from SARS-CoV-2 virus protection was not studied in animal models. The sponsor should provide follow up data if any long-term study in NHPs is ongoing. No data was provided on activity against the new variants (*ie*, alpha, beta, delta, gamma).

Safety pharmacology

No specific safety pharmacology studies were conducted. Limited safety pharmacology parameters e.g. body temperature were investigated in the toxicity studies in accordance with the WHO guideline on nonclinical evaluation of vaccines (WHO 2005[1]). Repeat dose toxicity studies raised no safety concerns over effects on vital organ systems.

[1] WHO (2005) WHO guidelines on nonclinical evaluation of vaccines. WHO Technical Report Series no. 927, Annex 1.

Pharmacokinetics

No pharmacokinetic studies on the vaccine were submitted and are generally not required for a vaccine per relevant guidelines. This is acceptable. Biodistribution of COVID-19 mRNA-1273 vaccine was also not determined. In animals the unprotected mRNA is likely degraded within minutes in biological fluids and is unlikely to persist in tissues. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics.

A tissue distribution study of a surrogate, mRNA-1647 [an mRNA-based cytomegalovirus (CMV) vaccine that contains 6 mRNA sequences in a 1:1:1:1:1:1 ratio] in SM-102-containing LNPs was studied in rats by the IM route. Each mRNA molecule was measured in selected organs/tissues using a multiplex branched DNA (bDNA) assay. Levels for all six mRNA-1647 constructs were detectable in plasma and tissues in the same ratio as in the test material. The highest mRNA-1647 concentrations were observed at the injection site, followed by the proximal and distal lymph nodes, spleen, eye, liver and plasma (and in other tissues, similar to and/or less than levels in plasma). Maximum concentrations (C_{max}) in tissues and plasma were between 2 and 24 hours post-dose. The elimination $t_{1/2}$ was 15 hours for muscle, 30-35 hours for lymph nodes and 63 hours for spleen. Low levels were detected in testes (less than in plasma) and trace or below limit of quantification levels in brain. Overall, the vaccine mRNAs were mainly retained at the injection site and distributed to local lymph nodes and spleen; only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues. The mRNA constructs did not persist beyond 1 to 3 days in tissues, except for injection site muscle, lymph nodes and spleen (detectable by 5 days). Overall, based on the submitted data modified mRNAs are likely degraded in tissues with half-lives ($t_{½}$) of 15-60 h.

Novel excipients

The LNP contains two novel excipients, SM-102 and PEG2000-DMG. No ADME study reports were submitted for these individual lipid components. An IV study in rats with a radiolabelled lipid SM-86 similar to SM-102, showed that the lipid was metabolised via ester hydrolysis to release the lipid tails, with the remaining fatty acid further metabolised by beta-oxidation. The head group (i.e., radioactivity) was rapidly eliminated via both biliary (via faecal) and urinary excretion with nearly complete elimination (~92% of dose) within 1 week after dosing and the majority in 24 h (~80% of dose). Moreover, these data indicate that after administration of LNPs containing SM-86, SM-86 distribution is consistent with the distribution of mRNA from the administered LNPs (i.e., highest levels of radioactivity following IV dosing of [^{14}C]-SM-86 included spleen, liver and plasma). Preliminary summary internal company data on SM-102 indicates that the elimination $t_{½}$ of SM-102 in PEG2000-DMG-containing LNPs after IV dosing in serum, liver, and spleen was 3.5, 9.7, 15 h, respectively, similar to the $t_{½}$ of SM-86 in PEG2000-DMG-containing LNPs (1.3, 8.8, and 11 h, respectively).

https://www.who.int/biologicals/areas/vaccines/TRS_987_Annex2.pdf?ua=1

Repeat dose toxicity

No GLP-compliant toxicity studies were carried out with mRNA-1273 vaccine. Only a non-GLP toxicity study was carried out with mRNA-1273 with 2 doses, 3 weeks apart (30-100 μg/dose or up to 400 μg/kg body weight; no necropsy). Six standard GLP-compliant toxicity studies were carried out with 5 modified mRNA-LNP vaccines from the same development platform [2 Zika virus vaccines - mRNA-1706, mRNA-1893; 1 hMPV/PIV3 vaccine - mRNA-1653; and 2 CMV vaccines - mRNA-1647, mRNA-1443] using SM-102-containing LNPs formulated with the same four lipid components. Rats were given 3-4 IM doses every 2 weeks (8.9 to 150 μg/dose; for up to 6 weeks [range: 1 month (3 doses) to 6 weeks (4 doses)] with additional assessments made following a short recovery period (2 weeks in all studies). The lack of a submitted GLP-compliant toxicity study with mRNA-1273 is acceptable based on a toxicity profile established with surrogate mRNA-LNP vaccines developed using the same platform. Notably, the observed effects (*ie*, toxicities; see below) can largely be attributed to the lipid components of LNP particles of the vaccine products and immune responses to the vaccine. The duration of the studies (up to 6 weeks maximum) and number of doses are considered acceptable. The dosing interval (2 weeks) was appropriate given the immune response peaks 2-3 weeks after dosing and the clinical dosing interval is 4 weeks. The two novel excipients (SM-102 and PEG2000-DMG) in the vaccine LNPs have been tested in the 6 repeat dose toxicity studies.

In the 6 repeat dose toxicity studies, all the 5 tested encapsulated mRNA vaccines in LNPs resulted in the expected antibody responses in all animals. All the tested surrogate mRNA vaccines were well tolerated with an acceptable safety profile at relatively high doses (up to 150 μg/dose or 600 μg/kg body weight). mRNA vaccine treatment-related findings were attributed to the immunogenicity of the vaccines or uptake of lipids (hepatic findings), which were partially/completely reversible following the 2 week recovery period. Dose-dependent findings comprised injection site reactions, effects on lymph nodes and spleen, increased cytokine levels, elevated body temperatures, haematology changes, increases in globulin, decreases in albumin and hepatic effects.

- Injection site reactions - swelling, oedema, erythema skin thickening and associated inflammation and mixed cell infiltrates (neutrophils, macrophages and lymphocytes) generally decreased by 72 h; some sciatic nerve inflammatory alterations are likely an extension of inflammation at the injection site.
- Draining lymph nodes to the injection site (inguinal, popliteal and iliac) - were enlarged with mixed cell inflammation (perinodal).
- Spleen - decreased cellularity (minimal to mild) of periarteriolar lymphoid sheath at ≥10 μg/dose, and frequently associated with increases in macrophages.
- Cytokine/chemokine levels - whilst transient increases were sometimes seen at ≥10 μg/dose and mostly at higher doses (*eg*, 96 μg/dose) at 6 h for IL-1β, IL-6, IP-10, MCP-1 and MIP-1α, this was consistent with an inflammatory response; and associated with elevated body temperature at ≥10 μg (eg, from 37.47 to 39.13°C), generally returning to baseline in 24 h.
- Haematology, coagulation and clinical chemistry findings: alterations were reported at ≥10 μg/dose and included increases in neutrophil, eosinophil, large unstained cell counts (LUC), decreases in lymphocyte counts, reticulocyte counts and platelet counts; increases in APTT and fibrinogen; increases in globulin and decreases in albumin.
- Liver findings – partially/completely reversible findings of hepatocyte vacuolation and Kupffer cell hypertrophy (no increases in serum transaminases), was probably a manifestation of hepatocyte uptake of LNP lipids.

In the non-GLP toxicity study with mRNA-1273, IM dosing of 30 - 100 µg/dose was well tolerated in rats (safety margin of 200× based on a dose of 400 µg/kg in rats *cf*. 2 µg/kg dose in a 50 kg human) with clinical observations and clinical pathology (haematology/clinical chemistry) findings consistent with those for the other 5 mRNA vaccines derived from the same mRNA development platform. mRNA-1273 vaccine elicited a dose-dependent antibody response 14 days after a 2nd dose.

The highest dose of lipids in the rat studies (~11.6 mg/kg, equivalent to 69.6 mg/m^2 in the rat study at up to 150 µg/dose hMPV/PIV3 mRNA vaccine) was approximately 50 times the clinical exposure of lipids (0.0387 mg/kg for a 50 kg person, equivalent to 1.3 mg/m^2), adjusted for body surface area.

Safety of the novel excipients was not assessed in a second species. Given both excipients are lipids/PEG lipids, potential lifetime exposure is expected to be low, lack of genotoxicity, and the availability of clinical data, the lack of repeat dose toxicity studies in a second species is acceptable.

Genotoxicity

No genotoxicity studies were conducted for the vaccine. This is in line with relevant guidelines for vaccines.

Genotoxicity was assessed for both new excipients SM-102 and PEG-2000-DMG in GLP-compliant *in vitro* bacterial reverse mutation and *in vitro* mammalian cell micronucleus assays with overall negative findings.

One *in vivo* bone marrow micronucleus assay in rats with luciferase mRNA in LNP by IV injection showed no increase in the incidence of micronuclei (highest dose: mRNA 3.21 mg/kg, total lipids 60 mg/kg, SM-102 28.5 mg/kg, PEG-2000-DMG 2.8 mg/kg), whilst a significant increase of micronucleated immature erythrocytes was seen in male rats study with a mRNA-based Zika vaccine (mRNA-1706) in LNPs at the highest dose (mRNA 5.2 mg/kg, total lipids 106 mg/kg, SM-102 60 mg/kg, PEG-2000-DMG 6 mg/kg). Based on negative *in vitro* clastogenicity findings, negative results in the *in vivo* study with luciferase mRNA at high IV doses of lipids, and low and infrequent doses in humans, on balance, the novel excipients SM-102 and PEG-2000-DMG are not expected to be genotoxic. The positive finding in male rats dosed with the Zika vaccine was possibly secondary to vaccine-induced inflammatory responses.

Carcinogenicity

Carcinogenicity studies were not conducted. This is acceptable based on its duration of use, and applicable guidelines. The novel lipid excipients are not expected to be carcinogenic based on the low exposure, duration of exposure and overall consideration of the absence of genotoxicity findings (see discussion above).

Reproductive toxicity

A single reproductive GLP-compliant developmental and reproductive [DART] toxicity was performed in rats with mRNA-1273. The mRNA-LNP vaccine (100 µg/dose) was administered to females twice before mating (28 and 14 days prior to mating) and twice during gestation (gestation days [GD] 1 and 13). mRNA-1273 vaccine elicited antibody responses to the SARS-CoV2 S2 protein in maternal animals (peaking on GD13). High antibody titres were also observed in fetuses on GD 21 and pups on postnatal day 21, indicating transfer of antibodies via placenta and milk. The only remarkable mRNA-1273 treatment-related finding comprised wavy ribs and increased nodules on ribs. Wavy ribs and rib nodules are common findings in rat fetuses and they typically resolve postnatally without medical intervention. There was no effect on pup growth and viability in delivered pups. The maternal mRNA dose (280-400 µg/kg before mating and during gestation) in rats was 140-200 times the human dose for a 50 kg person. The exposure to lipids in the LNP in rats was 25-36 times the human exposure based on dose adjusted for body surface area. Overall, there were no vaccine-related adverse effects on female fertility, pregnancy, embryofetal or postnatal (pre-weaning) development. The effect on male fertility has not been determined.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1. This category is considered appropriate based on the absence of adverse findings in the reproductive toxicity study in rats.

Local tolerance

As discussed above, all the 5 tested encapsulated surrogate mRNA-based vaccines formulated in LNPs were well tolerated locally in rats, where local reactions observed post IM dosing were generally limited to inflammation which generally decreased by 72 h and recovered by the end of the 2 week recovery period.

Paediatric use

mRNA-1273 is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for SPIKEVAX® detailed in the sponsor's draft **Risk Management Plan** (Part II Module SII: Nonclinical Part of the Safety Specification; Version 2.0, of 8 June 2021) are in general concordance with those of the Nonclinical Evaluator.

Key findings from nonclinical data are adequately identified. However, it should be noted that fertility was only studied in females and the effect on male fertility has not been determined.

PRODUCT INFORMATION

ROUND 1 EVALUATION

The following comments refer to the draft Product Information document version - "*SPIKEVAX 18yrs+_PI_V1.0_09July21"*. Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no nonclinical interaction studies. The proposed statement should be assessed by the clinical evaluator.

> "No interaction studies have been performed. Concomitant administration of Spikevax with other vaccines has not been studied."

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The statement proposed in Section 5.3 **Preclinical safety data** – ***Reproductive toxicity*** should be moved here with a minor modification (pertaining to the lack of study data for male rats).
In addition, the '*developmental toxicity study*' should be referred to as a '*combined fertility and developmental toxicity study.*

The preferred Australian spelling of "fetuses and "embryofetal" should be used in this section.

> "Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in females.
>
> In a combined fertility and developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of Spikevax was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in ~~foetuses~~ fetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryofetal or offspring development or postnatal development. No data are available of mRNA-1273 vaccine placental transfer or excretion in milk. ~~(see section 5.3 Preclinical Safety Data).~~ The effect on male fertility has not been determined."

Use in pregnancy

The sponsor proposes **Pregnancy Category B1** which is appropriate for this product as no embryofetal effects have been noted in a combined reproductive and development study in rats, as well as the following statement. Some minor modification to the text is suggested. Thus:

> "There is limited experience with use of Spikevax in pregnant women. ~~Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal embryofetal development, parturition, or post-natal development (see section 5.3 Preclinical Safety Data).~~
>
> A combined fertility and developmental toxicity study in rats did not show vaccine-related harmful effects on embryofetal development (see **Effects on Fertility**)

Administration of Spikevax in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and ~~foetus~~ fetus."

Use in lactation

It is recommended that findings of the rat study be stated.

"It is unknown whether Spikevax is excreted in human milk. *A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see **Effects on fertility**).*"

5.1 PHARMACODYNAMIC PROPERTIES

Statements on the mechanism of action are supported by nonclinical data. Minor editorial changes are suggested.

"Spikevax contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral spike protein. The expressed, membrane bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19."

5.3 PRECLINICAL SAFETY DATA

The TGA Form for providing PI information[2] does not generally include nonclinical toxicity or reproductive toxicity findings or any related statements in this section - only **Genotoxicity** and **Carcinogenicity**. Therefore, text other than genotoxicity and carcinogenicity statements should be deleted as indicated below. Text pertaining to **Fertility and Pregnancy** should, however, be moved as indicated above in the corresponding headings. The statements on genotoxicity and carcinogenicity are acceptable with some minor additional text.

"~~Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.~~

~~General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low."~~

~~**Reproductive Toxicity**~~

~~"In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of Spikevax was administered to female rats by the intramuscular route on four occasions:~~

[2] Form for Product Information approved by the Secretary under subsection 7D(1) of the Therapeutic Goods Act 1989. https://www.tga.gov.au/form-providing-product-information

~~28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of mRNA-1273 vaccine placental transfer or excretion in milk."~~

Genotoxicity

The statement should include the range of assays conducted together with a summary statement regarding weight of evidence and overall genotoxic potential. Additional text is recommended.

Proposed text:

> "In vitro and in vivo genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low."

Based on the submitted nonclinical data, the following text is recommended.

"The novel lipid components SM-102 and PEG-2000-DMG of the vaccine were negative in the bacterial reverse mutation Ames test and *in vitro* micronucleus test in human peripheral blood lymphocytes. A luciferase mRNA in SM102-containing lipid nanoparticles was negative in a rat bone marrow micronucleus assay (IV dose of SM-102 28.5 mg/kg, PEG-2000-DMG 2.8 mg/kg), whilst a surrogate ZIKA mRNA-based vaccine formulated in SM-102-containing lipid nanoparticles induced micronuclei in male rats, but not in females (IV dose of SM-102 60 mg/kg, PEG-2000-DMG 6 mg/kg). The weight of evidence suggests the genotoxicity potential of the novel lipid components SM-102 and PEG-2000-DMG is very low. The other components of SPIKEVAX (other lipids and mRNA) are not expected to be genotoxic."

Carcinogenicity

Recommended additional wording for this section is as follows:

> "Carcinogenicity studies were not performed. The components of the vaccine (lipids and mRNA) are not expected to have carcinogenic potential."

ROUND 2 EVALUATION

The following comments refer to the most recent draft Product Information document version – "*SPIKEVAX 18yrs+_PI_4.0_26July21*" accompanying the sponsor's pre-ACV response of 27 July 2021.

In the sponsor's response document, all of the above Round 1 changes were accepted as is (without modification). However, the sponsor proposed minor changes and reasons as shown below.

1. progenitor elasomeran ~~formulation~~ ~~vaccine formulation containing the same quantity of mRNA (100 micrograms)~~ –
"**clarification to differentiate Moderna formulation from that of Pfizer**"

2. ~~maternal animals~~ dams "**Moderna proposed amendment**"

The wording "progenitor" does not appear to be appropriate here. Minor changes to the revised statements are suggested as shown below.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

"Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in females.

In a combined fertility and developmental toxicity study, ~~0.2 mL of a progenitor elasomeran formulation~~ 100 µg mRNA (elasomeran) and other ingredients included in a single human dose of Spikevax was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in dams from prior to mating to the end of the study on lactation day 21 as well as in fetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo fetal or offspring development or postnatal development. No data are available on Spikevax vaccine placental transfer or excretion in milk. The effect on male fertility has not been determined."

APPENDIX 1 —NONCLINICAL DATA NOT REVIEWED IN THE SWISSMEDIC EVALUATION

The Round 1 report included a request for the sponsor to submit several studies mentioned, but not evaluated, in the Swissmedic report. These studies are evaluated below.

Pharmacology

S antigen expression

Study MOD-4112.1273

Evaluation of *in vitro* expression of SARS-CoV-2 mRNA and *in vivo* expression of mRNA-1273

Study details

- *In vitro* expression was evaluated in HEK293T cells transiently transfected with 0.003125 - 0.2 µg (dose titration) or 0.05 - 0.2 µg (main assay) of mRNA encoding SARS-CoV-2 S-2P using a commercial RNA transfection kit, TransIT®-mRNA transfection kit (Mirus). The mRNA was unformulated pre-clinical mRNA encoding the SARS-CoV-2 S-2P antigen. It was synthesized *in vitro* using an optimized T7 RNA polymerase-mediated transcription reaction with complete replacement of uridine by N1-methyl-pseudouridine. After 24, 48, 72 h (dose titration only) cells collected and assessed for expression of the encoded antigens using fluorescence-activated cell sorting (FACS). To detect surface protein expression, cells were stained with antibodies specific to the N-terminal domain (NTD: 4A8 mAb) and receptor binding domain (RBD: CR3022 mAb) epitopes of the SARS-CoV-2 spike protein and evaluated at 24 and 48 h.

- *In vivo* expression was evaluated in BALB/c mice following IM injection of 2 or 10 µg mRNA-1273. Assessments performed on immune cell populations using FACS harvested from spleen and draining lymph nodes of BALB/c mice (*n* = 6/group) 24, 48, 72 h post injection. mAbs specific to the NTD (using 4A8 mAb) and RBD (using CR3022 mAb) epitopes of S protein evaluated in plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) collected from both tissues.

Major findings

In vitro expression

- Sustained levels of SARS-CoV-2 S-2P antigens were observed in HEK293T cells over 24 -72 h in the dose titration assay, with optimal expression between 0.05-0.2 µg. Similar SARS-CoV-2 S-2P expression was observed by staining with mAbs that bind to the RBD (CR3022) and NTD (4A8) epitopes of SARS-CoV-2 S-2P. Similarly, mean fluorescent intensity (MFI) of positive antigen expressing cells was similar for cells stained with antibodies specific to the NTD and RBD epitopes, with a slight dose effect observed (Figure 1).

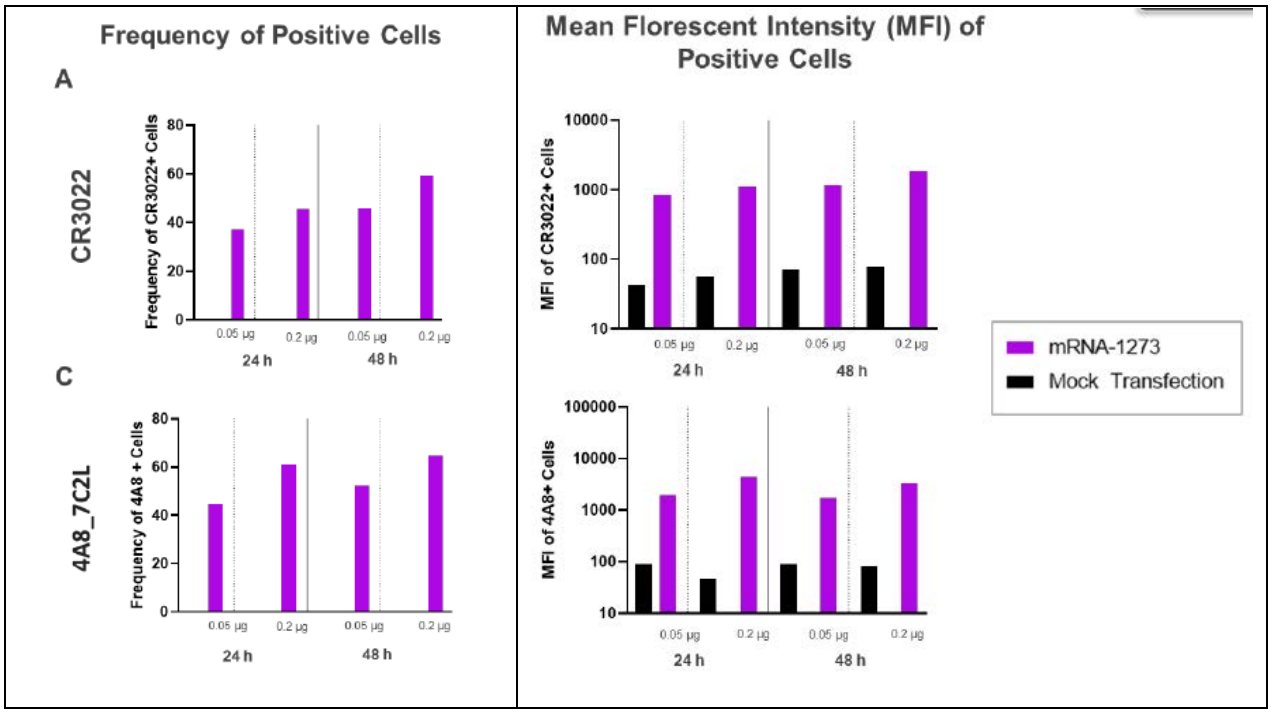


Figure 1. *In vitro* cell surface expression of the SARS-CoV-2 S-2P antigen after transfection of HEK293T Cells with mRNA encoding SARS-CoV-2 S-2P, measured by flow cytometry

In vivo expression

- Clinical observations – *not reported*
- Assessment of *in vivo* expression of mRNA-1273 in spleen and draining lymph nodes showed antigen expression (greater at the high dose) in dendritic cells with no major differences in RBD or NTD epitope expression.
    - spleen: antigen expression was observed in cDCs and pDCs irrespective of epitope staining, and antigen levels were dose-dependent at both timepoints tested (24 and 72 h post injection). The expression detected by mAb for the RBD was higher at 72 h than at 24 h.

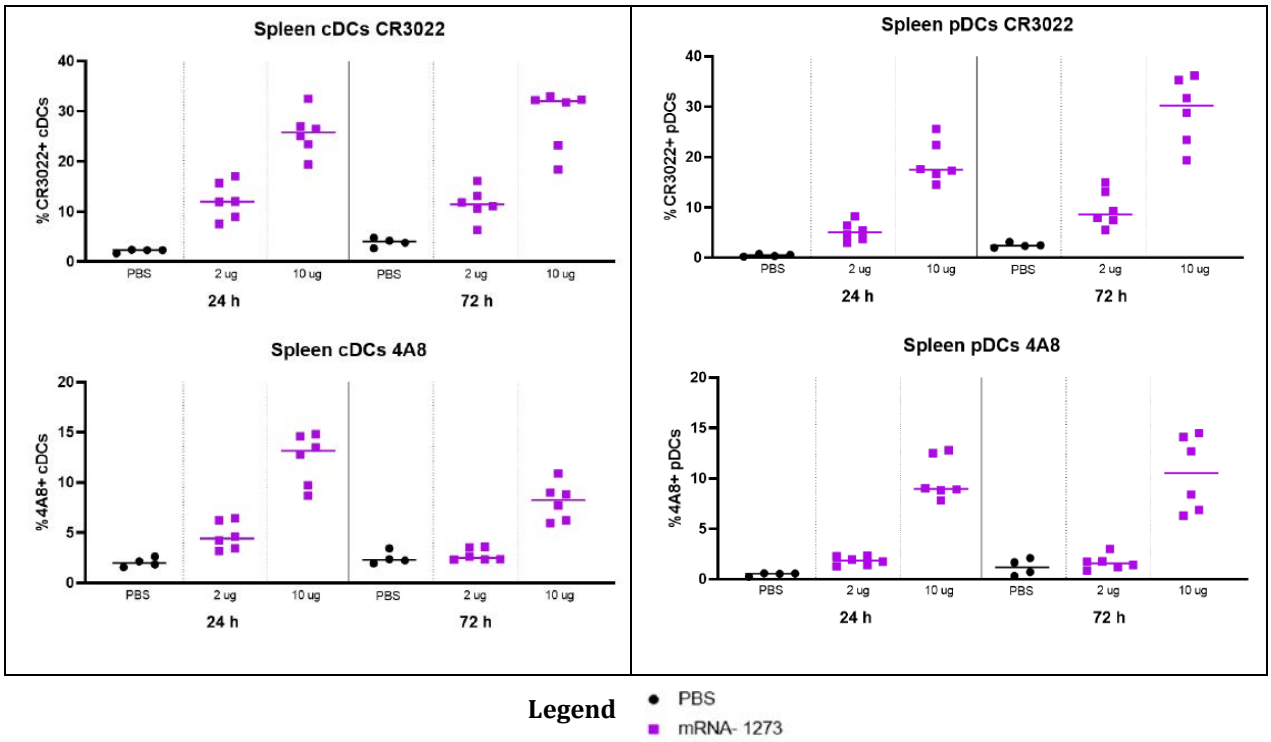


Figure 2. ***In vivo expression of mRNA-1273 in splenic cDCs and pDCs measured by flow cytometry using 4A8 and CR3022 mAbs***

- draining lymph nodes: expression detected by mAb for the RBD was lower than in spleen and for the NTD, similar to that in spleen, with peak expression at 48 h (decreasing to background level by 72 h for both epitopes).

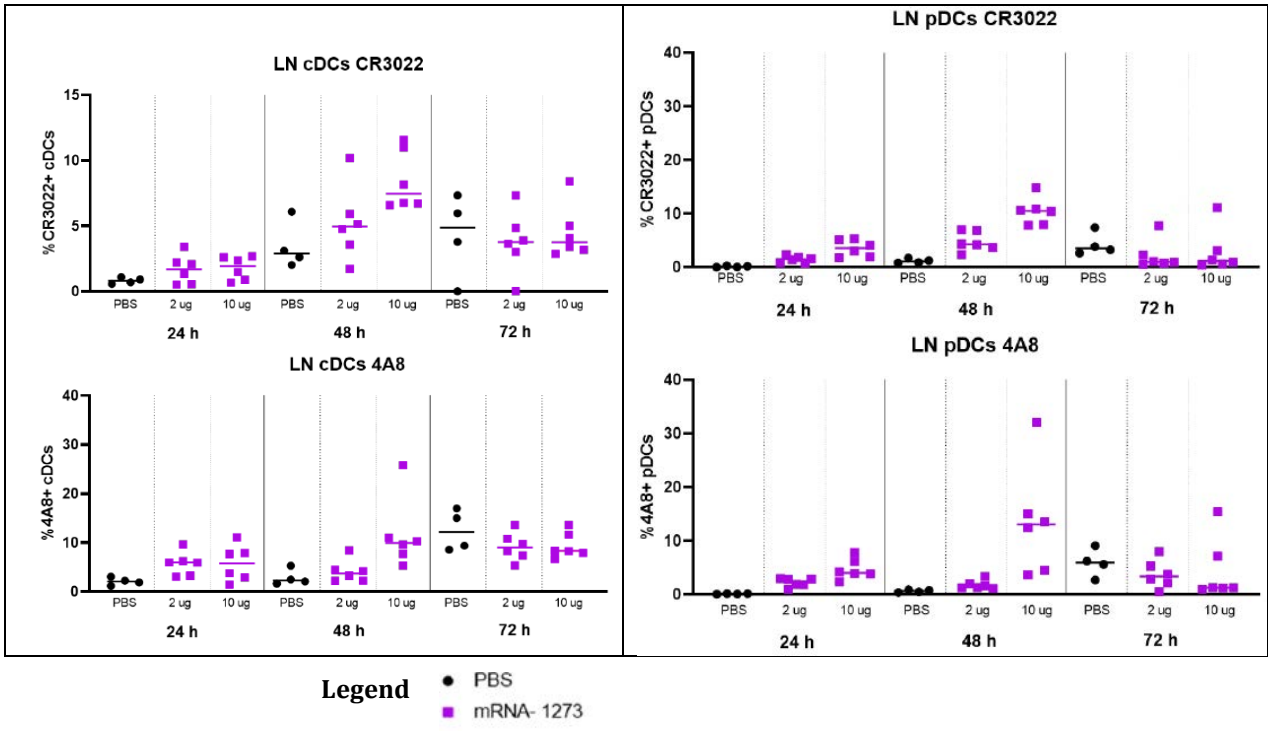


Figure 3. ***In vivo expression of mRNA-1273 in draining lymph node cDCs and pDCs measured by flow cytometry***

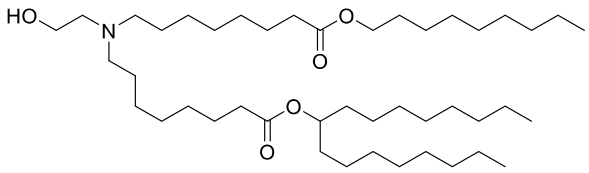
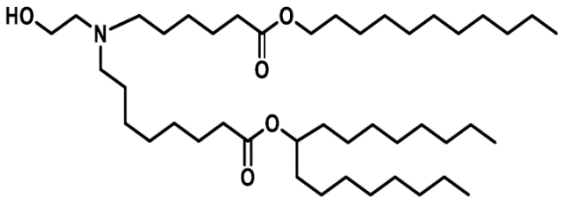
- Overall, similar levels of the expressed spike protein were detected in dendritic cells of spleen at 24 and 72 h post dose, while the expression in lymph nodes peaked 48 h and then significantly decreased by 72 h. However, higher expression levels of the RBD epitope was observed in spleen pDCs and cDCs than in lymph nodes.

Pharmacokinetics

Novel excipients

Study 2308-120

The pharmacokinetics, tissue distribution and excretion of SM-86, a structural analogue of SM-102, was investigated with [^{14}C]-SM-86-containing lipid nanoparticles (LNPs) encapsulating NT-FIX (Non-Translating Factor IX) mRNA following a single IV dose by monitoring [^{3}H-] lipid-marker or by QWBA [Quantitative whole body autoradiography] in rats

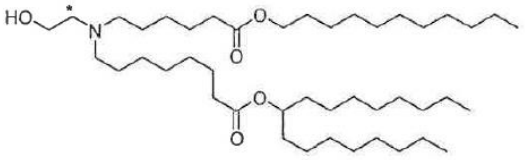
Structure of SM-86	**Structure of SM-102**
	
Chemical Name: Heptadecan-9-yl 8-((2-hydroxyethyl) (8-(nonyloxy)-8- oxyoctyl) amino)octanoate **Empirical Formula**: C44H87NO5	**Chemical Name**: Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate **Empirical Formula**: C44H87NO5

Study title

ADME Study of Pharmacokinetics, Excretion, and Tissue Distribution of [^{14}C]-SM-86 Containing Lipid Nanoparticles Encapsulating NT-FIX mRNA Following a Single Intravenous Infusion in Rats

Study details

- 10 min IV infusion of 2 mg/kg in Sprague Dawley (albino, non-pigmented) or Long-Evans (pigmented) rats.
- Radioactivity in blood, plasma, and excreta was measured by liquid scintillation counting (LSC) (n=5-6/sex/time point). Distribution in tissues was by QWBA [Quantitative whole body autoradiography; n=1/time point at 1, 10, 24, 48 and 168 h).
- The position of the radiolabel is shown below



[^{14}C]-Compound 18

* Denotes ^{14}C labeling position

Major findings

Clinical observations – not reported

Pharmacokinetics

Radioactivity plasma C_{max} in males and females was 25,800 ± 1350 and 37,800 ± 2610 ng-equivalents/g respectively and T_{max} was 15 min after the end of infusion. Levels of radioactivity in the plasma declined rapidly following C_{max} (>2-orders of magnitude by 6 h post dose with radioactivity not detected in both sexes by day 7.

Tissue distribution

- Radioactivity was widely distributed in tissues (see table below). In males at 1 h post dose, highest levels of radioactivity were in the liver, small intestinal contents, adrenal gland, spleen and kidney. In females, 1 h post dose, liver, adrenal gland, spleen and small intestinal contents showed highest levels. By 24 h radioactivity in tissues was significantly reduced (generally < 200 ng eq./g) and by day 7, radioactivity was mostly eliminated in males (some radioactivity still detected in adrenal, liver and spleen; < 100 ng eq./g) and in females (some radioactivity detected in female adrenal, brown fat, liver, ovary and spleen; ≤ 200 ng eq./g).

Tissue: blood ratio of radioactivity (determined by QWBA) in albino rats at 1 h

Tissue	Tissue radioactivity | Tissue: blood ratio^	
	Male	Female
liver	18122 | 8	21878 | 3
small intestinal contents	6966 | 3	6630 | 0.8
adrenal gland	6883 | 3	17030 | 2.1
spleen	6589 | 2.9	10061 | 1.3
kidney	4525 | 2	3623 | 0.4
lung	2057 | 0.9	3176 | 0.4
myocardium	1268 | 0.6	2752 | 0.3
lymph nodes	514 | 0.2	2289 | 0.3
testes	78 | 0.03	-
ovary	-	2074 | 0.3
brain [cerebellum/cerebrum]	88/60 | / 0.04/0.03	256/190 | 0.03/ 0.02

^Blood radioactivity at 1 h: males: 2251 ng eq./g; females: 8080 ng eq./g

- Biodistribution in pigmented and non-pigmented rats indicated no particular affinity for melanin-containing tissues.
- High levels of radioactivity in the intestinal contents is consistent with biliary excretion into the duodenum with eventual elimination in the faeces.

Excretion

- Urine was the major route of excretion of radioactivity (by 8 h: 39-47% of dose; by 24 h: 60-65%; by day 7: 63-68%), with moderate faecal excretion (by 24 h: 16-18%; by day 7: 21-26%) following biliary excretion into the duodenum.
- Overall, by 24 h and day 7, total excretion by the urinary and faecal routes was high (24 h and day 7: 80% and >90%, respectively of administered dose of radioactivity) in both sexes.

Sex	Collection period	Percent dose			
		Urine	Faeces	Cage wash	Total
Male (n=6)	0-8 h	47.30	0	-	-
	8-24 h	17.97	18.37	2.71	-
	24-48 h	2.06	1.98	0.36	-
	0-168 h	67.83	20.98	3.26	92.08
Female (n=6)	0-8 h	38.71	0.13		-
	8-24 h	20.91	16.21	2.17	-
	24-48 h	2.46	8.69	0.53	-
	0-168 h	62.69	25.86	2.86	91.41

Metabolism

The metabolic pathway for SM-86 proposed by the sponsor is shown in **Figure 4**.

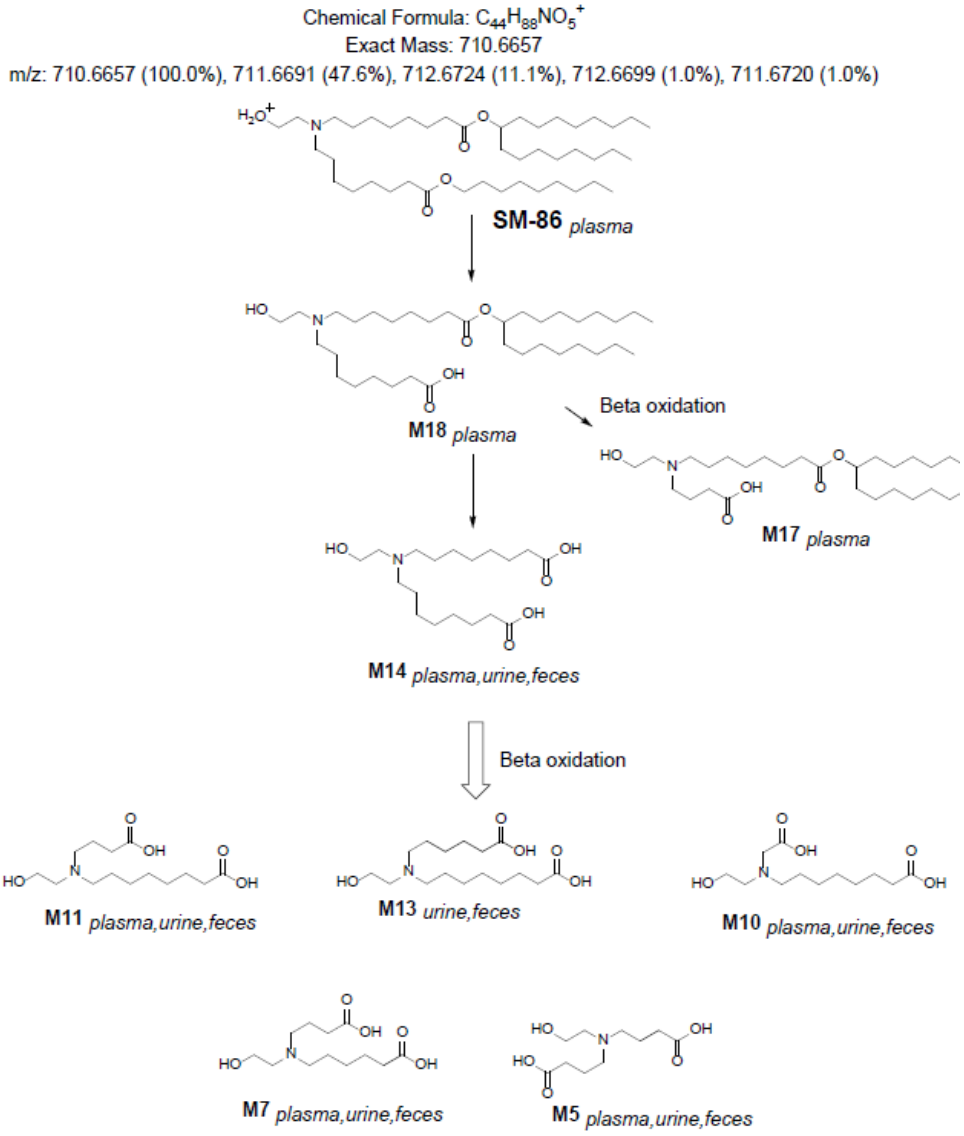


Figure 4. Proposed metabolic pathway for SM-86 in rats

- The metabolite profile of [^{14}C]-SM-86 in plasma, urine and faeces indicated 3-5 metabolites (3 in males and 5 in females) and unchanged [^{14}C]-SM-86 were present in plasma, 14 metabolites appear in the urine and 8 in the faeces. Metabolism of SM-86 occurs by hydrolysis of the ester groups followed by beta-oxidation of the resulting fatty acids.
- Unchanged SM-86 (up to 40% of total radioactivity) together with two metabolites (M11 and M14; 20-30 and 30-40% of total radioactivity, respectively) were present in plasma at 1 h postdose. At 10 h postdose, only M5 was detected (n=1/sex/time point at 1 and 10 h).
- The 3 metabolites detected in plasma were also main metabolites in urine (M5 ~16% of dose, M11 ~25% of dose, M14 ~8% of dose) and two in faeces (M11 ~8% of dose, M14 ~5% of dose). Other metabolites were <1% of dose in urine or faeces except for M3 (~3% of dose in urine), M7 (~2.5% of dose in urine), M9 (~1.4% of dose in urine) and M15 (~1.4% of dose in faeces). Pooled excreta were analysed for metabolites.

APPENDIX 2: COMMENTS ON THE SPONSOR'S RESPONSE TO ROUND 1 QUESTIONS

Question 1

As noted by SwissMedic, summarised data from cell-based experiments indicated no difference in mRNA half-life between unmodified mRNAs and the same sequences fully substituted with N1-methyl-pseudouridine. Please provide the report(s) when available.

Sponsor's response:
Report is not available (synopsis only provided), but will be provided when ready.
The sponsor stated: "*A report is not available, but will be provided as soon as it is ready. A synopsis of the methods used and results follow.*

Two methods for measuring mRNA half-life have been developed. One method is to electroporate mRNA into cells and measure mRNA abundance over time using either a branched DNA assay, quantitative reverse transcriptase PCR (qRT-PCR), or RNA-Seq (Figure 1A). Another method is to transfect cells (by means of lipofection) with an mRNA encoding a short-lived fluorescent reporter protein, and then measure cellular fluorescence over time. We can use a system of differential equations to infer mRNA half- life from the kinetics of fluorescence accumulation and decay over time (Figure 1B, similar to Mauger et al 2019 PNAS 116:24075-24083)."

TGA Comment: TGA awaits submission of the final report.

Question 2

According to the Swissmedic report, Moderna has performed a characterisation of *in vitro* expression of spike protein and antigen expression in cells at the injection site, in the draining lymph nodes, spleen and in systemic circulation in mice (Study MOD-4112.1273). Please provide this study report when available.

Sponsor's response: *Report provided*.

TGA Comment: The study is reviewed in Appendix 1 above.

Question 3

Please provide the bDNA assay qualification report for Study 5002121
(also requested by SwissMedic).

Sponsor's response: There is no bDNA assay qualification report.
Twelve (12) data Tables (Tables 1-12 data) of quality control and calibration assay results were provided in the response.

TGA Comment: The TGA requests more detailed information from the sponsor (i.e., any available data such as company data, internal research reports inclusive of methodology) to allow critical review and independent assessment of the study.

Question 4

Please provide the pharmacokinetic study with SM-86, a structural analogue of SM-102.

Sponsor's response: Report provided.

TGA Comment: The study is reviewed in Appendix 1 above.

Question 5

It is noted in the SwissMedic evaluation report "The pharmacokinetics of SM-102 was assessed in PEG2000-DMG-containing LNPs similar to mRNA-1273 after IV administration of a 0.2 mg/kg dose in rats (unpublished data) indicating SM-102 half-lives in serum, liver, and spleen of 3.5, 9.7, and 15 h, respectively." Please provide the study report on SM-102 in PEG2000-DMG-containing LNPs.

Sponsor's response: The Sponsor indicated that the pharmacokinetic study was "unpublished data" and provided a brief summary.

The sponsor stated "The pharmacokinetics of SM-102 was assessed in PEG2000-DMG containing LNPs similar to mRNA1273 after IV administration of a 0.2 mg/kg dose in rats (unpublished data) indicating SM-102 half lives in serum, liver, and spleen of 3.5, 9.7, and 15 h, respectively. These are very similar to those determined in the same experiment for SM-86 in otherwise identical PEG2000-DMG containing LNPs (1.3, 8.8, and 11 h, respectively) further supporting the sponsor's assertion of similar pharmacokinetic behaviour between these two novel lipids and the unlikelihood of accumulation upon repeat dosing via the mRNA-1273 clinical regimen. These were internal research studies and a formal report has not been produced for these studies. ..."

TGA Comment: TGA requests more detailed information from the sponsor (i.e., any available data such as company data, internal research reports inclusive of methodology) to allow critical review and independent assessment of the study.

Question 6

According to the SwissMedic evaluation report, a study in rhesus macaques (NHPs) is underway to evaluate antibody levels over the course of 1 year and protection from high-dose SARS-CoV-2 challenge 6 months and 1 year after vaccination with 100 μg mRNA-1273. Please provide the report of this study when available.

Sponsor's response: The sponsor indicated the study was repurposed to evaluate protection against the B.1.351 variant. The results are in the final stage of publication. In addition, other animals from this study are approximately 9 months after the primary immunisation. These animals will likely be challenged with the B.1.617.2 variant to evaluate long-term protection. These results, along with measurements of immunogenicity over the course of the study, will be provided once completed.

TGA Comment: TGA awaits submission of the final reports.

Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report Provisional Approval Pathway

Elasomeran (Spikevax)
(for the use in individuals 18 years of age and older)

Submission No: PM-2021-02994-1-2

Sponsor: Moderna Australia Pty Ltd

Pre-ACV report: 19 July 2021
Round 2 report: 27 July 2021
(Use in individuals aged between 12 and 17 years refer to pages 26 onwards)

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TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type:	New biological entity
Sponsor:	Moderna Australia Pty Ltd
Generic name:	**Elasomeran**
Trade name:	**Spikevax**
Dose form and strength:	Suspension for intramuscular injection; 0.2 mg/mL
Drug class:	Active immunisation to prevent COVID-19 disease (mRNA vaccine)
Submission No; eSubmission ID:	PM-2021-02994-1-2; e006131 - (0000)
RMP file No:	E21-324668
TRIM reference:	D21-2850947
EU-RMP Version:	Initial Submission – version 2.0 (tracked copy); date 8 June 2021; DLP 8 May 2021 Submitted on 16 July 2021: version 2.1; date 15 July 2021; DLP 31 May 2021 D21-2851278
ASA Version:	Initial Submission – version 0.1; date 3 July 2021 Submitted on 23 July 2021 – version 0.2; date 22 July 2021 D21-2884035
Evaluator:	s22 [redacted]
Peer Reviewer:	
Date authorised:	19 July 2021 (pre-ACV report) 27 July 2021 (Round 2)
RMP referral to ACV:	Meeting 23 (30 July 2021)
Pharmacovigilance activities:	Routine Follow-up questionnaires Clinical Trial
Risk minimisation Activities	Routine Department of Health initiated risk minimisation programs
Black Triangle Scheme:	Yes - new medicine
PSUR review issues:	Yes
IDMP referral:	Level 1 (Intensive Monitoring) - Provisionally registered new chemical / biological entity
RMP Compliance Tracker:	Choose an item.

SUMMARY

- Adjutor Healthcare Pty Ltd, as the regulatory agent for the Australian sponsor Moderna Australia Pty Ltd has applied to register a new biological entity, elasomeran (Spikevax) through the Provisional Approval Pathway. Spikevax is proposed to be used for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen involves two intramuscular injections (0.5 mL each), 28 days apart.
- The initial submission included EU-RMP version 1.1 (date 1 March 2021; DLP 21 December 2020), tracked version 1.2 [date 31 May 2021; DLP 21 December 2020] and tracked version 2.0 (date 8 June 2021; DLP 8 May 2021] and ASA version 0.1 [date 3 July 2021]. With this initial submission the sponsor was seeking approval for the use this vaccine for individuals 12 years and older. However, following discussions with the TGA, the sponsor is currently seeking approval for the target population of adults 18 years and older in the first instance.
- On 16 July 2021, the sponsor provided EU RMP version 2.1 (date 15 July 2021; DLP 31 May 2021), in which the summary of safety concerns has been updated to include myocarditis (including myopericarditis) and pericarditis as important potential risks.
- On 23 July, the sponsor provided an updated ASA version 0.2 (date 22 July 2021), which referenced the EU RMP version 2.1.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies described in EU RMP version 2.1 are summarised below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Anaphylaxis	✓*	✓†	✓	–
	Myocarditis (including myopericarditis)	✓*	✓†	✓	–
	Pericarditis	✓*	✓†	✓	–
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	✓*	✓†	–	–
Missing information	Use in pregnancy and while breast-feeding	✓	✓†	✓	–
	Long-term safety	✓	✓†	–	–
	Use in immunocompromised subjects	✓	✓†	✓	–
	Interaction with other vaccines	✓	✓†	✓	–
	Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	✓	✓†	✓	–
	Use in subjects with autoimmune or inflammatory disorders	✓	✓†	✓	–

*Follow-up questionnaires
†Clinical studies

- At this stage, the summary of safety concerns is considered acceptable from an RMP perspective.

- The proposed pharmacovigilance plan is acceptable from an RMP perspective. The clinical evaluator/TGA delegate will assess the acceptability of the clinical study plan that is proposed to fulfil the requirement of the provisional registration.
- Only routine risk minimisation measures are proposed. This is in line with the other COVID-19 vaccines currently approved for use in Australia. At this stage, routine risk minimisation measures, together with the risk minimisation activities launched by the Department of Health, are considered acceptable to minimise the risks associated with Spikevax.

NEW AND OUTSTANDING RECOMMENDATIONS - ROUND 2

The recommendations included in the Round 2 RMP report, along with consideration of the sponsor responses, are located in Section 6.1 (Recommendations 3, 12 and 16). The sponsor has satisfactorily addressed these recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

> *The Spikevax EU-Risk Management Plan (RMP) (version 2.1, dated 15 July 2021; DLP 31 May 2021), with Australian Specific Annex (version 0.2, dated 22 July 2021), included with submission PM-2021-02994-1-2, 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).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of 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. Each report must have been prepared within ninety calendar days of the data lock point for that report.*
>
> *Additional to the routine submission of the routine PSURs, expedited monthly, 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.*

Spikevax (elasomeran) 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 products entire period of provisional registration.

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.

Other advice to the Delegate

1. The following matters regarding the proposed PI are raised to the delegate's attention:

- The SmPC has the following information regarding myocarditis and pericarditis, which is not included in the draft PI for Spikevax:

Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

- The following statement, which is included in the PI documents for other COVID-19 vaccines, approved in Australia, has not been included in the draft PI for Spikevax.

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.

2. It is expected that the acceptability of the clinical study plan for provisional registration will be assessed by the clinical evaluator/delegate.

3. The conditions of registration relevant to the clinical study plan are to be imposed by the delegate.

Issues for PSUR Review (for internal use only)

The current practice in RMS is to review the PSURs for COVID-19 vaccines This requirement will be revisited at the time of receipt of the PSUR.

Rationale for IDMP Inclusion (for internal use only)

Level 1 (Intensive Monitoring) - Provisionally registered new vaccine against COVID-19 disease.

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MAIN BODY

1. BACKGROUND

Adjutor Healthcare Pty Ltd, as the regulatory agent for the Australian sponsor Moderna Australia Pty Ltd has applied to register a new biological entity, elasomeran (Spikevax) through the Provisional Approval Pathway. Spikevax is proposed to be used for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen involves two intramuscular injections (0.5 mL each), 28 days apart.

The initial submission included EU-RMP version 1.1 (date 1 March 2021; DLP 21 December 2020), tracked version 1.2 [date 31 May 2021; DLP 21 December 2020] and tracked version 2.0 (date 8 June 2021; DLP 8 May 2021] and ASA version 0.1 [date 3 July 2021]. With this initial submission the sponsor was seeking approval for the use this vaccine for individuals 12 years and older. However, following discussions with the TGA, the sponsor is currently seeking approval for the target population of adults 18 years and older.

On 16 July 2021, the sponsor provided EU RMP version 2.1 (date 15 July 2021; DLP 31 May 2021), in which the summary of safety concerns has been updated to include myocarditis (including myopericarditis) and pericarditis as important potential risks.

On 23 July, the sponsor provided an updated ASA version 0.2 (date 22 July 2021), which referenced the EU RMP version 2.1.

1.1. INDICATION

Section 4.1 (Therapeutic Indications) of the proposed Product Information (PI) document states:

> *Spikevax 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.*

The active substance of Spikevax is 0.10 mg mRNA encoding the pre fusion stabilised spike glycoprotein of SARS-CoV-2, embedded in lipid nanoparticles. The following information regarding the mode of action of Spikevax has been extracted from the EU RMP:

> *COVID-19 Vaccine Moderna encodes for the perfusion stabilized spike glycoprotein of SARS-CoV-2. After intramuscular injection, cells at the injection site take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional spike glycoprotein that is inserted into the cellular membrane of the expressing cell(s). The spike glycoprotein is membrane bound, mimicking the presentation of natural infection. The expressed spike glycoprotein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen, which elicits both T-cell and B-cell responses. The immune response to the spike glycoprotein results in functional antibody (Ab) and T-cell responses and in the generation of memory immune cell populations.*

As at 16 July 2021, there have been 188, 655,968 confirmed cases of COVID-19, including 4,067,517 deaths worldwide[1]. In Australia, between 3 January 2020 and 16 July 2021 there have been 31,516 confirmed cases and 912 deaths[2].

1.2. DOSAGE AND ADMINISTRATION

The Dosage and Administration section of the PI states:

Spikevax is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose. The vaccine comes in a ready to use solution (without dilution) once thawed.

There is no data on the interchangeability of Spikevax with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of Spikevax should receive the second dose of Spikevax to complete the vaccination course.

Spikevax comes in multidose vials. Ten or 15 doses (of 0.5 mL each) can be withdrawn from each vial. An additional overfill is included in each vial to ensure that 10 or 15 doses of 0.5 mL can be delivered.

The vials should be stored frozen between -25° C to -15°C, and can be kept for 1 hour at room temperature (15°C to 25° C).

1.3. OVERSEAS REGULATORY STATUS

Many countries, including the following, have approved/authorised the use of this vaccine in individuals 18 years and older:

Country/Region	Date of approval/ Authorisation	Regulatory status
United States	18 Dec 2020	Emergency Use Authorization (FDA)
Canada	23 Dec 2020	Interim order (Health Canada)
European Union	6 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA)
United Kingdom	31 Mar 2021	Conditional Marketing Authorisation (MHRA)
Switzerland	12 Jan 2021	Temporary Marketing Approval (SwissMedic)
Singapore	3 Feb 2021	Pandemic Special Access Route (PSAR) application

[1] WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data
[2] Australia: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data

Japan	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act

On 7 July 2021, the US FDA reissued the letter of Emergency Use Authorization, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 18 years of age and older[3].

1.4. QUALITY OF THE SUBMISSION

The EU RMP and the ASA have been prepared in the recommended formats and are effective for evaluation. The initial submission included EU-RMP versions 1.1 (date 1 March 2021; DLP 21 December 2020), 1.2 [(tracked) date 31 May 2021; DLP 21 December 2020] and 2.0 [(tracked) (date 8 June 2021. The ASA that was provided (version 0.1; date 3 July 2021) referenced the EU RMP version 1.1.

On 16 July 2021, the sponsor provided an updated EU RMP version 2.1 (date 15 July 2021; DLP 31 May 2021) and committed to provide an updated ASA as soon as it becomes available (D21-2851781).

In the absence of an ASA relating to the most current EU RMP (version 2.1), the available ASA (version 0.1) and the latest EU RMP (version 2.1) have been considered in this pre-ACV RMP report, especially considering the expedited timeframes.

2. SAFETY SPECIFICATION

2.1. NONCLINICAL ADVICE ON SAFETY SPECIFICATION

The nonclinical evaluator's report states[4]:

> *Results and conclusions drawn from the nonclinical program for SPIKEVAX® detailed in the sponsor's draft Risk Management Plan (Part II Module SII: Nonclinical Part of the Safety Specification; Version 2.0, of 8 June 2021) are in general concordance with those of the Nonclinical Evaluator.*
> *Key findings from nonclinical data are adequately identified. However, it should be noted that fertility was only studied in females and the effect on male fertility has not been determined.*

2.2. CLINICAL ADVICE ON SAFETY SPECIFICATION

The clinical delegate did not raise any concerns regarding the safety specification detailed in the RMP[5].

2.3. PROPOSED SUMMARY OF SAFETY CONCERNS

The sponsor has proposed the following summary of safety concerns:

[3] US FDA Letter of Authorisation reissued
[4] Nonclinical evaluation report dated 15 July 2021 – TRIM Ref: D21-2850729
[5] Delegate's overview dated 23 July 2021 – TRIM Ref: D21-2883396

Summary of safety concerns	
Important identified risks	Anaphylaxis
	Myocarditis (including myopericarditis)
	Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast-feeding
	Long-term safety
	Use in immunocompromised subjects
	Interaction with other vaccines
	Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in subjects with autoimmune or inflammatory disorders

Myocarditis and pericarditis have been reported following vaccination with COVID-19 vaccines. Though the number of these reports are small when compared to the vaccination rates, these risks are serious and could impact the benefit risk balance of this vaccine. The sponsor has appropriately updated the summary of safety concerns to include these two risks.

According to the EMA's Safety Update Report[6] (dated 14 July 2021) for Spikevax, PRAC has concluded its assessment of immune thrombocytopenia and decided that although nine cases were considered possibly related to the vaccine, no clear causal relationship could be established in any of these cases. The sponsor is expected to closely monitor this risk and report in the Monthly Safety Summary Reports (MSSRs)/ Periodic Safety Update Reports (PSURs).

The EU RMP states that the observed local reactogenicity was 84.2% in participants treated with mRNA-1273 at the first injection and 88.6% at the second injection. Systemic reactogenicity has been observed in 54.9% of participants at the first injection and in 79.4% at the second injection. The adverse reactions associated with reactogenicity are described in the proposed PI and CMI, and will continue to be monitored through clinical trial follow up, as well as routine pharmacovigilance.

Considering the currently available data, the above summary of safety concerns is considered acceptable from an RMP perspective.

3. PHARMACOVIGILANCE PLAN

3.1. PROPOSED PHARMACOVIGILANCE PLAN

Routine pharmacovigilance measures are conducted to monitor the risks of Spikevax.

The following follow-up questionnaires are proposed as part of routine pharmacovigilance activities:

[6] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-14-july-2021_en.pdf

i) Anaphylaxis questionnaire
This questionnaire is intended to collect structured information on severe cases of anaphylactic reaction including anaphylaxis. It is intended to assist with capturing information that can support case classification using the Brighton Collaboration case definition.

ii) COVID- 19/Vaccine Failure Questionnaire
This questionnaire is intended to better characterise the extent and severity of COVID-19 disease reported after vaccination by Spikevax. This questionnaire is to be used following the reporting of vaccine failure and/or COVID-19 disease cases and/or AESI associated with COVID-19 disease after vaccination.

These two questionnaires have been appended to the ASA and are fit for purpose.

iii) Myocarditis and Myopericarditis Questionnaire
This questionnaire is intended to collect structured information on cases of myocarditis or myopericarditis. It is intended to assist with capturing information that can support case classification using the myocarditis Brighton Collaboration case definition as well as the CDC working case definition on acute myocarditis.

iv) Pericarditis Questionnaire
This questionnaire is intended to collect structured information on cases of pericarditis. It is intended to assist with capturing information that can support case classification using the CDC working case definition on acute pericarditis

The questionnaires for myocarditis and pericarditis are not included in the EU RMP version 2.1, and therefore have not been assessed.

Adverse events of special interest (AESI):
The EU RMP states, for all routine and additional pharmacovigilance activities proposed, the sponsor has taken into consideration the list of AESIs prepared by the following regulatory agencies and vaccine expert groups:

- Brighton Collaboration (Safety Platform for Emergency vACcines)
- ACCESS protocol
- US Centres for Disease Control and Prevention (preliminary list of AESI for VAERS surveillance)
- Medicines and Healthcare products Regulatory Agency (unpublished guideline).

The sponsor's measures to monitor AESI are acceptable. The ASA states that the routine pharmacovigilance activities are "*identical to what is specified in the EU-RMP*". It is expected that the sponsor will monitor the AESI in Australia using the follow-up questionnaire mentioned above.

The following are the ongoing and planned additional pharmacovigilance activities:

Safety concern	Additional activity	Proposed actions/ outcomes	Planned submission date
Ongoing studies			
- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) - Anaphylaxis - Long -term safety	Study mRNA-1273-P301 Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Adults Aged 18 Years and Older	Evaluate long -term safety data and durability of vaccine effectiveness (VE)	Final CSR: 31 December 2022
- Anaphylaxis - Long -term safety	Study 20-0003 Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARSCoV-2 spike-specific T cell responses. Follow up period extended by an additional 12 months for 24 months follow-up total after the second dose. Assessment of a booster dose	Final CSR: 01 November 2022
- Anaphylaxis	Study mRNA-1273-P201 Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Adults ≥ 18 Years	Safety, reactogenicity, and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster	Final CSR: mid-APR 2022

-Anaphylaxis -Long-term safety	Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer Blind, Placebo Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARSCoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age	Evaluate the safety, reactogenicity, and effectiveness	Final CSR: Q3 2022
-Use in immunocompromised subjects -Interaction with other vaccines, as possible -Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders) -Use in subjects with autoimmune or inflammatory disorders	Study mRNA-1273-P901 Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S	Evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273, and of 2 doses of vaccine in preventing COVID-19 and severe COVID-19 disease. -Effectiveness stratified by age, sex, race/ethnicity, comorbid conditions. -Effectiveness of two doses of vaccine in preventing COVID-19 among immunocompromised patients. -Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Moderna will also evaluate prevention of COVID-19 when Moderna COVID-19 Vaccine is given concomitantly with another vaccine, in line with current Advisory Committee on Immunization Practice recommendations (e.g., seasonal flu vaccine), as feasible. -Durability of one or two doses of COVID19 Vaccine Moderna against COVID-19 and severe COVID-19 disease will also be assessed	Final study report: 14 Apr 2025
-Anaphylaxis -Use in immunocompromised subjects (AESI)	Study mRNA-1273-P304 A Phase 3b, Open Label, Safety and Immunogenicity Study of SARSCoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls	Evaluate the safety and reactogenicity of the vaccine in adult liver or kidney single organ transplant recipients and healthy controls Evaluate the immunogenicity of the vaccine in adult liver or kidney single organ transplant recipients and healthy controls	Final CSR: 31 Jan2024

Planned Studies			
-Anaphylaxis -Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) -Long-term safety -Myocarditis and pericarditis (AESI and emerging validated safety signals)	Study mRNA-1273-P903 Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	Final study report: 30 June 2023
-Anaphylaxis -Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) -Use in pregnancy -Long-term safety - Interaction with other vaccines -Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) -Use in subjects with autoimmune or inflammatory disorders	Study mRNA-1273-P904 A Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA1273 Vaccine in the EU	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals in European populations. Electronic database assessment of use in pregnant women	Final study report: 31 December 2023
-Use in pregnancy and while breast-feeding	Study mRNA1273 - P902 Observational pregnancy outcome study	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy. Evaluate infant outcomes.	Final study report: 30 June 2024

Australian subjects are not proposed to be included in any of the above studies. However, the outcomes of these studies are expected to be relevant to the Australian population.
The sponsor has provided the clinical study plan for provisional registration in the ASA. The adequacy of the clinical study plan will be considered by the clinical evaluator and/or the TGA delegate.

3.2. ADEQUACY OF PROPOSED PHARMACOVIGILANCE PLAN

The EU RMP states, as per EMA's guidance for RMPs of COVID-19 vaccines (coreRMP19 guidance v2.0[7]) the sponsor will prepare Monthly Safety Summary Reports (MSSRs). The ASA does not contain any information regarding submission of MSSRs to the TGA. While it is noted that the ASA states the pharmacovigilance activities will be the same as described in the EU RMP, the sponsor should include a commitment that it will submit MSSRs to the TGA.

The sponsor should note that the contents of the MSSRs, at the minimum, should include the following:

i. Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
ii. Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women)
iii. Interval and cumulative number of reports per HLT and SOC
iv. Number of reports in Australia and Global
v. Exposure data, stratified by country, age groups, race and ethnicity
vi. Changes to the reference safety information in the interval
vii. Summary of the designated medical events
viii. Ongoing and closed signals in the interval
ix. Reports on number and relevant cases, including time-to-onset and Observed/Expected analyses for the following:
- List of AESI
- RMP safety concerns

x. Fatal reports – numbers and relevant cases, including observed/expected analyses
xi. Number and relevant cases:
- Vaccination failure / lack of efficacy (including confirmed and suspected cases)
- Vaccination errors
- Potential interaction with other vaccines/concomitant treatments

xii. Summary of any outcomes of routine pharmacovigilance activities (as presented in the EU RMP Part III and applied in the Australian context) that have a potential impact on the benefit/risk balance of the vaccine should be included for the purpose of rapid signal detection and communication activities.
xiii. Risk/benefit considerations

The ASA should be updated to include the sponsor's commitment that the MSSRs will, at the minimum, specifically include the above data. The sponsor should provide this updated ASA to the TGA for review prior to supply of the product.

Adequacy of the pharmacovigilance plan will be re-assessed once the above recommendations are addressed by the sponsor.

3.3. PLANNED STUDIES

No Australian specific studies have been planned. The data from the studies planned to be conducted overseas will be applicable to the Australian population. The RMP should be revised as warranted by the study outcomes and be submitted to the TGA for review.

[7] coreRMP19 requirements for COVID-19 vaccines v2.0 (europa.eu)

3.4. SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN - RESPONSE TO PRE-ACV RMP REPORT

Section 3.2 (Additional Pharmacovigilance Activities) of the updated ASA (version 0.2) states:

> *Moderna commits to providing TGA with Monthly Safety Summary Reports (MSSRs) which will include all information outlined in Table 36 of the EU-RMP.*

However, Table 36 of the EU RMP does not include all data types that were recommended by the RMP evaluator (in section 3.2 above). The sponsor should commit to provide MSSRs that include all the information specified in section 3.2 of this report.

The sponsor should also note that the MSSRs are considered as routine pharmacovigilance. Thus, the statements regarding MSSRs should be included in the section 'Routine pharmacovigilance activities in Australia' of the ASA.

In the table 5 (Summary of the RMP in Australia), 'Labelling' has been included as a routine pharmacovigilance activity. As labelling is a routine risk minimisation activity, during the next update of the ASA this table should be revised to briefly indicate the routine pharmacovigilance activities that are proposed for Australia.

4. RISK MINIMISATION PLAN

4.1. PLANNED RISK MINIMISATION ACTIVITIES

Only routine risk minimisation measures are proposed for Spikevax. This is in line with the other COVID-19 vaccines currently approved for use in Australia. At this stage, routine risk minimisation measures, together with the risk minimisation activities launched by the Department of Health, are considered acceptable to minimise the risks associated with Spikevax.

4.1.1. Product labelling

4.1.1.1. Product Information

(Clean copy of the PI is at - D21-2826636)

PRAC recommended (page 2 of EMA's COVID-19 Safety Update Report for Spikevax dated 14 July 2021) to include information regarding myocarditis and pericarditis in the product information document, together with a warning to raise awareness among healthcare professionals and people taking these vaccines. In this regard, the SmPC includes the following message, which is not included in the proposed PI for Australia. This discrepancy is raised to the delegate's attention:

> *Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.*

As a provisionally registered vaccine, the sponsor must include a statement in the PI explaining that this vaccine and indication are provisional, with the term 'provisional approval' appearing

in bold. This statement must be included in Section 4.1 (Therapeutic Indications) of the PI as shown below. The term 'provisional approval' should appear in bold.
Section 4.1 (Therapeutic Indications) in PIs of currently approved COVID-19 vaccines in Australia have the following format:

> Spikevax has **provisional approval** for the indication below:
>
> 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.
>
> 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.

The above deficits in Section 4.1 of Spikevax PI are raised to the delegate's attention.

Spikevax is a new biological entity, and as such meets the inclusion criteria for the Black Triangle Scheme. The following symbol and statement have been added to the top of the first page of the PI. The words 'medicinal product' should be replaced by the word 'vaccine':

> ▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

4.1.1.2. Consumer medicine information

(Clean copy of the CMI is at D21-2826638)

Information regarding myocarditis and pericarditis has not been included in the CMI. In the event that myocarditis/pericarditis develops, the vaccinees/caregivers should be able to identify the relevant symptoms. Therefore, the sponsor should update the CMI to include advice on myocarditis and pericarditis. The sponsor may wish to use wording similar to the text included in Patient Information Leaflet distributed in the EU[8]. The updated CMI should be provided to the TGA prior to supply of the product.

The Sponsor should also consider including more detailed information on the CMI summary page. The CMI for Comirnaty vaccine may be used as a guide for the types of information that should be included on this summary page for consumers.

In section 2 of the summary page, the statement "Do not use if you have ever had an allergic reaction […]" should be changed to read as "You should not be given Spikevax if you have ever had an allergic reaction […]".

The word 'medicine' should be changed to 'vaccine' in the following statements:

[8] https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

i) At the top of the summary page: "If you are worried about being given this medicine […]".
ii) In the wording that accompany the black triangle symbol
iii) Page 4 - Do not take this vaccine ~~medicine~~ if you are allergic to any of these ingredients.

Where the CMI refers to the disease the vaccine is proposed to prevent, the wording should be revised from 'COVID-19' to 'COVID-19 disease'. For example, 'Spikevax is a vaccine used to prevent COVID-19 disease'.

Section on 'What if I am taking other medicines' should include a statement advising the consumers to inform the doctor or pharmacist if any other vaccine has been received recently.

It is recommended to include a message on stress related reactions that may occur in association with vaccination and advise that these reactions are temporary.

This vaccine meets the eligibility criteria for inclusion in the Black Triangle Scheme. The black triangle symbol and statement have been included at the top of the first page of the CMI. The word 'medicine' should be changed to 'vaccine'.

▼ This vaccine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. You can report side effects to your doctor, or directly at www.tga.gov.au/reporting-problems.

As a provisionally registered vaccine to prevent COVID-19 disease, the sponsor must include the following statement in the CMI explaining that this vaccine and the indication are provisional. This statement must be included below the name of the vaccine in the CMI. The term 'provisional approval' should appear in bold (The sponsor could refer to Comirnaty CMI).

"This medicine has **provisional approval** in Australia for (insert indication). This approval has been granted on the basis of short term safety and efficacy data. Evidence of longer term efficacy and safety from ongoing clinical trials and vaccination in the community continues to be gathered and assessed."

4.1.2. Additional risk minimisation activities

The sponsor has not proposed additional risk minimisation activities. This is the same as that for other COVID-19 vaccines approved in Australia. The Australian Government's vaccine rollout programs address some of the aspects of risk minimisation. These programs, together with the PI and the CMI, are considered acceptable to minimise the risks associated Spikevax. At this stage, the absence of additional risk minimisation measures is considered acceptable.

4.2. Risk management plan - Response to Pre-ACV report

It is noted that the statement "It is very important that you receive your second dose" has been included in the summary page. The consumers should be made aware that they may not be fully protected against COVID-19 disease if the second dose it not taken. Therefore, it is recommended to include following the advice in the CMI summary page:

You may not be protected if you only receive one dose, so a second dose is important.

A message to inform the limitations of vaccine effectiveness is recommended to be included in the CMI with a statement such as;

> You may not be fully protected against COVID-19 disease until fourteen days after your second dose.

The sponsor's attention is raised to a minor oversight in section 5.2 of the ASA:
The statement "*Routine risk minimisation activities as described in Table 3 are sufficient to manage the safety of Spikevax*" should be corrected to refer to Table 4. This revision can be made during the next update of the ASA.

The sponsor provided a further updated CMI and it is found at D21-2939300. The above recommendations have been addressed.

5. EVALUATION OF SPONSOR RESPONSE TO ROLLING QUESTIONS

5.1. ACM ADVICE

ACV minutes are pending.

5.2. RECONCILIATION OF RECOMMENDATIONS MADE IN ROLLING QUESTIONS SENT 8 JULY 2021

Recommendation 1: The ASA that has been submitted states it is related to the EU RMP version 1.1 (dated 1 March 2021), and Moderna has recently informed the TGA that the RMP is currently being updated. Please provide an ASA that is related to the most recent version of the EU RMP (i.e. the EU RMP version that is proposed to be evaluated for the current submission) as soon as practicable.
Sponsor's response: On 16 July 2021, the sponsor submitted an updated EU RMP version 2.1. The sponsor stated an updated ASA will be provided as soon as available.
RMP evaluator comment: This approach is acceptable.

6. EVALUATION OF SPONSOR RESPONSE TO PRE-ACV RMP RECOMMENDATIONS

The sponsor's responses are at D21-2875891

Recommendation 2: Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
Sponsor's response: The Sponsor confirms that any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications will be addressed in a revised RMP and ASA.
RMP evaluator comment: The sponsor's response is noted.
Recommendation 3: In an updated ASA, the sponsor should include a commitment to submit Monthly Summary Safety Reports to the TGA. This commitment should also state that these reports will, at the minimum, include the data specified in Section 3.2 of this report.
Sponsor's response: The Sponsor has amended the ASA to include a commitment that Monthly Summary Safety Reports will be submitted to the TGA, and that these reports will, at a minimum, include the data specified in Section 3.2 of the TGA's RMP Evaluation Report. *An updated ASA (Version 0.2) was submitted to TGA on 22 July 2021 with the response to the Milestone 2 letter.*
RMP evaluator comment: Table 36 of the EU RMP does not include all data types that were recommended by the RMP evaluator (in section 3.2 above). The sponsor should commit to provide MSSRs that include all the information specified in section 3.2 of this report.
Recommendation 4: An updated ASA, referring to EU RMP version 2.1 should be provided to the TGA as soon as practicable.
Sponsor's response: An updated ASA (Version 0.2) was submitted to TGA on 22 July 2021 with the response to the Milestone 2 letter.
RMP evaluator comment: The sponsor has provided an ASA referring to EU RMP version 2.1.
Recommendation 5: The words 'medicinal product' in the statement accompanying the black triangle should be replaced by the word 'vaccine'.
Sponsor's response: The Sponsor confirms that the words 'medicinal product' in the statement accompanying the black triangle have been replaced by the word 'vaccine'. *Please find revised clean and annotated version of the proposed PI enclosed in Module 1.3.1.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.

Recommendation 6: The sponsor should include advice on myocarditis and pericarditis in the CMI.
Sponsor's response: The Sponsor has included advice on myocarditis and pericarditis in section 2 of the CMI, in line with text included in the EU PIL for Spikevax. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 7: As a provisionally registered vaccine to prevent COVID-19 disease, the sponsor must include a statement in the CMI explaining that this vaccine and the indication are provisional.
Sponsor's response: The Sponsor will include a statement in the CMI explaining that this vaccine and the indication are provisional. *Revised clean and annotated versions of the proposed CMI are enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has included a statement explaining that this vaccine and the indication are provisionally approved in Australia.
Recommendation 8: In some of the messages included in the CMI, the word 'medicine' should be changed to 'vaccine' as required. This includes the statement accompanying the black triangle.
Sponsor's response: The Sponsor has revised the CMI to use the word 'vaccine' in the place of 'medicine' as recommended. Please find amended annotated and clean versions enclosed in Module 1.3.2.
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 9: Where the CMI refers to the disease this vaccine is proposed to prevent, the wording should be revised from 'COVID-19' to 'COVID-19 disease'.
Sponsor's response: The Sponsor has amended the wording of the disease the vaccine is proposed to prevent to 'COVID-19 disease' throughout the CMI. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 10: Section on 'What if I am taking other medicines' should include a statement advising the consumers to inform the doctor or pharmacist if any other vaccine has been received recently.
Sponsor's response: The Sponsor has amended the section 'What if I am taking other medicines' as recommended. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 11: It is recommended to include a message on stress related reactions that may occur in association with vaccination and advise that these reactions are temporary.
Sponsor's response: The Sponsor has included a message on stress-related reactions in section 2 of the CMI. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 12: More detailed information should be included in the CMI summary page. The sponsor is advised to refer to Comirnaty CMI for guidance.
Sponsor's response: The Sponsor has included more detailed information in the CMI summary page, in line with that approved for the Comirnaty CMI. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has updated the summary page to include most of the information recommended by the RMP evaluator. However, the sponsor is recommended to further revise the CMI to include information as to why taking both doses is important and advice on the limitations of vaccine effectiveness. See section 4.2 for details.
Recommendation 13: In section 2 of the summary page, the statement "Do not use if you have ever had an allergic reaction […]" should be changed to read as "You should not be given Spikevax if you have ever had an allergic reaction […]".

Sponsor's response: The Sponsor has amended section 2 of the summary page as recommended. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 14: If the PI is updated, any other relevant updates should be made to the CMI.
Sponsor's response: The Sponsor confirms that any relevant updates made to the PI will also be made to the CMI.
RMP evaluator comment: The sponsor's commitment is noted.
Recommendation 15: The CMI revised as per above recommendations, should be provided to the TGA for review at least 4 weeks prior to supply of the product.
Sponsor's response: The Sponsor hereby provides the amended CMI, revised per the above recommendations, with this response. *Please find amended annotated and clean versions enclosed in Module 1.3.2.*
RMP evaluator comment: The sponsor has provided an updated CMI.

6.1 Reconciliation of Round 2 recommendations

Recommendation 3: The sponsor has stated that Monthly Safety Summary Reports will include all information outlined in Table 36 of the EU-RMP. Table 36 of the EU RMP does not include all data types that were recommended by the RMP evaluator (listed in section 3.2 of this report). The sponsor should commit to provide all the information specified in section 3.2 of this report in the Monthly Safety Summary Reports.
Sponsor's response: The Sponsor has amended the ASA to include a commitment that Monthly Summary Safety Reports will be submitted to the TGA, and that these reports will, at a minimum, include the data specified in Section 3.2 of the TGA's RMP Evaluation Report. *An updated ASA (Version 0.3) is enclosed in Module 1.8.2 of this response.*
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 12: The summary page of the CMI should include a message to inform the consumers that receiving one dose of the vaccine may not provide protection against COVID-19 disease.
Sponsor's response: The Sponsor has amended the proposed CMI summary page to include a message to inform consumers that receiving one dose of the vaccine may not provide protection against COVID-19 disease.
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.
Recommendation 16: The CMI should include the message that individuals may not be fully protected until 14 days after their second dose of Spikevax.:
Sponsor's response: The Sponsor has amended the proposed CMI to include a message that individuals may not be fully protected until 14 days after their second dose of Spikevax.
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation.

Risk Management Plan Evaluation Report Priority Review Pathway

Elasomeran (Spikevax)
(for the use in individuals aged between 12 and 17 years)

Round 1: 9 August 2021
Round 2: 3 September 2021

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RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type:	New biological entity
Sponsor:	Moderna Australia Pty Ltd
Generic name:	**Elasomeran**
Trade name:	**Spikevax**
Dose form and strength:	Suspension for intramuscular injection; 0.2 mg/mL
Drug class:	Active immunisation to prevent COVID-19 disease (mRNA vaccine)
Submission No; eSubmission ID:	PM-2021-02994-1-2; e006131 - (0000)
RMP file No:	E21-324668
TRIM reference:	D21-2850947
EU-RMP Version:	Version 2.1; date 15 July 2021; DLP 31 May 2021
ASA Version:	Version 0.3; date 5 August 2021
Evaluator:	s22 [redacted]
Peer Reviewer:	
Date authorised:	9 August 2021 (Round 1) 3 September 2021 (Round 2)
RMP referral to ACV:	Meeting 24 (26 August 2021)
Pharmacovigilance activities:	Routine Follow-up questionnaires Clinical Trial
Risk minimisation Activities	Routine Department of Health initiated risk minimisation programs
Black Triangle Scheme:	Yes - new medicine
PSUR review issues:	Yes
IDMP referral:	Level 1 (Intensive Monitoring) - Provisionally registered new chemical / biological entity
RMP Compliance Tracker:	No

SUMMARY

- Adjutor Healthcare Pty Ltd, as the regulatory agent for the Australian sponsor Moderna Australia Pty Ltd is seeking approval to use elasomeran (Spikevax) in individuals of 12 to 17 years of age through the Provisional Approval Pathway. The proposed dosing regimen involves two intramuscular injections (0.5 mL each), 28 days apart, which is the same as for the adult population.
- The below report includes the evaluation of EU RMP version 2.1 (date 15 July 2021; DLP 31 May 2021), which was evaluated for the adult indication. The sponsor provided an updated ASA version 0.3 (date 5 August 2021). However, this version did not include any additional information specific to the adolescent population.
- The summary of safety concerns, pharmacovigilance plan and the risk minimisation plan are the same as those evaluated for the adult population.
- The ACV highlighted the importance of monitoring myocarditis and pericarditis events in Australia. The sponsor has proposed a follow-up questionnaire to monitor myocarditis/myopericarditis and pericarditis events in Australia, which is designed to capture the parameters included in ACV advice.
- From an RMP perspective, use of Spikevax in adolescents 12 to 17 years of age is not expected to warrant any significant changes to the safety specification and risk management plan. The RMP and the ASA that were evaluated in this submission are acceptable.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

> *The Spikevax EU-Risk Management Plan (RMP) (version 2.1, dated 15 July 2021; DLP 31 May 2021), with Australian Specific Annex (version 0.2, dated 22 July 2021), included with submission PM-2021-02994-1-2, 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).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of 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. Each*

report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, 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.

Spikevax (elasomeran) 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 products entire period of provisional registration.

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.

7. BACKGROUND

The sponsor is seeking approval to use Spikevax for individuals between 12 and 17 years of age. The RMP in relation to the use of Spikevax for individuals 18 years and above was evaluated under the same submission PM-2021-02994-1-2. The updated ASA version 0.3 (dated 5 August 2021) provided by the sponsor did not include any additional information specific to the adolescent population. Therefore, this RMP evaluation for the adolescent indication has been focussed on EU RMP version 2.1 (dated 15 July 2021; DLP 31 May 2021) and ASA version 0.2 (dated 22 July 2021).

7.1. INDICATION

The proposed indication is:

> *Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.*

7.2. DOSAGE AND ADMINISTRATION

Dosage and administration are the same as for the adult population:

> *Spikevax is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose.*

7.3. OVERSEAS REGULATORY STATUS

Use of Spikevax for individuals 12 years of age and above has conditional marketing authorisation in the EU. Spikevax is also available for use in the UK, Switzerland, Japan and Canada.

8. SAFETY SPECIFICATION

8.1. NONCLINICAL ADVICE ON SAFETY SPECIFICATION

The nonclinical evaluator did not raise any specific concerns regarding the safety specification for the adolescent population discussed in the RMP[9].

8.2. CLINICAL ADVICE ON SAFETY SPECIFICATION

The delegate's overview[10] did not include any concerns regarding the safety specification for the adolescent population discussed in the RMP.

8.3. PROPOSED SUMMARY OF SAFETY CONCERNS

The summary of safety concerns is the same as that proposed for the adult population.

The ongoing Phase 2/3 study (mRNA-1273-P203) is investigating the safety, reactogenicity, and efficacy in healthy adolescents aged 12 to 18 years. EU RMP version 2.1 reported that this study enrolled a total of 2486 patients who received mRNA-1273 vaccine. The majority of the

[9] Nonclinical evaluation report (Round 2) dated 29 July 2021 – TRIM Ref: D21-2803355
[10] Delegate's overview dated 13 August 2021 TRIM Ref: D21-2974181

solicited adverse reactions occurred in participants who received mRNA-1273 as compared to placebo and, most of these adverse events were grade 1 to grade 2 in severity. Myocarditis and pericarditis reported in the post-market setting were not observed in the clinical trials. This could be due to the limited number of participants in the clinical trials as compared to the number vaccinated in post-authorisation phase. The risks of myocarditis (including myopericarditis) and pericarditis are now included as important identified risks in the safety summary and will be closely monitored.

The EMA concluded[11] "*The overall safety profile of Spikevax determined in adults was confirmed in the adolescent study; the* CHMP *therefore considered that the benefits of Spikevax in children aged 12 to 17 outweigh the risks, in particular in those with conditions that increase the risk of severe COVID-19*".

From an RMP perspective, the risks for the adolescents between 12 to 17 years of age would not be significantly different from the population 18 years and above. The acceptability of the summary of concerns will be re-assessed once the advice from non-clinical, clinical evaluators and the ACV is obtained.

9. PHARMACOVIGILANCE PLAN

Routine and additional pharmacovigilance measures are the same as those reviewed for the adult indication.

The ASA has been updated to indicate that the Monthly Safety Summary Reports will include the data that is listed in Section 3.2 of this report.

The sponsor has provided the clinical study plan for provisional registration in the ASA. The adequacy of the clinical study plan will be considered by the clinical evaluator and/or the TGA delegate.

9.1.1. Round 2 update

The ACV highlighted the importance of monitoring myocarditis and pericarditis events in Australia. The sponsor has proposed a follow-up questionnaire to monitor myocarditis/myopericarditis and pericarditis events in Australia, which is designed to capture the parameters included in ACV advice. This is acceptable.

10. RISK MINIMISATION PLAN

The risk minimisation plan is the same as what was evaluated for the adult indication. Inclusion of adolescents 12 to 17 years of age in the indication is not expected to require changes to the current risk minimisation plan.

[11] COVID-19 vaccine Spikevax approved for children aged 12 to 17 in EU | European Medicines Agency (europa.eu)

10.1. PLANNED RISK MINIMISATION ACTIVITIES - ROUND 1

10.1.1. Product labelling

10.1.1.1. Product Information

The TGA requested revisions to the PI during the evaluation of the adult indication. A PI document that includes the indication of individuals 12 years of age and above, which also includes those TGA requested revisions, is still pending.

Spikevax should be included in the black triangle scheme. Therefore, the black triangle symbol and the appropriate accompanying text (same as what was included for the adult indication) should be included in the PI.

The sponsor must include a statement in the PI explaining that the vaccine and indication have provisional approval, same as what was included for the adult indication.

10.1.1.2. Consumer medicine information

The TGA requested revisions to the CMI during the evaluation of the adult indication. A CMI document that includes the indication of individuals 12 years of age and above, which also includes those TGA requested revisions, is still pending.

Spikevax should be included in the black triangle scheme. Therefore, the black triangle symbol and the appropriate accompanying text (same as what was included for the adult indication) should be included in the CMI.

The sponsor must include a statement in the CMI explaining that the vaccine and indication have provisional approval, same as what was included for the adult indication.

10.1.2. Round 2 update

The sponsor has satisfactorily updated the CMI as per RMP recommendations (Annotated CMI - D21-3052062, Clean CMI - D21-3052059). The updated CMI is acceptable.

The sponsor informed the delegate that it does not consider a DHCP letter to address myocarditis/pericarditis is necessary in Australia (D21-3043482).

At Round 2, the risk minimisation plan remains acceptable.

11. ACV ADVICE

ACV ratified minutes are at D21-3046655. It is noted the following advice of relevance to the RMP has been provided:

> *The ACV advised that the sponsor, via the Risk Management Plan, should provide a specific case reporting form with categorical variables (for example, troponin levels, ECG results, echocardiogram results) to prompt and collect sufficient information to allow classification of the event using Brighton Collaboration or CDC criteria. This should also facilitate comparisons to Australian background rates.*

12. EVALUATION OF SPONSOR RESPONSE TO ROUND 1 RECOMMENDATIONS

Recommendation 17. The sponsor is requested to provide the most updated PI and the CMI that include the indication of individuals 12 years of age and older.
Sponsor's response: The Sponsor provided the updated PI and the CMI.
RMP evaluator comment: The sponsor has satisfactorily addressed this recommendation (see section .

APPENDIX 1 – LIST OF ACRONYMS

ACV	Advisory Committee on Vaccines
ASA	Australian Specific Annex
CDC	Centres for Disease Control and Prevention
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
MSSR	Monthly Safety Summary Report
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration

Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: Elasomeran and davesomeran

Product name: SPIKEVAX BIVALENT ORIGINAL/ OMICRON BA.4-5

Sponsor: Moderna Australia Pty Ltd

Submission number: PM-2022-04824-1-2

eSubmission number: e006838 (0001, 0003, 0004)

Date of first round report: 31 January 2023

TRIM reference: D23-5075397

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*, 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>.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical Classification (WHO)
CDC	Centers for Disease Control and Prevention (US)
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMI	consumer medicines information
CMQ	custom MedDRA query
CoV	coronavirus
COVID-19	coronavirus disease 2019
CSP	clinical study protocol
CSR	clinical study report
eCTD	electronic common technical document
EMA	European Medicines Agency
EoS	end of study
EU	European Union
EUA	emergency use authorisation
EvQ	evaluator's question
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLSM	geometric least squares mean

Abbreviation	Meaning
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titre
HIV	human immunodeficiency virus
ID50	50% inhibitory dose
IM	intramuscular
IQR	interquartile range
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MERS-CoV	Middle East respiratory syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	messenger ribonucleic acid
nAb	neutralising antibody
P205 Part G	Study mRNA-1273-P205 Part G
P205 Part F	Study mRNA-1273-P205 Part F, cohort 2
PI	product information
PP	per protocol
PPIS	Per-Protocol Immunogenicity Set
PPIS – Neg	Per-Protocol Immunogenicity Set – SARS-CoV-2 Negative
PsVNA	pseudotyped virus neutralising assay
RMP	Risk Management Plan
RT-PCR	reverse transcription polymerase chain reaction
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain

Abbreviation	Meaning
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SRR	seroresponse rate
Study P205	Study mRNA-1273-P205
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
US	United States
VE	vaccine efficacy
VOC	variant of concern
WHO	World Health Organisation
YOA	years of age

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1. Submission details

1.1. Identifying information

Submission number	PM-2022-04824-1-2
eSubmission number	e006836
eSubmission sequences covered in this report	0001, 0003, 0004
Sponsor	Moderna Australia Pty Ltd
Trade name	SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5*
Active substance	elasomeran/davesomeran

*For simplicity, the product will henceforth be referred to as SPIKEVAX BA.4-5 or its investigational name mRNA-1273.222.

1.2. Submission type

This is a Category 1 Type A application is for the provisional registration of a new Omicron bivalent (original/BA.4-5) COVID-19 vaccine, mRNA-1273.222, containing elasomeran and davesomeran (new biological entity). This application consists of rolling submissions.

1.3. Drug class and therapeutic indication

SPIKEVAX BA.4-5 is a COVID-19 vaccine that contains mRNA encapsulated in lipid nanoparticles and belongs to the WHO ATC groups: Vaccines; Viral vaccines; Other viral vaccines; COVID-19 vaccines (ATC code J07BX03). It induces active immunity to the spike protein of SARS-CoV-2, which is the virus that causes COVID-19.

The vaccine is a fixed dose combination of two active ingredients: elasomeran and davesomeran. Elasomeran is a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Davesomeran is a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral S protein of SARS-CoV-2 (Omicron BA.4-5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

The proposed therapeutic indication is shown below (verbatim from the proposed PI):

> *As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.*

It should be noted that the currently approved bivalent vaccine SPIKEVAX BIVALENT ORIGINAL/OMICRON (elasomeran/imelasomeran) (AUST R 389513 and 396452) is approved for booster immunisation in **individuals 18 YOA and older**.

1.4. Dosage forms and strengths

SPIKEVAX BA.4-5 is presented in two pack forms:

i) 10 x 2.5 mL multidose vials
ii) 10 x pre-filled syringes.

Both are at a concentration of 0.1 mg/mL. See Table 1 for further details on the composition.

Table 1. SPIKEVAX BA.4-5 qualitative and quantitative composition

Strength	Presentation	Dose(s)	Composition
0.1 mg/mL	Multidose vial (blue flip-off cap)	5 doses of 0.5 mL each	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
		10 doses of 0.25 mL each	One dose (0.25 mL) contains 12.5 micrograms of elasomeran and 12.5 micrograms of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
	Pre-filled syringe	1 dose of 0.5 mL For single use only. Do not use the pre-filled syringe to deliver a partial 0.25 mL volume.	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

1.5. Dosage and administration

SPIKEVAX BIVALENT is administered intramuscularly (IM), preferably in the deltoid muscle.

The sponsor proposes two different doses depending on the age of the recipient:

i) **12 years and older**: 0.5 mL containing 50 mcg
ii) **6 to <12 years**: 0.25 mL containing 25 mcg

1.6. Proposed changes to the product documentation

Not applicable. This is a Type A application, and no prior PI is available for SPIKEVAX BA.4-5.

2. Background

2.1. Information on the condition being treated

COVID-19 is a disease caused by infection with the pandemic virus SARS-CoV-2, which was first recognised internationally in late 2019 and in Australia by early 2020. It is manifested by respiratory, systemic and other organ-related symptomatology.

Disease severity is mainly related to respiratory presentations, and generally increases with age. Mortality in unvaccinated individuals with untreated disease is rare in childhood but increases steeply beyond 60 years of age.

In the absence of highly effective prophylactic or therapeutic medicines, active immunisation through vaccination represents the best means of preventing hospitalisation and deaths at an individual level and controlling the pandemic at a societal level.

Emerging mutated SARS-CoV-2 variants of concern pose challenges for current vaccination strategies, which until recently have been based on inducing immunity to the non-mutated spike protein that was sequenced in the original wild-type virus.

2.2. Current treatment options

COVID-19 treatments that have been provisionally approved by the TGA[1] are shown in Table 2:

Table 2. COVID-19 treatments that have been provisionally approved by the TGA

Effective date	Sponsor	Name
a. 24 February 2022	AstraZeneca Pty Ltd	tixagevimab and cilgavimab (EVUSHELD) a. For pre-exposure prophylaxis in individuals 12 years and over
18 January 2022	Merck Sharp & Dohme (Australia) Pty Ltd	molnupiravir (LAGEVRIO)
18 January 2022	Pfizer Australia Pty Ltd	nirmatrelvir + ritonavir (PAXLOVID)
6 December 2021	Celltrion Healthcare Australia Pty Ltd	regdanvimab (REGKIRONA)
1 December 2021	Roche Products Pty Ltd	tocilizumab (ACTEMRA)
15 October 2021	Roche Products Pty Ltd	casirivimab + imdevimab (RONAPREVE)
20 August 2021	GlaxoSmithKline Australia Pty Ltd	Sotrovimab (XEVUDY)
a. 10 July 2020 b. 6 May 2022	Gilead Sciences Pty Ltd	remdesivir (VEKLURY) a. For treatment of COVID-19 in adults and adolescents (aged 12 years and weighing at least 40 kg) with pneumonia, requiring supplemental oxygen. b. For treatment of: • adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2, who require supplemental oxygen • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19

COVID-19 vaccines that have been provisionally approved by the TGA[2] are shown in Table 3:

[1] https://www.tga.gov.au/covid-19-treatments-provisional-registrations (accessed 15/12/2022).
[2] Available at: https://www.tga.gov.au/covid-19-vaccine-provisional-registrations (accessed 15/12/2022).

Table 3. COVID-19 vaccines that have been provisionally approved by the TGA

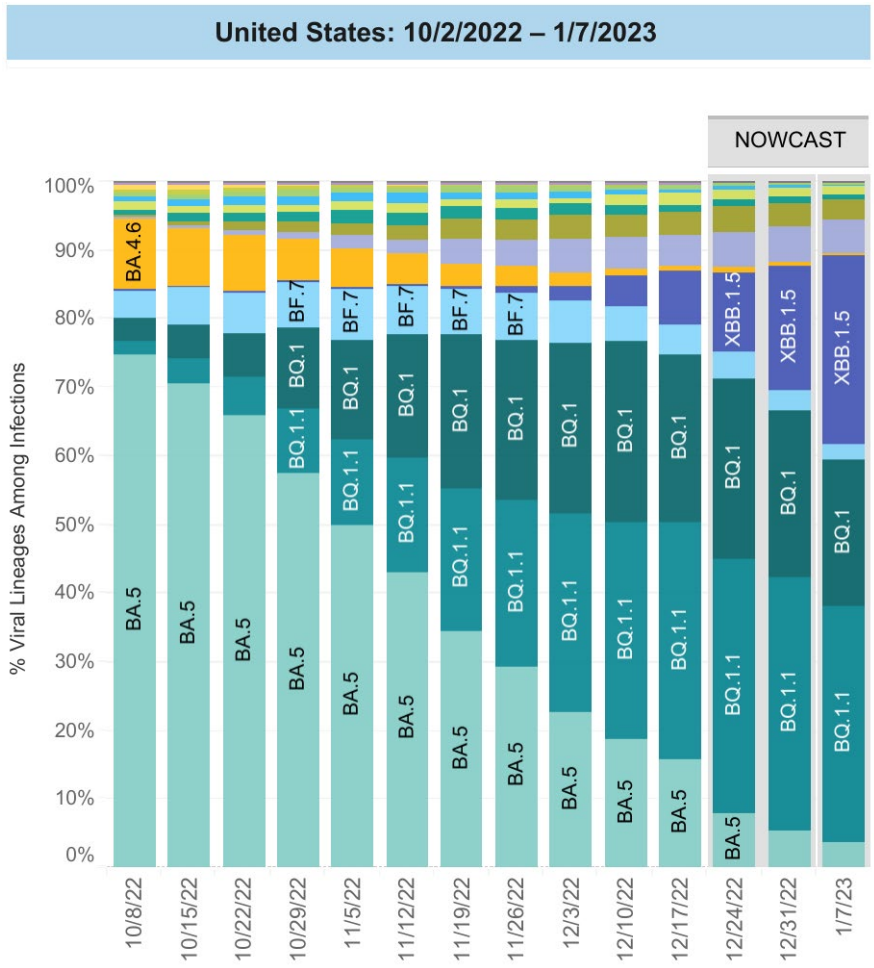
Effective date	Sponsor	Name	Type
a. 19 January 2022 b. 9 June 2022 c. 22 July 2022	Biocelect Pty Ltd on behalf of Novavax Inc	NUVAXOVID (NVX-CoV2373) a. For individuals aged 18 years and over b. Booster dose for individuals aged 18 years and over c. For individuals aged 12 years and over	Protein vaccine
a. 9 August 2021 b. 3 September 2021 c. 7 December 2021 d. 17 February 2022 e. 19 July 2022 f. 19 October 2022	Moderna Australia Pty Ltd	SPIKEVAX (elasomeran) a. For individuals aged 18 years and over b. For individuals aged 12 years and over c. Booster dose for individuals aged 18 years and over d. For individuals aged 6 years and over e. For individuals aged 6 months and over f. Booster dose for individuals aged 12 years and over	mRNA
29 August 2022	Moderna Australia Pty Ltd	SPIKEVAX Bivalent Original/Omicron (elasomeran/imelasomeran) Booster dose for individuals aged 18 years and over	mRNA
25 June 2021	Janssen-Cilag Pty Ltd	COVID-19 Vaccine Janssen For individuals aged 18 years and over	Viral vector
a. 15 February 2021 b. 8 February 2022	AstraZeneca Pty Ltd	VAXZEVRIA (previously COVID-19 Vaccine AstraZeneca) a. For individuals aged 18 years and over b. Booster dose for individuals aged 18 years and over	Viral vector
a. 25 January 2021 b. 22 July 2021 c. 26 October 2021 d. 3 December 2021 e. 27 January 2022 f. 7 April 2022 g. 20 September 2022 h. 29 September 2022	Pfizer Australia Pty Ltd	COMIRNATY (tozinameran) a. For individuals aged 16 years and over b. For individuals aged 12 years and over c. Booster dose for individuals aged 18 years and over d. For individuals aged 5 years and over e. Booster dose for individuals aged 16-17 years old f. Booster dose for individuals aged 12-15 years old g. Booster dose for individuals aged 5-11 years old h. For individuals aged 6 months and over	mRNA
27 October 2022	Pfizer Australia Pty Ltd	COMIRNATY Original/Omicron BA.1 (tozinameran and riltozinameran) Booster dose for individuals aged 18 years and over	mRNA

2.3. Clinical rationale

The sponsor's rationale for developing mRNA-1273.222 is presented in Section 2.5.1.3.1. of the Clinical Overview [e006836 (0004-) - Clinical Summary - mRNA-1273-P205 Part H Clinical Summary of Day 29 Interim Results (#13)].

In November of 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant at the time with > 30 mutations in the spike protein, granting it transmissibility advantages. Soon after its emergence, Omicron rapidly became dominant worldwide. This was followed by emergence of various Omicron subvariants (BA.2, BA.2.75.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, XBB.1 and others). As of January of 2023, BA.5 subvariant remains one of the major lineages in the US, but has been largely taken over by BQ and XBB subvariants (Figure 1).[3]

Figure 1. COVID-19 Variant Proportions in United States



The sponsor has provided the following statement in the Clinical Overview to support the development of mRNA-1273.222:

> *Specifically, it is required for the variant-targeting booster vaccines to elicit superior neutralising antibody responses, compared to the original vaccine (mRNA-1273), against the variant contained in the modified vaccine. It is also highly desirable for the*

[3] CDC COVID Data Tracker: Variant Proportions (accessed 09/01/2023).

modified booster vaccine to retain the immune response against the ancestral SARS-CoV-2 and to elicit a broad response against multiple variants, maintaining protection against previous variants of concern as well as to protect against future variants. Retaining protection against previous variants is important because infection-induced immunity, especially with Omicron, does not appear to elicit robust immune responses against previous variants.

COVID-19 continues to be a significant public health issue to Australians. As of 15 December 2022, the 7-day rolling averages are as follows:[4]

- number of cases identified: 15,761
- number of people hospitalised: 3,384
- number of people in ICU: 98
- number of deaths: 14

Cumulatively, there have been 10,938,096 confirmed cases and 15,718 deaths in Australia due to COVID-19 as of 22 December 2022.[5]

Evaluator's comments

It is acknowledged that there is an ongoing need to address the evolving antigenic variation of SARS-CoV-2 in both the global and Australian context. In addition, the rationale for using a bivalent vaccine is also justified.

While predictably so, a major concern is that subvariants BA.4 and BA.5 are likely to be overtaken by other subvariants in the near future.

2.4. Formulation

2.4.1. Formulation development

SPIKEVAX BIVALENT uses mRNA-based platform in which the mRNA is encapsulated with a proprietary LNP. The product contains equal amount of two mRNA-1273 molecules: CX-024414 and CX-034476. CX-024414 encodes for the S-2P of Wuhan-Hu-1, while CX-034476 encodes for the S-2P of the SARS-CoV-2 Omicron variants (BA.4/BA.5). The LNPs encapsulating the mRNA are designed to increase its delivery efficiency and improve vaccine tolerability.

2.4.2. Excipients

The list of excipients remains unchanged from SPIKEVAX. The list is presented in Section 6.1 of the draft PI (see below).

[4] Coronavirus (COVID-19) case numbers and statistics | Australian Government Department of Health and Aged Care (accessed 15/12/2022).
[5] Australia: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data (accessed 22/12/2022).

Heptadecan-9-yl 8-[2-hydroxyethyl-(6-oxo-6-undecoxyhexyl)amino]octanoate
Cholesterol
Distearoylphosphatidylcholine
1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
Trometamol
Trometamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for injections

2.5. Regulatory history

2.5.1. Australian regulatory history

Not applicable. SPIKEVAX BA.4-5 has not been previously registered in Australia.

For the regulatory history of SPIKEVAX and SPIKEVAX BIVALENT (Original/Omicron), refer to Table 3.

2.5.2. Orphan drug designation

Not applicable. SPIKEVAX BA.4-5 has not been designated as an orphan product.

2.5.3. Related submissions

Not applicable. The evaluator is not aware of any related submissions.

2.5.4. Overseas regulatory history

The sponsor has supplied a summary of the countries that have approved SPIKEVAX BA.4-5. This summary was provided in the initial submission (sequence 0001: e006836 (0004-) - Foreign regulatory status). See Table 4.

Table 4. Foreign Regulatory Status for SPIKEVAX BA.4-5

Country/Region	Date of Submission	Date of Authorisation	Details
United States of America	29 August 2022 (rolling submission; date above marks the final documentation submitted)	31 August 2022	Emergency Use Authorisation (EUA): 18 years of age and older
	6-11y: 02 September 2022 12-17y: 19 September 2022 (rolling submission; date above marks the final documentation submitted)	12 October 2022	Emergency Use Authorisation (EUA): 6 years to < 18 years of age
Canada	12 September 2022	04 November 2022	As a booster dose for active immunization against COVID-19 caused by the SARS-CoV-2 virus in individuals 18 years of age and older.
European Union	23 September 2022	Positive EC decision received on 20 October 2022	For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, who have previously received at least a primary vaccination course against COVID-19.
Great Britain			
Switzerland			
Singapore			
Japan	05 October 2022	01 November 2022	As a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Evaluator's comments

It is noted that there is a significant variability in terms of the target age. Note that only FDA has allowed the vaccine for individuals as young as 6 YOA (although initially 18 YOA).

EvQ: What is the sponsor's justification for lowering the target age to 6?

EvQ: For US/EU/Canada, were the approvals based on evaluation of clinical data with mRNA-1273.222 (i.e. Study P205 Part H)?

2.6. Guidance

The evaluator referred to the following TGA guidance:

- Guidance 8: Product information.
- Form for providing product information.
- Reformatting product information: frequently asked questions.

The evaluator referred to the following TGA-adopted guidance:

- ACCESS Consortium: Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines (14/09/2021).
- ACCESS Consortium: Points to consider for strain changes in authorised COVID-19 vaccines in an ongoing SARS-CoV-2 pandemic (5/03/2021).
- ACCESS Consortium: Access consortium statement on COVID-19 vaccines evidence (4/12/2020).
- EMEA: Guidelines on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005) (18/10/2006).
- EMEA: Points to Consider on Applications with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99) (31/05/2002).
- EMEA: Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99) (27/07/2000).

The evaluator referred to the following additional guidance:

- US FDA: Emergency use authorisation for vaccines to prevent COVID-19: guidance for industry (25/05/2021).
- WHO: Evaluation of COVID-19 vaccine effectiveness (interim guidance) (17 March 2021).
- EMA: EMA considerations on COVID-19 vaccine approval (EMA/592928/2020) (16/11/2020).
- US FDA: COVID-19: developing drugs and biological products for treatment or prevention: guidance for industry (February 2021).
- US FDA: Development and licensure of vaccines to prevent COVID-19: guidance for industry (June 2020).
- WHO: Guidelines on clinical evaluation of vaccines: regulatory expectations, Annex 9 (2017).
- US FDA: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: Guidance for Industry (September 2007).
- WHO: Design of vaccine efficacy trials to be used during public health emergencies – points of consideration and key principles (not dated).

2.7. Evaluator's commentary on the background information

The background information is considered to be satisfactory.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The application has been presented in an eCTD format. There are three sequences that contained evaluable clinical data (0001, 0003, 0004).

- Sequence 0001:
  - Module 1:
    - Administrative information including: cover letter, application forms, Paediatric Development Program, foreign regulatory status
  - Module 2:
    - Clinical overviews and addenda:
      - Clinical Overview: mRNA-1273 booster 12-17 years
      - Clinical Overview addendum: mRNA-1273 booster 12-17 years
      - Clinical Overview: mRNA-1273 booster 6-11 years
      - Clinical Overview: mRNA-1273.214 bivalent booster
      - Clinical Overview addendum: Comparison of mRNA-1273.214 and mRNA-1273 boosters against Omicron subvariants BA.4-5
  - Module 5:
    - Clinical study data:
      - Study mRNA-1273-P203
      - Study mRNA-1273-P204
      - Study mRNA-1273-P205

- Sequence 0003:
  - Module 1:
    - Cover letter, draft PI (AU), draft CMI (AU), approved overseas PIs (Canada, EU, US), CHMP clinical evaluation report, EU Risk Management Plan (RMP)

- Sequence 0004:
  - Module 1:
    - Cover letter, clean and annotated draft PIs (v1.2_07Dec22), Australian Specific Annex (ASA)
  - Module 2:
    - Clinical Overview – Study mRNA-1273-P205 Part H, Day 29 interim results
  - Module 5:
    - Clinical data for Study mRNA-1273-P205 Part H, Day 29 interim results, including tables and narratives for SAEs.

3.2. Paediatric data

The submission does not include any clinical data on individuals <18 YOA. The sponsor has indicated that they have an agreed Pediatric Plan (US), with the first submission due in March 2024.

In addition, the sponsor has provided the following statement:

> *ModernaTX Inc. has an agreed initial Pediatric Study Plan (iPSP). Deferral from having to submit a Pediatric Assessment in the USA have been accepted by FDA in the iPSP because data from pediatric studies were not available at the time of the US BLA submission. Clinical studies are ongoing and the planned studies are agreed with FDA.*

3.3. Good clinical practice

The sponsor has stated that the clinical studies were conducted in compliance with Good Clinical Practice guidelines.

3.4. Evaluator's commentary on the clinical dossier

There is no clinical study report for the pivotal study (mRNA-1273-P205 Part H) in the current submission. The sponsor has only provided a clinical overview along with tables and narratives from the Day 29 interim analyses, which are considered to be evaluable, but normally would be considered to be suboptimal for a Type A application.

4. Pharmacokinetics

Not applicable to vaccines.

5. Pharmacodynamics

For vaccines, pharmacodynamics would generally refer to immunogenicity following administration of the product. Immunogenicity data are presented in Section 7 of this CER.

6. Dosage selection for the pivotal studies

There is no apparent dosage selection study for mRNA-1273.222.

The specified amount of 50 μg is consistent with the previously approved boosters (≥12 YOA for mRNA-1273 and ≥18 YOA mRNA-1273.214).

For children ≤6 YOA, the sponsor has proposed 25 μg of mRNA-1273.222, which is consistent with the approved dose for mRNA-1273 in this age group.

7. Clinical efficacy

7.1. Studies providing evaluable immunogenicity data

Following studies included in the current submission provided evaluable immunogenicity data:

- **Study P205 Part H (mRNA-1273.222):** New bivalent boost data with mRNA-1273.222 in adults ≥18 YOA.
- **Study P205 Part G (mRNA-1273.214):** Re-provision of existing adult bivalent boost data for the Omicron bivalent vaccine mRNA-1273.214 (original/BA.1), previously evaluated by TGA (PM-2022-02203-1-2).
- **Study P203 Part C booster (mRNA-1273 prototype):** Re-provision of existing adolescent (12y-17y) data with mRNA-1273 prototype boost (SPIKEVAX original), previously evaluated by TGA (PM-2022-00685-1-2).
- **Study P204 booster (mRNA-1273 prototype):** New paediatric (6y-11y) data with mRNA-1273 prototype boost (SPIKEVAX original) from study P204.

Evaluator's comment:

Of the four studies, only **Study P205 Part H** presents immunogenicity data for mRNA-1273.222. The evaluator considers this study to be the main (i.e. pivotal) study to support the current submission.

Studies **P205 Part G, P203 Part C booster,** and **P204 booster** do not present any clinical data for mRNA-1273.222, and therefore are considered to be supportive studies. For **P205 Part G** and **P203 Part C booster**, only the relevant parts will be discussed in this CER as they have been previously evaluated by TGA.

7.2. Pivotal or main efficacy studies

7.2.1. Study P205 Part H (mRNA-1273.222)

Evaluator's comment:

It should be noted that there is no clinical study report for Study P205 Part H. As such, the study information is obtained from the supplied Clinical Summary and Clinical Study Protocol (CSP) – Amendment 9. Because of this, several detailed aspects of the study are largely lacking.

Study mRNA-1273-P205 is an ongoing Phase 2/3, open-label study to evaluate the immunogenicity, safety, and reactogenicity of various monovalent and multivalent vaccines, including: mRNA-1273, mRNA-1273.211, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.2d14, and mRNA-1273.222. As of the current submission, the study contains 8 parts: A (1, 2), B, C, D, E, F, G, and H.

Study mRNA-1273-P205 Part H aims to assess whether a single administration of mRNA-1273.222 50 µg as a second booster dose elicits a superior antibody response against Omicron BA.4/5 compared to a single booster dose of mRNA-1273 50 µg (Part F, Cohort 2) as a second booster dose.

Study P205 Part H consists of clinical data with mRNA-1273.222. The current submission consists of Day 29 interim results.

7.2.1.1. Study design, objectives, locations and dates

Study design

Study mRNA-1273-P205 is an ongoing Phase 2/3, open-label study that investigates the immunogenicity, safety, and reactogenicity of 50 µg of mRNA-1273.222 when administered as a second booster dose to adults who previously received 2 doses of 100 µg mRNA-1273 as a primary series and a single booster dose of mRNA-1273 50 µg. There is no contemporaneous control group. Instead, a previous cohort (Part F, Cohort 2) that received 50 µg of mRNA-1273 as a second booster dose after previously having received 2 doses of mRNA-1273 100 µg as a primary series and a booster dose of mRNA-1273 50 µg serves as the within-study comparator group for Part H.

Study vaccine (mRNA-1273.222 50 µg) was administered as a single dose on Day 1. Additional safety and/or immunogenicity study visits were planned to occur on Days 8, 15, 29, 91, and 181 (end of study [EoS]). Study visits were to include scheduled safety phone calls at Day 8, and every 2 weeks from Day 43 to Day 169 to collect AEs, MAAEs, AESIs, AEs leading to withdrawal, SAEs, pregnancies, and information about concomitant medications and receipt of non-study vaccinations.

Objectives

For objectives and endpoints for Part H, refer to Table 5.

Locations and dates

According to the Clinical Overview, the dosing period for Study P205 Part H was 10 August to 23 August 2022. The dosing period for Study 205 Part F was 18 February 2022 to 8 March 2022.

The CSP states that Study P205 (from Part A to Part H) is to be conducted in approximately 25 sites in the United States and its territories.

Table 5. Objectives and Endpoints of Study mRNA-1273-P205 Part H

Objectives	Endpoints
Primary	
• To demonstrate non-inferiority of the antibody response of a second booster dose of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second booster dose against Omicron BA.4/5 based on GMT ratio and SRR difference at Day 29 • To demonstrate superiority of the antibody response of a second booster dose of mRNA 1273.222 compared to mRNA-1273 (50 µg) administered as a second booster dose against the Omicron BA.4/5 based on GMT ratio at Day 29 • To demonstrate non-inferiority of the antibody response of mRNA-1273.222 50 µg compared to mRNA-1273 50 µg when administered as a second booster dose against the ancestral SARS-CoV-2 D614G based on GMT ratio and SRR difference at Day 29	• GMT ratio of Omicron BA.4/5 GMT of mRNA-1273.222 over the Omicron BA.4/5 GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 • SRR difference between mRNA-1273.222 against Omicron BA.4/5 and mRNA-1273 against Omicron BA.4/5 at Day 29 • GMT ratio of the ancestral SARS-CoV-2 D614G GMT of mRNA-1273.222 over the ancestral SARS-CoV-2 D614G GMT of mRNA-1273 at Day 29 • SRR difference between mRNA-1273.222 and mRNA-1273 against the ancestral SARS-CoV-2 D614G at Day 29
• To evaluate the safety and reactogenicity of mRNA-1273.222 50 µg	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after injection • Unsolicited adverse events (AEs) during the 28-day follow-up period after injection • Serious AEs (SAEs), MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study
Secondary	
• To evaluate the immunogenicity of mRNA-1273.222 50 µg as a second booster dose against the ancestral SARS-CoV-2 (and other variants) compared to a second booster dose of mRNA-1273 50 µg at all timepoints post-booster	• GMT ratio of mRNA-1273.222 50 µg and mRNA-1273 50 µg against ancestral SARS-CoV-2 (and other variants) at all timepoints post-booster • SRR difference between mRNA-1273.222 50 µg and mRNA-1273 50 µg against ancestral SARS-CoV-2 and variants of concern at all timepoints post-booster
Exploratory	
• To assess for symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants: – Primary case definition per the P301 (COVE) study – Secondary case definition based on the CDC criteria: the presence of 1 of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive reverse transcriptase polymerase chain reaction (RT-PCR) test on a respiratory sample – Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterize the SARS-CoV-2 genomic sequence of viral isolates and compare with the vaccine sequence • Characterize the immune responses to vaccine breakthrough isolates

Evaluator's comment:

It should be noted that several aspects of the study adversely affect the internal validity of the study. It is not ideal that Study P205 is open-label in nature. In addition, a lack of contemporaneous comparator is also suboptimal, particularly given that the nature of the virus and community (including infection rate, vaccination, immunity, knowledge and behaviour) continues to change over time.

It is understood that Part F Cohort 2 also served as a comparator for Part G (mRNA-1273.214) in the previous submission (PM-2022-02203-1-2).

For a detailed evaluation of Study Part F Cohort 2, refer to the CER for PM-2022-02203-1-2 (D22-5796589).

7.2.1.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for Study P205 are outlined in the CSP [e006836 (0004-) - mRNA-1273-P205 Clinical Study Protocol Amendment 9 (#33)].

The major inclusion criteria are:

- Male or female of at least 18 YOA. Females had to be of nonchildbearing potential, including use of contraceptives such as OCPs.
- Received a 2 dose primary series of mRNA-1273 followed by a 50 µg booster dose of mRNA-1273 in at least 3 months prior to enrolment.

The major exclusion criteria are:

- Significant exposure to someone with SARS-CoV-2 infection or COVID-19 14 days prior to the screening visit.
- Has known history of SARS-CoV-2 infection within 3 months prior to enrolment.
- Is acutely ill or febrile (temperature ≥ 38.0°C) less than 72 hours prior to or at the screening visit or Day 1.
- Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care.
- Has a current or previous diagnosis of immunocompromising condition to include HIV, or immune-mediated disease requiring immunosuppressive treatment, or other immunosuppressive condition.
- Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to screening (for corticosteroids ≥ 10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.
- Has a documented history of myocarditis or pericarditis within 2 months prior to screening visit (Day 0).
- Has received or plans to receive any licensed vaccine ≤ 28 days prior to the injection (Day 1) or a licensed vaccine within 28 days before or after the study injection, with the exception of influenza vaccines, which may be given 14 days before or after receipt of a study vaccine.

Evaluator's comments:

The exclusion criteria include several conditions, including: concurrent SARS-CoV-2 infection, acute or unstable chronic diseases, immunosuppression (from disease or treatment), and history of myocarditis. While the rationale for some of these exclusions are understood, it will affect the external validity of the analyses. In particular, it should be noted that people with

chronic diseases and immunosuppression will be the priority population for COVID-19 vaccination.

7.2.1.3. Study treatments

The study treatment involved administration of 50 µg mRNA-1273.222 as an IM second booster dose.

7.2.1.4. Efficacy variables and outcomes

Table 5 summarises the primary, secondary, and exploratory endpoints.

For the prespecified primary objectives, there were 5 corresponding success criteria:

1) Non-inferiority of the antibody response of the second booster dose of 50 µg mRNA-1273.222 compared with the second booster dose of 50 µg mRNA-1273 based on the GMR against Omicron BA.4/BA.5;
2) Non-inferiority of the antibody response of the second dose of 50 µg mRNA-1273.222 compared to the second booster dose of 50 µg mRNA-1273 against Omicron BA.4/BA.5 based on the difference in SRR, if:
    a. the lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/BA.5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/BA.5 at Day 29) is >-5%, then the non-inferiority of mRNA-1273.222 against Omicron BA.4/BA.5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 5%.
    b. the lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against Omicron BA.4/BA.5 at Day 29 - 50 µg mRNA-1273 against Omicron BA.4/BA.5 at Day 29) is >-10% but ≤-5%, then non-inferiority of mRNA-1273.222 against Omicron BA.4/BA.5 compared to that of mRNA-1273 is demonstrated based on a non-inferiority margin of 10%.
3) Non-inferiority of the antibody response of the second booster dose of 50 µg mRNA-1273.222 compared to the second booster dose of 50 µg mRNA-1273 based on GMR against the ancestral SARS-CoV-2;
4) Non-inferiority of the antibody response of the second dose of 50 µg mRNA-1273.222 compared to the second booster dose of 50 µg mRNA-1273 against ancestral based on the difference in SRR. The lower bound of the 95% CI of the SRR difference (50 µg mRNA-1273.222 against the ancestral SARS-CoV-2 D614G at Day 29 - 50 µg mRNA-1273 against ancestral SARS-CoV-2 D614G at Day 29) is >-10%.
5) Superiority of the antibody response of the second booster dose of 50 µg mRNA-1273.222 compared to the second booster dose of 50 µg mRNA-1273 based on the GMR against Omicron BA.4/BA.5.

The endpoint testing sequence prespecified that all 4 endpoints must first be met to test for the fifth endpoint.

Non-inferiority was considered met when the lower bound of the 95% CI of GMR is > 0.667 (1/1.5) and of SRR difference is > -10%. Superiority was considered met when the lower bound of the 95% CI of GMR is >1 and for the difference in SRR > 0.

If non-inferiority was demonstrated for both Omicron BA.4/BA.5 and ancestral SARS-CoV-2 with D614G (based on GMR and SRR), the lower bound of 95% CI of GMR was compared to 1, and if greater than 1, then superiority against Omicron BA.4/BA.5 was demonstrated.

Superiority of the mRNA-1273.222 antibody response against Omicron BA.4/BA.5, compared to mRNA-1273, was considered as demonstrated if superiority based on GMR was met at Day 29.

7.2.1.5. Randomisation and blinding methods

As per the CSP, this is an open-label study. No randomisation or blinding was planned.

7.2.1.6. Analysis populations

The following analysis sets were considered for Study P205 Part H:

- **Full Analysis Set (FAS)**: The FAS consisted of all participants who received study vaccine.
- **The PP Set for efficacy**: consisted of all participants in the FAS who received the planned dose of study vaccination, who were SARS-CoV-2 negative pre-booster (i.e. had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid pre-booster of 2nd booster dose), and had no major protocol deviations that impact key or critical data.
- **Per-Protocol Immunogenicity Set (PPIS):** consisted of all P205 participants in the FAS who met all the criteria listed below:
    - Received the planned dose of study vaccine per schedule.
    - Had pre-booster and Day 29 (occurring between 21 and 42 days after vaccination) neutralising antibody data.
        - against the Omicron (B.1.1.529) BA.1 variant for Part F.
        - against the Omicron (B.1.1.529) BA.4/5 variant for Part H.
    - Had no major protocol deviations that impacted key or critical data.
    - Had no HIV infection.
- **Per-Protocol Immunogenicity Set – SARS-CoV-2 Negative (PPIS – Neg)**: consisted of participants who met all requirements for the PP Immunogenicity Set and had no serologic or virologic evidence of SARS-CoV-2 infection at pre-booster of 2nd booster dose baseline.
- **Safety Set**: consisted of all participants who received study vaccine. The Safety Set was used for all analyses of safety except for the solicited AEs.
- **Solicited Safety Set**: consisted of all participants who received study vaccine and contributed any solicited AE data. The Solicited Safety Set was used for the analyses of solicited AEs.

The number of participants in each analysis set for Studies P205 Part H and Part F are shown in Table 6.

Table 6. Number of Participants in Each Analysis Set – 2nd Booster Dose: Studies 205 Part H and Part F

	P205 Part H	P205 Part F
	mRNA-1273.222 50 µg (N=511) n (%)	mRNA-1273 50 µg (N=379) n (%)
All enrolled	511	379
Full analysis Set[a]	511 (100)	376 (99.2)
Per-protocol efficacy set	216 (42.3)	266 (70.2)
Per-protocol immunogenicity set[a]	490 (95.9)	366 (96.6)
Per-protocol immunogenicity SARS-CoV-2 negative set[a]	209 (40.9)	259 (68.3)
Safety Set	511	376
Solicited safety set[b]	508 (99.4)	350 (93.1)

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

7.2.1.7. Sample size

The planned target enrolment was approximately 500 participants for Part H. Assuming 40% of participants would be excluded from the PPIS-Neg (due to a SARS-CoV-2 infection pre-booster), with approximately 300 participants in 50 µg mRNA-1273.222 and 260 participants in 50 µg mRNA-1273 (Part F, Cohort 2-50 µg mRNA-1273) in the PPIS and PPIS-Neg, there was approximately 60% power to demonstrate the primary immunogenicity objectives with an alpha of 0.05 (2-sided) at Day 29.

With approximately 500 participants exposed to 50 µg mRNA-1273.222, there was at least 90% probability in this group to observe 1 participant reporting an AE if the true rate of AEs is 1%.

Evaluator's comment:

The specified power of 60% for Study P205 Part H is lower than the commonly accepted power of at least 80%.

The quoted ≥90% probability to observe 1 participant reporting an AE (if the true rate of AE is 1%) is considered to be too low to detect rarer AEs including peri/myocarditis.

7.2.1.8. Statistical methods

50 µg mRNA-1273.222 given as a second booster dose was to be compared to 50 µg mRNA-1273 given as a second booster dose (in Part F, Cohort 2). The primary immunogenicity objective was to be assessed in the PPIS-Neg. Descriptive summaries of antibody GMTs, GMFR, and SRR were to be provided.

For the primary immunogenicity objective, there were 5 hypotheses to be tested as shown below and in Figure 2.

Hypotheses for Part H

i) 50 µg mRNA 1273.222, as a second booster dose, against Omicron BA.4/5 is non-inferior to the second booster dose of 50 µg mRNA 1273 against Omicron BA.4/5 based on the

GMT ratio of mRNA 1273.222 against Omicron BA.4/5 at Day 29 compared to mRNA 1273 against Omicron BA.4/5 at Day 29 with a non-inferiority margin of 1.5.

ii) 50 µg mRNA 1273.222, as a second booster dose, against Omicron BA.4/5 is non-inferior to the second booster dose of 50 µg mRNA 1273 against Omicron BA.4/5 based on the difference in SRR at Day 29 with a non-inferiority margin of 5%.

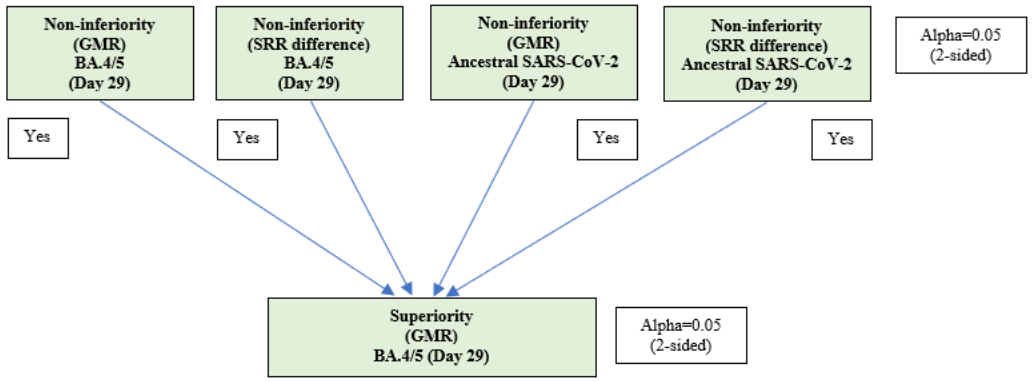
iii) 50 µg mRNA 1273.222, as a second booster dose, against ancestral SARS-CoV-2 D614G is non-inferior to the second booster dose of 50 µg mRNA 1273 against ancestral SARS-CoV-2 D614G based on the GMT ratio of mRNA 1273.222 against ancestral SARS-CoV-2 D614G at Day 29 compared to mRNA 1273 against ancestral SARS-CoV-2 D614G at Day 29 with a non-inferiority margin of 1.5.

iv) 50 µg mRNA 1273.222, as a second booster dose, against ancestral SARS-CoV-2 D614G is non-inferior to the second booster dose of 50 µg mRNA 1273 against ancestral SARS-CoV-2 D614G based on the difference in SRR at Day 29 with a non-inferiority margin of 10%.

v) 50 µg mRNA 1273.222, as a second booster dose, against Omicron BA.4/5 is superior to the second booster dose of 50 µg mRNA 1273 against Omicron BA.4/5 based on the GMT ratio of mRNA 1273.222 against Omicron BA.4/5 at Day 29 compared to mRNA 1273 against Omicron BA.4/5 at Day 29.

The primary immunogenicity objective was considered met if non-inferiority at Day 29 were demonstrated against BA.4/5 and ancestral SARS-CoV-2 D614G based on GMR and SRR differences.

Figure 2. Statistical Hypotheses Testing for Part H



For statistical analyses, an ANCOVA model was performed to assess the difference in antibody responses between mRNA-1273.222 and mRNA-1273 groups, with antibody titres post-booster as a dependent variable, and a group variable (mRNA-1273.222 and mRNA-1273) as the fixed effect, adjusting for age groups (< 65, ≥ 65 years) and pre-booster antibody titres. The GMTs (95% CI) estimated by the GLSM from the model for each group and the GMR (mRNA-1273.222 compared with mRNA-1273) estimated by the ratio of GLSM from the model (95% CIs) were provided. The GMR and 95% CI were used to assess the between group difference in antibody responses. The number and percentage of participants who achieved seroresponse was summarised with 95% CI calculated using the Clopper-Pearson method. The differences of SRR between mRNA-1273.222 and mRNA-1273 were calculated with 95% CI based on stratified Miettinen-Nurminen method adjusted for age groups. Seroresponse was defined as a change from below the LLOQ to equal or above 4 × LLOQ for those whose baseline is <LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ.

Seroresponse were derived based on two types of baselines: i) Pre-vaccination (Pre-Dose 1 of the primary series), and ii) Pre-booster baseline.

For participants without pre-Dose 1 antibody titre information, seroresponse was defined as ≥ 4 × LLOQ for participants with negative SARS-CoV-2 status at their pre-dose 1 of primary series, and these participants antibody titre were deemed <LLOQ at pre-dose 1 of primary series. For subjects who were without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status was used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

A supportive analysis was also performed using the per-protocol set for immunogenicity, using an ANCOVA model to assess the antibody responses, with antibody titres at Day 29 post-booster as the dependent variable and vaccine group variable as the fixed effect, adjusting for age groups (<65, ≥65 years), pre-booster SARS-CoV-2 infection status, and pre-booster titres. The SRR difference between mRNA-1273.222 and mRNA-1273 was calculated with 95% CI based on stratified Miettinen-Nurminen method adjusted for the pre-booster SARS-CoV-2 infection status and age group.

A pre-planned subgroup analysis for the SARS-CoV-2 infection positive pre-booster participants was performed using an ANCOVA model to assess for neutralising antibody differences between the mRNA-1273.222 and mRNA-1273 groups based on GMRs with 95% CIs for the ancestral SARS-CoV-2 with D614G and Omicron BA.4/BA.5. Lastly, a sensitivity analysis was performed by excluding all records after SARS-CoV-2 infection. All analyses were conducted using SAS Version 9.4 or higher.

7.2.1.9. Participant flow

In the mRNA-1273.222 50 µg booster dose group (P205 Part H), 511 participants received the booster dose (Table 7). Of these, 305 participants (59.7%) enrolled from Study P301 in which they had received the primary series and the first booster dose of mRNA-1273; 206 of the 511 participants (40.3%) had received the primary series and the first booster dose of mRNA-1273 under the EUA in the United States. The median follow-up time from the mRNA-1273.222 50 µg booster dose injection was 37 days (range 5 to 45 days). Of the 511 participants who received the mRNA-1273.222 50 µg booster dose, 4 participants discontinued from the study (2 withdrawal of consent by participant, 1 death and 1 lost to follow-up) (Table 7).

In the mRNA-1273 50 µg booster dose group (P205 Part F), 379 participants enrolled and 376 received the booster dose (Table 7). Of the 376 participants, 263 participants (69.9%) enrolled from study mRNA-1273 P301 where they had received the primary series and the first booster dose of mRNA-1273; 113 of the 376 participants (30.1%) had received the primary series and the first booster dose of mRNA-1273 under the EUA in the United States. The median follow-up time from mRNA-1273 50 µg booster injection was 127 days (range 64 to 136 days). Of the 376 participants who received the mRNA-1273 50 µg booster dose, 98.4% participants were still on study by the data cut-off date (06 Jul 2022) (Table 7).

Table 7. Participant Disposition – 2nd Booster Dose: P205 mRNA-1273.222 and mRNA-1273 (Full Analysis Set)

	P205 Part H	P205 Part F
	mRNA-1273.222 50 µg (N=511) n (%)	mRNA-1273 50 µg (N=376) n (%)
Number of participants		
Received injection	511	376
Completed study[a]	0	0
Discontinued from study	4 (0.8)	6 (1.6)
Reason for study discontinuation		
Death	1 (0.2)	1 (0.3)
Lost to follow-up	1 (0.2)	4 (1.1)
Withdrawal of consent by participant	2 (0.4)	1 (0.3)
Other	0	0

Percentages are based on the number of participants in the Full Analysis Set

[a] Study completion for Part H is defined as a participant who completed 6 months of follow-up after the injection. Study completion for Part F is defined as a participant who completed 12 months of follow-up after the injection.

7.2.1.10. Major protocol violations/deviations

The clinical overview does not provide any information regarding protocol violations/deviations for Study P205 Part H. Without a study report, there is no source of this information.

Evaluator's comment:

EvQ: The sponsor should submit a summary of major protocol violations/deviations for Study P205 Part H.

7.2.1.11. Baseline data

In the mRNA-1273.222 50 µg booster dose group (dosed 10 August to 23 August 2022), 316/511 participants (61.8%) were female, most were White (426/511 [83.4%]), and the median age was 50.0 years (range: 19 to 89 years) (Table 8). 105/511 participants (20.5 %) were ≥ 65 YOA. Most participants were not Hispanic or Latino (448/511 [87.7%]). The median time between dose 2 of the primary series to the first booster dose was 251 days (range 67 to 533 days) and the median time between the first booster dose to the mRNA-1273.222 50 µg booster dose was 289 days (range 103 to 371 days). At baseline, 286 of 511 mRNA-1273.222 participants (56.0 %) had evidence of prior SARS-CoV-2 infection (Table 8).

In the mRNA-1273 50 µg booster dose group (dosed 18 February 2022 to 8 March 2022), 190/376 participants (50.5 %) were female, most were White (322/376 [85.6%]), and the median age was 60.5 years (range: 20 to 96 years) (Table 8). 150/376 participants (39.9%) were ≥ 65 years of age. Most participants were not Hispanic or Latino (339/376 [90.2%]). The median time between dose 2 of the primary series and the first booster dose was 242 days (range 170 to 438 days) and the median time between the first booster dose and the mRNA-1273 booster dose was 134 days (range 90 to 310 days). At baseline, 101 of 376 mRNA-1273 participants (26.9%) had evidence of prior SARS-CoV-2 infection (Table 8).

Table 8. Participant Demographics and Baseline Characteristics – 2nd Booster Dose: mRNA-1273.222 and mRNA-1273 (Safety Set)

	P205 Part H mRNA-1273.222 50 µg (N=511)	P205 Part F mRNA-1273 50 µg (N=376)
Age (years), n	511	376
Mean (SD)	50.8 (14.81)	57.6 (15.22)
Median (mix, max)	50.0 (19, 89)	60.5 (20, 96)
Age subgroups		
≥ 18 and < 65 years	406 (79.5)	226 (60.1)
Mean (SD)	45.5 (11.56)	48.0 (11.39)
Median (mix, max)	46.0 (19, 64)	48.5 (20, 64)
≥ 65 years	105 (20.5)	150 (39.9)
Mean (SD)	71.1 (5.35)	72.1 (6.03)
Median (mix, max)	70.0 (65, 89)	70.0 (65, 96)
Gender, n (%)		
Male	195 (38.2)	186 (49.5)
Female	316 (61.8)	190 (50.5)
Race, n (%)		
White	426 (83.4)	322 (85.6)
Black or African American	56 (11.0)	28 (7.4)
Asian	11 (2.2)	16 (4.3)
American Indian or Alaska Native	1 (0.2)	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)
Multiracial	8 (1.6)	2 (0.5)
Other	6 (1.2)	2 (0.5)
Not reported	2 (0.4)	3 (0.8)
Unknown	1 (0.2)	1 (0.3)
Ethnicity, n (%)		
Hispanic or Latino	58 (11.4)	37 (9.8)
Not Hispanic or Latino	448 (87.7)	339 (90.2)
Not reported	4 (0.8)	0
Unknown	1 (0.2)	0
Body mass index (kg/m^2), n	509	376
Mean (SD)	31.10 (8.024)	30.80 (7.509)
Median (mix, max)	29.94 (13.9, 64.4)	29.37 (18.4, 61.8)
Pre-booster RT-PCR results, n (%)		
Negative	488 (95.5)	366 (97.3)
Positive	10 (2.0)	2 (0.5)
Missing	13 (2.5)	8 (2.1)
Pre-booster Elecsys Anti-SARS-CoV-2 Results, n (%)		
Negative	226 (44.2)	276 (73.4)
Positive	282 (55.2)	100 (26.6)
Missing	3 (0.6)	0
Pre-booster SARS-CoV-2 Status, n (%) [a]		
Negative	216 (42.3)	267 (71.0)
Positive	286 (56.0)	101 (26.9)
Missing	9 (1.8)	8 (2.1)
Time between dose 2 of primary series to 1st booster dose (days), n	509	374
Mean (SD)	274.6 (71.40)	258.0 (56.89)
Median (mix, max)	251.0 (67, 533)	242.0 (170, 438)
Time between the 1st booster dose to 2nd booster dose (days), n	509	374
Mean (SD)	279.9 (41.72)	133.6 (21.47)
Median (mix, max)	289.0 (103, 371)	134.0 (90, 310)

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

Percentages are based on the number of participants in the Safety Set.

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

Evaluator's comments:

There are certain notable differences between Study P205 Part H and Part F participants. While the mean and median ages are comparable between the two groups, the proportion of ≥65 YOA Part H is approximately half of that in Part F (20.5% and 39.9%, respectively). Given that there may be a significant difference in immune response in these two age subgroups, such a large difference in the ≥65 YOA proportion between Part H and Part F may adversely affect the validity of the comparison.

In addition, there is almost a two-fold difference in the mean duration between the 1st and 2nd booster doses (279.9 days for Part H and 133.6 days for Part F). This may also have certain impacts on the immune memory response following a 2nd booster.

The pre-booster SARS-CoV-2 positive rate was noticeably higher in Part H than Part F (56.0% and 26.9%, respectively). This is likely to reflect the ongoing rise in the cumulative COVID-19 cases in the current pandemic. However, it should also be noted that those who previously had SARS-CoV-2 infection are also likely to reach higher antibody titre post 2nd booster dose, as has been demonstrated with mRNA-1273.214 in PM-2022-02203-1-2. Again, this could affect the validity of the comparison between Part H and Part F.

7.2.2. Results for the immunogenicity outcome

7.2.2.1. Results for the primary immunogenicity outcome

The primary immunogenicity objective of Study mRNA-1273-P205 Part H was to compare the immunogenicity of mRNA-1273.222 50 µg when administered as a second booster dose to the immunogenicity of mRNA-1273 50 µg as the second booster in Study P205 Part F, Cohort 2. In both parts, the participants were adults ≥18 YOA had previously received a 2-dose primary mRNA-1273 100 µg vaccine series and a booster dose of 50 µg mRNA-1273. The primary analysis population for the primary objective was the PPIS-Neg population (participants with no prior infection).

Immunogenicity in participants without previous SARS-CoV-2 infection at pre-booster

In the PPIS-Neg population, the observed GMT (95% CI) against Omicron BA.4/BA.5 at pre-booster was 87.9 (72.2,107.1) and increased to 2324.6 (1921.2, 2812.7) 28 days after the booster dose for mRNA-1273.222; the GMFR (95% CI) for the GMTs 28 days after the booster compared to pre-booster was 26.4 (22.0, 31.9) (Table 9). In the mRNA-1273 group, the observed GMT (95% CIs) at pre-booster was 136.1 (116.3, 159.3) and increased to 488.5 (427.4, 558.4) 28 days after the booster dose; the GMFR (95% CI) was 3.6 (3.3, 4.0).

The ANCOVA-estimated neutralising antibody GMTs (95% CI) against Omicron BA.4/BA.5 adjusted for pre-booster titre and age group were 2747.3 (2399.2, 3145.9) and 436.7 (389.1, 490.0) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively. The GMR (95% CI) was 6.29 (5.27, 7.51), meeting the prespecified criterion for non-inferiority (lower bound of CI >0.667).

The Omicron BA.4/BA.5 SRRs (95% CI), using the pre-Dose 1/pre-primary vaccination values as baseline, were 98.1% (95.2, 99.5) and 86.4% (81.6, 90.3) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively; the SRR difference (95% CI) was 12.1%(6.9, 17.3) meeting the non-inferiority criterion (lower bound of CI >-5%). In addition, when the analysis was performed using the pre-2nd booster values as baseline, the Omicron BA.4/BA.5 SRRs (95% CI) were 90.9% (86.2, 94.4) and 37.8% (31.9, 44.0) 28 days after the mRNA 1273.222 and mRNA-1273 booster doses, respectively; the SRR difference (95% CI) was 53.9% (46.7, 61.2), also meeting the non-inferiority criterion.

The observed GMT (95% CI) against the ancestral SARS-CoV-2 D614G at pre-booster was 796.9 (678.7, 935.8) and increased to 7322.4 (6386.2, 8395.7) 28 days after the booster dose for mRNA-1273.222; the GMFR (95% CI) for the GMTs 28 days after the booster compared to pre-booster was 9.2 (7.9, 10.6). In the mRNA-1273 group, the observed GMT (95% CI) against ancestral SARS-CoV-2 D614G at pre-booster was 1515.4 (1347.5, 1704.2) and increased to 5651.4 (5055.7, 6317.3) 28 days after the booster dose; the GMFR (95% CI) was 3.7 (3.4, 4.1).

The ANCOVA-estimated neutralising antibody GMTs (95% CI) against ancestral SARS-CoV-2 (D614G) adjusted for pre-booster titre and age group were 9555.8 (8593.6, 10625.7) and 4882.2 (4457.7, 5347.1) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively. The GMR (95% CI) was 1.96 (1.70, 2.25), meeting the prespecified criterion for non-inferiority (lower bound of CI >0.667).

The SRRs (95% CI) against the ancestral SARS-CoV-2 D614G, using the pre-Dose 1/pre-primary vaccination values as baseline were 100% (98.3, 100.0) and 100% (98.6, 100.0) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively. The SRR difference was 0, meeting the non-inferiority criterion. In addition, the analysis was performed using the pre-2nd booster values as baseline, the SRRs (95% CI) against the ancestral SARS-CoV-2 (D614G) were 80.4% (74.3, 85.5) and 42.9% (36.7, 49.1) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively; the SRR difference (95% CI) was 37.3% (29.0, 45.6), also meeting the non-inferiority criterion (lower bound of CI >-10%).

Table 9. Ancestral SARS-CoV-2 (D614G) and Omicron (BA.4/BA.5) Neutralising Antibody Titres (ID50) mRNA-1273.222 50 µg and mRNA-1273 50 µg Administered as Second Booster Doses - Per-Protocol Immunogenicity – SARS-CoV-2 Negative Set (Participants without Infection at Pre-booster)

	Omicron BA.4/BA.5		Ancestral SARS-CoV-2	
Antibody: PsVNA nAb ID_{50} titers	**P205 Part H mRNA-1273.222 50 µg (N=209)**	**P205 Part F mRNA-1273 50 µg (N=259)**	**P205 Part H mRNA-1273.222 50 µg (N=209)**	**P205 Part F mRNA-1273 50 µg (N=259)**
Pre-booster, n	209	259	209	259
Observed GMT (95% CI)[a]	87.9 (72.2, 107.1)	136.1 (116.3, 159.3)	796.9 (678.7, 935.8)	1515.4 (1347.5, 1704.2)
Day 29, n	209	259	209	259
Observed GMT (95% CI)[a]	2324.6 (1921.2, 2812.7)	488.5 (427.4, 558.4)	7322.4 (6386.2, 8395.7)	5651.4 (5055.7, 6317.3)
Observed GMFR (95% CI)[a]	26.4 (22.0, 31.9)	3.6 (3.3, 4.0)	9.2 (7.9, 10.6)	3.7 (3.4, 4.1)
GLSM [Estimated GMT] (95% CI)[b]	2747.3 (2399.2, 3145.9)	436.7 (389.1, 490.0)	9555.8 (8593.6, 10625.7)	4882.2 (4457.7, 5347.1)
GMR (95% CI)[b]	**6.29 (5.27, 7.51)**		**1.96 (1.70, 2.25)**	
Seroresponse rate (pre-dose 1 as baseline)				
N1	209	257	209	259
n/N1 (%)[c], (95% CI)[d]	205/209 (98.1) (95.2, 99.5)	222/257 (86.4) (81.6, 90.3)	209/209 (100) (98.3, 100)	259/259 (100) (98.6, 100.0)
Difference in seroresponse rates (95%)[e]	12.1 (6.9, 17.3)		0	
Seroresponse rate (pre-booster as baseline)				
N2	209	259	209	259
n/N2 (%)[c], (95% CI)[d]	190/209 (90.9) (86.2, 94.4)	98/259 (37.8) (31.9, 44.0)	168/209 (80.4) (74.3, 85.5)	111/259 (42.9) (36.7, 49.1)
Difference in seroresponse rates (95%)[e]	53.9 (46.7, 61.2)		37.3 (29.0, 45.6)	

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

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

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

N2 = number of participants with non-missing data at pre-booster baseline and the corresponding timepoint

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

[b] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.

[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x LLOQ if the participant's baseline (pre-Dose 1/pre-booster) is below the LLOQ, or at least a 4-fold rise if the baseline (pre-Dose/pre-booster) is equal to or above the LLOQ. For participants without pre-Dose 1 antibody titer information, seroresponse (using pre-Dose 1 baseline) is defined as ≥4*LLOQ for participants with negative SARS-CoV-2 status at their pre-dose 1 of the primary series, and these titers are imputed as <LLOQ at pre-dose 1 of primary series. For participants without SARS-CoV-2 status information at pre-dose 1 of primary series, their pre-booster SARS-CoV-2 status is used to impute their SARS-CoV-2 status at their pre-dose 1 of primary series.

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

[e] 95% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences. The stratified Miettinen-Nurminen estimate of the CI cannot be calculated when the seroresponse rate in both groups is 100%, absolute difference is reported.

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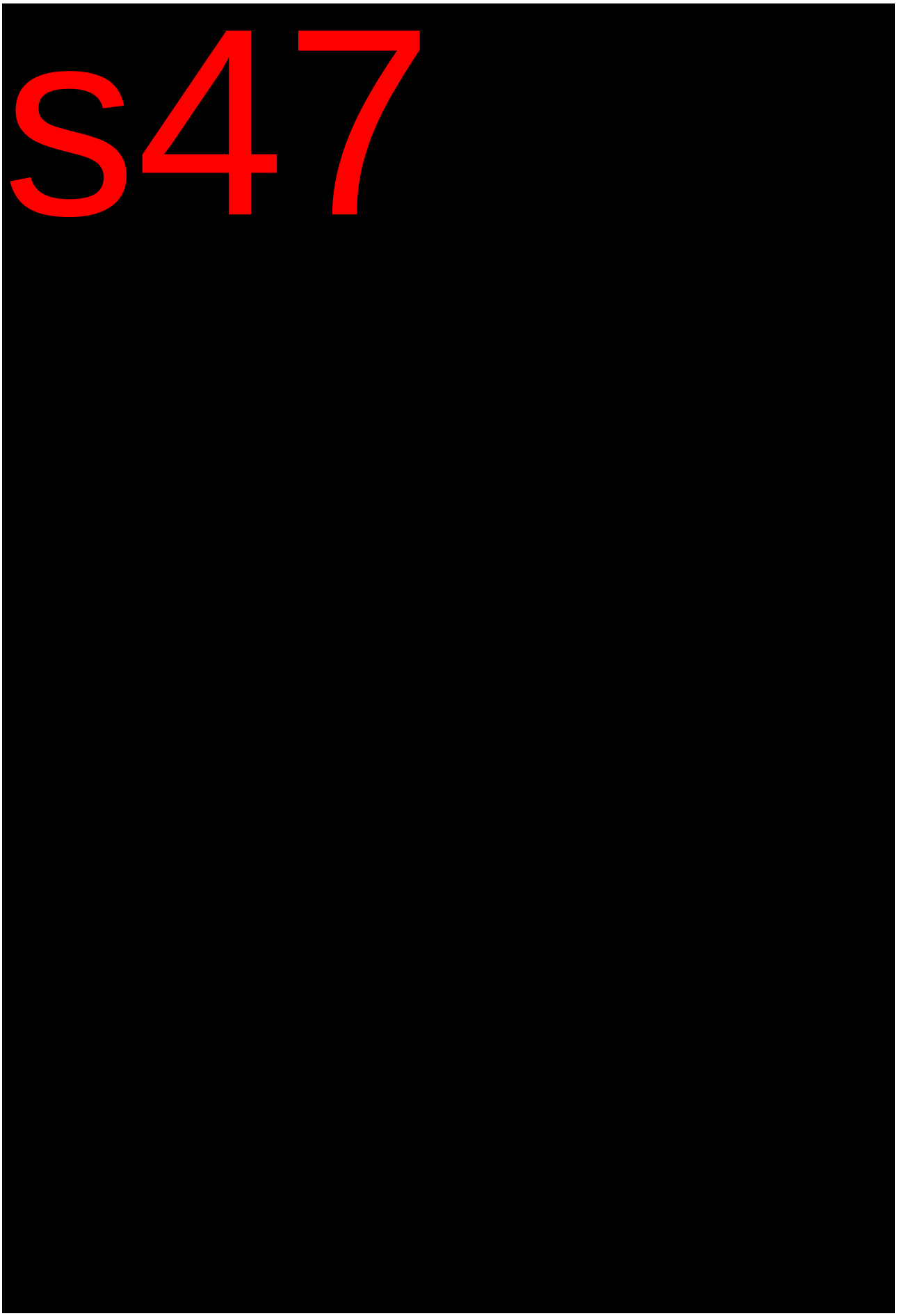
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7.2.2.2. Results for other immunogenicity outcomes

Subgroup analysis by age (≥ 18 to < 65 years and ≥ 65 years of age)

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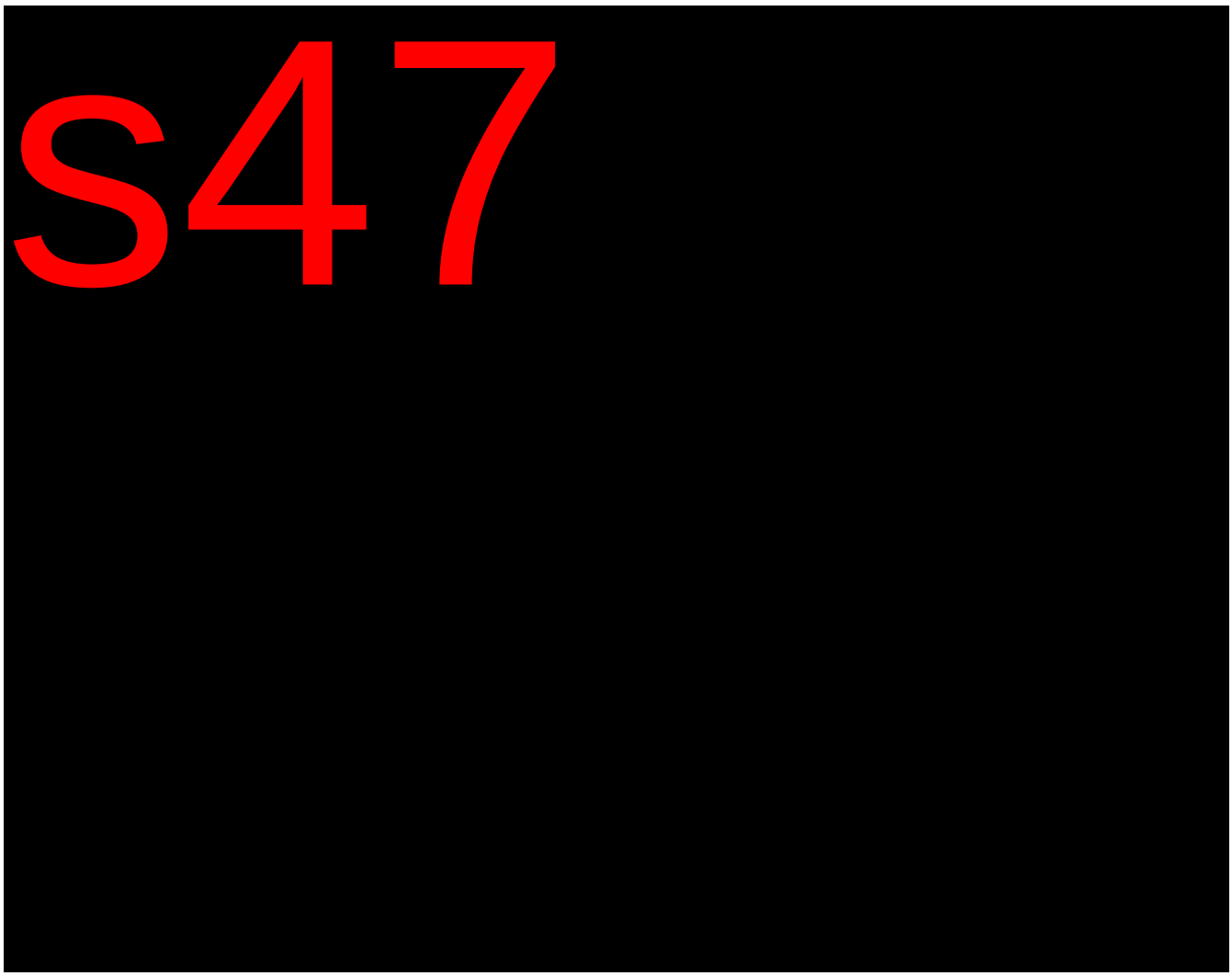
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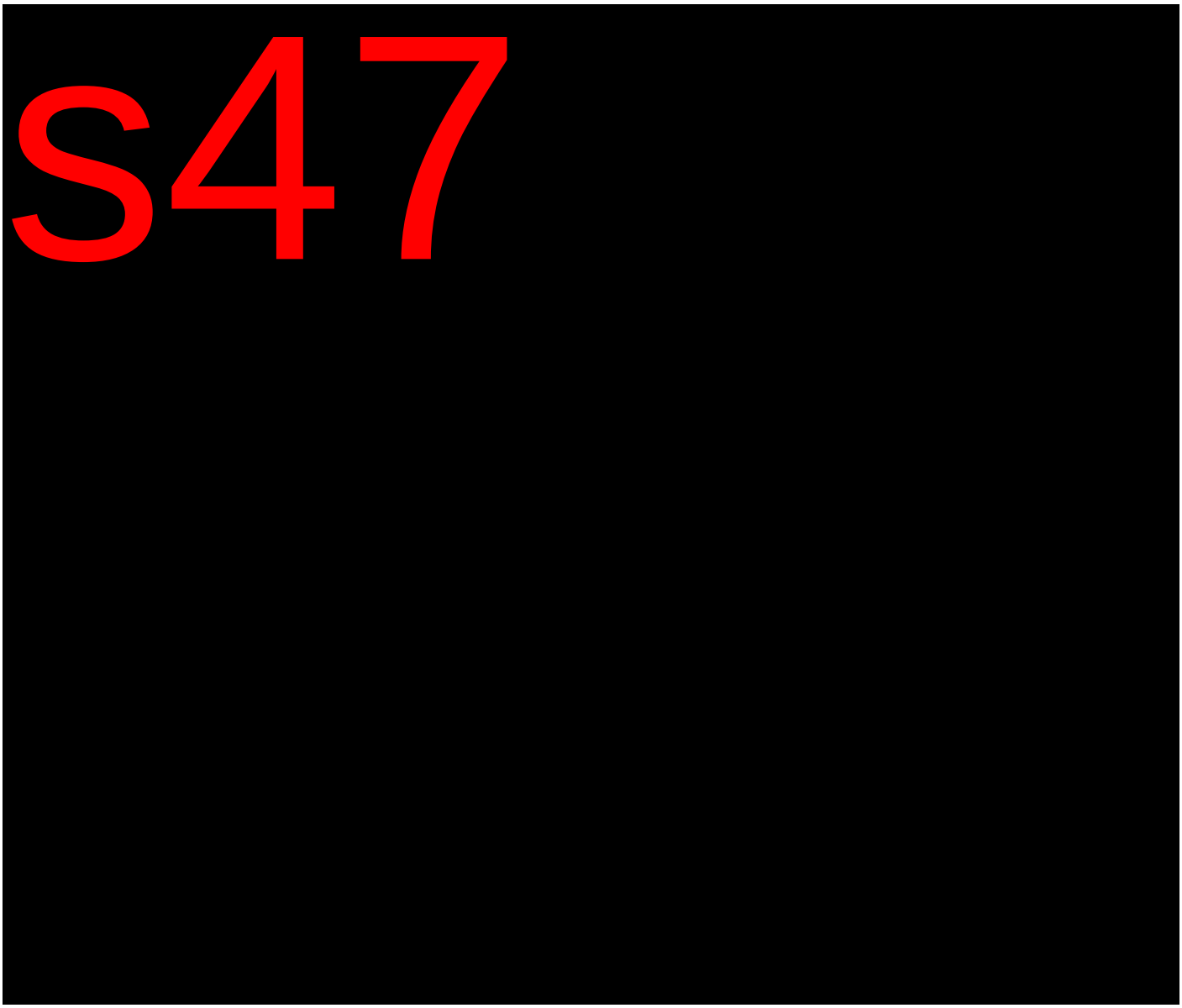
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7.2.3. Results for clinical efficacy outcomes

SARS-CoV-2 incidence rates after the mRNA-1273.222 and mRNA-1273 booster vaccines

While Study P205 was not designed to evaluate the vaccine effectiveness, SARS-CoV-2 infection cases have been counted in Part H and Part F. Summaries of the symptomatic (per primary and per secondary case definition) and asymptomatic SARS-CoV-2 infections post-booster are provided in Table 15. The definitions used for SARS-CoV-2 infection are detailed in Section 6.5.1. of the Statistical Analysis Plan [e006836 (0004-) - mRNA-1273-P205 Statistical Analysis Plan v5.0 (#70)]. Infections were counted starting 14 days after the booster dose (mRNA-1273.222 50 µg) through the follow-up time of this interim analysis.

In the mRNA-1273.222 50 µg booster dose group of participants without prior infection (PP Efficacy Set) with a median of 37 days of follow-up, 12 participants (5.6%) had SARS-CoV-2 infection starting at least 14 days after the 50 µg booster dose. Among the 12 participants with SARS-CoV-2 infection, 5 participants (2.3%) met the primary case definition of COVID-19, and 7 participants (3.2%) met the secondary case definition of COVID-19. The remaining 5 participants (2.3%) had an asymptomatic infection. No participants with COVID-19 had an emergency room visit or hospitalisation due to the COVID-19 event. Similar results were observed for the FAS population (Table 15).

The Day 29 interim analysis infection rates for mRNA-1273 50 µg booster dose group (enrolled in February-March 2022), with a median of 57 days of follow-up duration, showed that 9 participants (2.4%) from PP Efficacy Set had SARS-CoV-2 infection starting at least 14 days after the 50 µg booster dose. Among the 9 participants with SARS-CoV-2 infection, 2 participants (0.5%) met both the primary case definition of COVID-19 and the secondary case definition of COVID-19. The remaining 7 participants had an asymptomatic infection.

Table 15. Summary of COVID-19 Infections (Second Booster Dose: mRNA-1273.222 50 µg)

	Per Protocol Efficacy Set P205 Part H mRNA-1273.222 50 µg (N=216) n (%)	Full Analysis Set P205 Part H mRNA-1273.222 50 µg (N=511) n (%)
Primary case definition of COVID-19 (per Study P301) starting 14 days after injection, n[a]	5 (2.3)	6 (1.2)
Secondary case definition of COVID-19 (CDC criteria) starting 14 days after injection, n[b]	7 (3.2)	8 (1.6)
SARS-CoV-2 infection starting 14 days after injection, n	12 (5.6)	17 (3.3)
Asymptomatic SARS-CoV-2 infection starting 14 days after injection, n	5 (2.3)	9 (1.8)

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

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

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

Evaluator's comments

The number of SARS-CoV-2 infection cases in Part H and Part F are too small to draw a meaningful conclusion. In addition, the two parts took place in different settings, and therefore it is difficult to make an objective comparison.

7.3. Other studies

7.3.1. Study P205 Part G (mRNA-1273.214)

Study P205 Part G was previously evaluated by TGA (PM-2022-02203-1-2), and therefore not fully discussed in this CER. Refer to the CER for PM-2022-02203-1-2 (D22-5796589) for further details.

Study P205 Part G evaluated the safety, reactogenicity, and immunogenicity of 50 µg of mRNA 1273.214 when administered as a second booster dose in adults who previously received 2 doses of 100 µg mRNA-1273 as a primary series and a single booster dose of 50 µg mRNA-1273. As is the case with Study P205 Part H, the sponsor provided P205 Part F as the within-study, non-contemporaneous comparator group for P205 Part G.

In the P205 Part G vs Part F analysis, the primary immunogenicity objective was to compare the immunogenicity of mRNA-1273.214 50 µg and mRNA-1273 50 µg as a second booster. In both parts, the second booster was given to adults who previously received a 2-dose primary mRNA-1273 100 µg vaccine series and a booster dose of 50 µg mRNA-1273.

Based on the primary immunogenicity analysis in PPSI-Neg Set, the following findings were made:

- Neutralising antibody against the Omicron (B.1.1.529) variant:
  - The observed GMT (95% CI) at pre-booster in P205 Part G was 298.1 (258.8, 343.5) and increased to 2372.4 (2070.6, 2718.2) at 28 days after the booster dose with mRNA-1273.214; the GMFR (95% CI) for the GMTs at 28 days after the booster compared to pre-booster was 8.0 (7.2, 8.8).

  - The observed GMTs (95% CIs) at pre-booster in P205 Part F were 332.0 (282.0, 390.9) and increased to 1473.5 (1270.8, 1708.4) at 28 days after the booster dose with mRNA-1273; the GMFR (95% CI) was 4.4 (4.0, 5.0).
  - The GMR (97.5% CIs) of the estimated GMTs in Part G and Part F was 1.75 (1.49, 2.04), meeting the prespecified superiority criterion (lower bound of CI >1).
- Neutralising antibody against ancestral SARS-CoV-2 (D614G):
  - The estimated GMTs adjusted for pre-booster titre and age group were 6422.3 (5990.1, 6885.7) and 5286.6 (4887.1, 5718.9) 28 days after the mRNA-1273.214 and mRNA-1273 booster doses, respectively.
  - The GMR (97.5% CI) was 1.22 (1.08, 1.37), meeting the prespecified criterion for non-inferiority (lower bound of CI ≥0.67).

In addition, a subgroup analysis in participants with evidence of SARS-CoV-2 infection at baseline showed that mRNA-1273.214 demonstrated higher immunogenicity against Omicron (B.1.1.529) and ancestral SARS-CoV-2 (D614G) with the Day 29 GMR of 1.898 (97.5% CI: 1.499, 2.403) and 1.272 (97.5% CI: 1.070, 1.512), respectively.

Based on the key secondary analysis of SRR, the following findings were made:

- The Omicron (B.1.1.529) SRRs (95% CI) were 100% (98.9, 100) and 99.2% (97.2, 99.9), 28 days after the mRNA-1273.214 and mRNA-1273 booster doses, respectively, and the SRR difference (97.5% CI) was 1.5% (-1.1, 4.0) meeting the non-inferiority criterion (lower bound of CI >-10%).
- The SRR (95% CI) against the ancestral SARS-CoV-2 (D614G) was 100% (98.9, 100 and 98.6, 100) 28 days after the mRNA-1273.214 and mRNA-1273 booster doses, respectively, with an SRR difference of 0. Therefore, the key secondary immunogenicity objective was also met.

An exploratory immunogenicity analysis was performed after mRNA-1273.214 50 µg and mRNA-1273 50 µg second booster doses (Day 29) on binding antibody GMT to ancestral SARS-CoV-2, Alpha, Beta, Delta, Gamma, and Omicron (B.1.1.529) in PPSI (regardless of baseline SARS-CoV-2 status) population. Based on this analysis, mRNA-1273.214 50 µg booster dose demonstrated superiority at Day 29, compared to mRNA-1273.214 50 µg, as shown in the following GMR (95% CI) results.

- Ancestral SARS-CoV-2: 1.138 (1.068, 1.213).
- Alpha: 1.165 (1.093, 1.241).
- Beta: 1.142 (1.071, 1.217).
- Delta: 1.095 (1.031, 1.163).
- Gamma: 1.160 (1.087, 1.238).
- Omicron (B.1.1.529): 1.232 (1.149, 1.321).

Immunogenicity comparison of mRNA-1273.214 50 µg with mRNA-1273 50 µg against the Omicron subvariants BA.4, BA.5

The sponsor presented immunogenicity comparison of mRNA-1273.214 50 µg with mRNA-1273 50 µg against the Omicron subvariants BA.4, BA.5.

In the primary analysis set (PPSI – Neg, reflecting participants without prior SARS-CoV-2 infection), the observed GMTs (95% CI) against Omicron BA.4, BA5 GMTs (95% CI) pre-booster were 115.6 (98.5, 135.6) and increased to 727.4 (632.8, 836.1) at 28 days after the booster dose for mRNA-1273.214 with a GMFR (95% CI) of 6.3 (5.7, 6.9) (Table 16). The GMTs (95% CIs) were 139.7 (119.5, 163.3) pre-booster and 492.1 (431.1, 561.9) in the mRNA-1273 at 28 days after the booster dose and GMFR (95% CI) was 3.5 (3.2, 3.9). The GMR (95% CI) for the comparison of mRNA-1273.214 50 µg booster dose with the mRNA-1273 50 µg booster dose was 1.69 (1.51, 1.90) with the lower bound of the CI > 1.

In the PPSI – Pos population (participants with prior SARS-CoV-2 infection), the pre-booster GMTs (95% CI) against Omicron BA.4, BA.5 subvariant were 719.5 (531.6, 973.9) which increased to 2337.4 (1825.5, 2992.9) 28 days after the mRNA-1273.214 booster dose with a GMFR (95% CI) of 3.2 (2.8, 3.8). The GMTs (95% CIs) were 609.1 (448.1, 828.1) pre-booster and 1270.8 (987.3, 1635.8) in the mRNA-1273 group at 28 days after the booster dose and GMFR (95% CI) was 2.1 (1.8, 2.4). The GMR (95% CI) for the comparison of mRNA-1273.214 50 µg booster dose with the mRNA-1273 50 µg booster dose was 1.60 (1.34, 1.91) with a lower bound of the CI > 1.

In the PPSI population (participants with and without prior SARS-CoV-2 infection), the pre-booster GMT (95% CI) against Omicron BA.4, BA.5 subvariant was 172.7 (147.4, 202.3) which increased to 940.6 (826.3, 1070.6) 28 days after the mRNA-1273.214 booster dose with a GMFR (95% CI) of 5.4 (5.0, 5.9). The GMTs (95% CIs) were 209.3 (179.5, 244.1) pre-booster and 645.4 (570.1, 730.6) in the mRNA-1273 group at 28 days after the booster dose and GMFR (95% CI) was 3.1 (2.8, 3.3). The GMR (95% CI) for the comparison of mRNA-1273.214 50 µg booster dose with the mRNA-1273 50 µg booster dose was 1.68 (1.52, 1.84) with a lower bound of the CI > 1.

In all participants, regardless of prior SARS-CoV-2 infection, mRNA-1273.214 50 µg elicited numerically greater nAb responses against the Omicron subvariants BA.4, BA.5 compared to mRNA-1273 50 µg (nominal alpha of 0.05). Results were also consistent across age groups, 18-65 years old and above 65 years.

Table 16. Summary of Neutralising Antibody Geometric Mean Titres for Omicron BA.4, BA.5 Variant - Comparison Between mRNA-1273.214 50 µg and mRNA-1273 50 µg Booster Doses

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

Abbreviations: CI = confidence interval; GLSM=geometric least squares mean; GMFR = geometric mean fold-rise (post-baseline/baseline titers); GMT = geometric mean titer; ID_{50} = 50% inhibitory dilution; LOD = limit of detection; mRNA = messenger ribonucleic acid; nAb = neutralizing antibody; PPSI = per-protocol set for immunogenicity; PPSI – Neg = per-protocol Set for immunogenicity – SARs-CoV-2 Negative at baseline; PPSI – Pos = per-protocol Set for immunogenicity – SARS-CoV-2 Positive at baseline; PsVNA = pseudotyped virus neutralization assay.

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

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

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

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

7.3.2. Study P203 Part C booster (mRNA-1273 prototype)

Study P203 Part C is an extension of Study P203. Study P203 is a Phase 2/3 study originally designed as a randomised, observer-blind, placebo-controlled study evaluating the safety, reactogenicity, and effectiveness of a two-dose mRNA-1273 vaccine (100µg) primary series in healthy adolescents 12 to 17 YOA. The study later transitioned to an open-label phase. This allowed unblinding of study participants and crossover of those participants randomised to placebo to receive the mRNA-1273 primary series. A protocol amendment (Part 1C-1) was

later implemented to evaluate administration of a 50 µg mRNA-1273 booster dose to ongoing study participants from Study P203. A booster dose was administered at least 5 months after completion of the mRNA-1273 primary series. This data has been previously assessed by TGA (PM-2022-00685-1-2). The sponsor has re-submitted this data to support the bivalent vaccine mRNA-1273.222 in the 12 to 17 years age group.

The primary immunogenicity objective of the booster phase of Study P203 was to infer effectiveness of the 50 µg booster of mRNA-1273 by comparing post-booster immune responses (Day 29) in adolescents to those obtained post-Dose 2 of the primary series (Day 57) in young adults (18 to 25 years of age) in Study P301.

The result of the P203 vs P301 comparison are summarised as follows.

Immunogenicity:

Serum nAb level was assessed at Day 29 for P203 adolescents (PP Immunogenicity Subset pre-booster SARS-CoV-2 negative; PPIS-Neg), and compared to those following primary series in young adults (Study Day 57; 18 to 25 YOA) in Study P301. The GMR of P203 booster dose Day 29 GMC compared with young adults in Study P301, Day 57 GMC was 5.1 (95% CI: 4.5, 5.8), meeting the non-inferiority criteria (i.e. lower bound of the 95% CI >0.667 (1/1.5); point estimate ≥0.8); the SRR difference was 0.7% (95% CI: -0.8, 2.4), meeting the non-inferiority criteria (lower bound of the 95% of the SRR difference >-10%) (Table 17). The prespecified success criteria for the primary immunogenicity objective were met.

Table 17. Serum nAb (PsVNA) GMC and SRR Among Recipients in Study P203 post-booster Compared with Young Adults in Study P301 Post-Primary Series: (Per-Protocol Immunogenicity Subset – Pre-Booster SARS-CoV-2 negative)

	Study P203: ≥12 to 17 Years BD-Day 29 N = 257	Study P301: ≥18 to ≤25 Years Day 57 N = 295		
Serum nAb Level (PsVNA, AU/mL)	**GMC 95% CI N1 = 257**	**GMC 95% CI N1 = 294**	**GMR Study P203 vs Study P301 95% CI**	**Met Success Criteria?**
	7172.0 6610.4, 7781.4	1400.4 1272.7, 1541.0	5.1 4.5, 5.8	Yes
Seroresponse Rate (PsVNA)	**% (n/N1) 95% CI**	**% (n/N1) 95% CI**	**Difference in Seroresponse Rate (%) 95% CI**	**Met Success Criteria?**
	100 (257/257) 98.6, 100.0	99.3 (292/294) 97.6, 99.9	0.7 -0.8, 2.4	Yes

Abbreviations: AU = arbitrary units; BD = booster dose; CI = confidence interval; GMC=geometric mean concentration; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay

N: the number of participants in Per-Protocol Immunogenicity Subset for booster – Pre-booster SAS-CoV-2 negative in P203 or Per-Protocol Immunogenicity Subset for primary series in P301.

N1: the number of participants who have nAb data available at the timepoint(s) for specific analysis.

The log-transformed antibody levels are analyzed using *t*-test method with the group variable (adolescents in P203 and young adults in P301), and 95% CI is calculated based on the *t*-distribution. The resulting means and 95% CIs are back-transformed to the original scale for presentation of the GMC and GMR with 95% CIs.

Seroresponse rate at BD-Day 29 from baseline (predose 1 of the primary series) is defined as the % of participants with a change from below LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method. Seroresponse rate difference 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

COVID-19 incidence rate:

In adolescents boosted with a 50 µg mRNA-1273, the COVID-19 incidence rate was 4.676 cases/1000 person-months from Jan 2022 to May 2022. In Jan 2022, the COVID-19 incidence rate was 88.9 cases/1000 person-months among P203 participants completing the primary series, but not yet boosted (1696 participants at risk; data cut-off 31 Jan 2022, data snapshot of 02 Mar 2022). In contrast, during this same month of observation, the COVID-19 incidence rate in adolescents boosted with a 50 µg booster was 9.778 cases/1000 person-months (1 case out of 353 participants at risk). Although highly dependent on various factors within the community, the incidence rates post-booster were numerically lower than those among adolescents receiving only primary series.

7.3.3. Study P204 booster (mRNA-1273 prototype)

7.3.3.1. Overview

Study P204 is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 years through 11 years, 2 years to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion.

Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a booster (mRNA-1273, 25 µg) to all children enrolled in the 6 through 11 years age group, which could be administered from 6 months post-dose 2 of the primary series (mRNA-1273, 50 µg). Participants receiving a booster were followed for safety and immunogenicity.

For immunogenicity, the primary objective of the booster phase of Study P204 was to infer effectiveness of the booster dose by comparing post-booster immune responses (Day 29) to those obtained post-Dose 2 of the primary series (Day 57) in young adults (18 to 25 YOA) in Study P301, where 93% efficacy was demonstrated. Effectiveness of the 25 µg mRNA-1273 booster was inferred if post-booster immune responses (nAb GMC and SRR) meet prespecified non-inferiority criteria (for both GMC and SRR) compared to those measured following completion of the 100 µg mRNA-1273 primary series among a subset of young adults (18 to 25 years) in the pivotal mRNA-1273 efficacy trial (P301). Demonstration of non-inferiority required meeting the following pre-defined success criteria:

i) GMR between the children and the young adults: the lower bound of the 95% CI of the GMR (GMC P204 Day 29/GMC P301 young adult Day 57) >0.667 (or > 1/1.5).
ii) Difference in SRR between these same groups: the lower bound of the 95% of the SRR difference >-10%.

7.3.3.2. Participant flow

A total of 1294 participants 6 through 11 years of age received the mRNA-1273 25 µg booster dose. One participant discontinued the study due to withdrawal of consent, which was not due to AEs.

7.3.3.3. Baseline data

The demographics and baseline characteristics of participants in the Study P204 Safety Set are presented in Table 18. The mean age was 8.5 years, with 51.9% being male, and 65.7% being White in ethnicity. The race and ethnicity demographics of the boosted participants were similar to that in the original P204 study and Study P301. Approximately 33% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 18. P204 Participant Demographics and Baseline Characteristics Safety Set (6 through 11 years)

	mRNA-1273 25 µg – Booster N=1294 n (%)
Age (Years)	
n	1294
Mean (SD)	8.5 (1.62)
Median	8.0
Min, Max	6, 11
Sex, n (%)	
Male	672 (51.9)
Female	622 (48.1)
Race, n (%)	
White	850 (65.7)
Black	142 (11.0)
Asian	101 (7.8)
American Indian or Alaska Native	6 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	153 (11.8)
Other	24 (1.9)
Not Reported	14 (1.1)
Unknown	3 (0.2)
Ethnicity, n (%)	
Hispanic or Latino	202 (15.6)
Not Hispanic or Latino	1079 (83.4)
Not Reported	10 (0.8)
Unknown	3 (0.2)
Race and Ethnicity Groupa, n (%)	
White non-Hispanic	699 (54.0)
Communities of Color	593 (45.8)
Missing	2 (0.2)
Weight (kg)	
N	1294
Mean (SD)	33.69 (11.379)
Median	30.82
Min, Max	15.4, 103.7
Pre-booster SARS-CoV-2 Statusb, n (%)	
Negative	763 (59.0)
Positive	432 (33.4)
Missing	99 (7.7)

Abbreviations: bAb = binding antibody; BD = booster dose; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.

[a] White non-Hispanic is defined as White and non-Hispanic. Communities of color includes all others whose race or ethnicity is not unknown, unreported, or missing.

[b] Pre-booster SARS-CoV-2 Status: Negative is defined as having a negative RT-PCR test and a negative serology test (based on bAb specific to SARS-CoV-2 nucleocapsid) at the time of BD. Positive is defined as having either positive RT-PCR test or positive serology (anti-SARS -CoV-2 nucleocapsid) on the date of BD.

7.3.3.4. Results for immunogenicity outcomes

Initial data supporting effectiveness of the mRNA-1273 primary series (50 µg) was derived from P204 participants 6 through 11 years and the P301 young adult comparator group (to assess non-inferiority). The comparison was based on nAb titres (ID50).

In the P204 PPIS-Neg group (N=95), pre-booster (Day 1) nAb GMC was 485.6 (95% CI: 423.1, 557.3), whereas on Day 29 the GMC was 5847.5 (95% CI: 5212.3, 6560.1) (Table 19). Post-boost GMC increased approximately 12-fold from pre-booster GMC.

Antibody responses (nAb, GMC) were also assessed among the subgroup of participants with evidence of prior SARS-CoV-2 infection at the pre-booster visit (N=27). Previously infected participants, as expected, had higher nAb titres measured at the pre-booster visit (GMC: 4513.3 [95% CI: 2979.3, 6837.1]) compared to participants without prior evidence of infection (GMC: 485.6 [95% CI: 423.1, 557.3]). Administration of the booster nonetheless enhanced serum nAb levels (Day 29 GMC: 8903.7 [95% CI: 6736.9, 11767.6]).

Table 19. Serum nAb Levels against Ancestral SARS-CoV-2 (D614G PsVNA, VAC62 assay) by Pre-booster SARS-CoV-2 Status in the P204 (6 through 11 years) PPIS

P204, 6 through 11 years, boosted	Pre-booster SARS-CoV-2 Status		
Timepoint/Parameter	**Negative N = 95**	**Positive N=27**	**Overall N=129**
Pre-Dose 1 Baseline GMC (95% CI)	N1=88 7.9 (7.2, 8.7)	N1=25 7.3 (6.2, 8.7)	N1=120 7.6 (7.1, 8.3)
BD-Day 1 (pre-booster) GMC (95% CI)	N1=95 485.6 (423.1, 557.3)	N1=27 4513.3 (2979.3, 6837.1)	N1=129 780.3 (635.5, 958.2)
BD-Day 29 GMC	N1=95	N1=27	N1=129
Timepoint/Parameter	**Negative N = 95**	**Positive N=27**	**Overall N=129**
(95% CI)	5847.5 (5212.3, 6560.1)	8903.7 (6736.9, 11767.6)	6586.1 (5906.6, 7343.8)
GM fold-rise[a] (BD-Day 29/BD-Day 1) (95% CI)	N1=95 12.0 (10.3, 14.1)	N1=27 2.0 (1.4, 2.8)	N1=129 8.4 (7.0, 10.2)
Seroresponse Rate at BD-Day 29 from pre-Dose 1 of primary series % (n/N1) (95% CI)	100% (88/88) (90.5, 100.0)	100% (25/25) (86.3, 100.0)	100% (120/120) (97.0, 100.0)

Abbreviations: BD = booster dose; CI = confidence interval; GMC = geometric mean concentration of nAb (D64G PsVNA, "VAC62" assay); LLOQ = lower limit of quantification; nAb = neutralizing antibody; PPIS = Per-Protocol Immunogenicity Subset for booster.

[a] GM fold-rise refers to the fold rise in GMC at the two defined timepoints

N: the number of participants in PPIS – pre-booster SARS-CoV-2 negative, positive or overall.

N1: the number of participants who have nAb data available at the time point(s) for specific analysis.

The t-distribution of the log-transformed values or the difference in the log-transformed values is used for the mean 95% CI calculation, then back transformed to the original scale for presentation of GMC or GM fold-rise 95% CI.

Seroresponse rate at BD-Day 29 from pre-Dose 1 of primary series is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.

Results supporting the non-inferiority analysis are summarised in Table 20. Serum nAb levels (measured by PsVNA) for children 6 through 11 years in the PPIS-Neg and the comparison with those from young adults (18 to 25 years of age) in Study P301 are displayed. The GMR of P204 Day 29 GMC compared to P301 young adults Day 57 GMC was 4.2 (95% CI: 3.5, 5.0]), meeting the non-inferiority criteria (i.e. lower bound of the 95% CI > 0.667); the SRR difference was 0.7% (95% CI: -3.5, 2.4), meeting the non-inferiority criteria (lower bound of the 95% of the SRR difference >-10%).

Table 20. Serum nAb against Ancestral Strain (PsVNA, VAC62) GMC and SRR among P204 (6 through 11 years) Booster Recipients Post-booster Compared to P301 Young Adults Post-primary Series: (PPIS-Neg)

	Study P204: ≥6 through 11 Years BD-Day 29 N=95	Study P301: ≥18 to ≤25 Years Day 57 N=295		
Serum nAb level (PsVNA, AU/ml)	GMC 95%LS CI N1=95	GMC 95% CI N1=294	GMR Study P204 vs. Study P301 95% CI	Met Success Criteria[a]?
	5847.5 4999.6, 6839.1	1400.4 1281.1, 1530.8	4.2 3.5, 5.0	Yes
Seroresponse Rate (SRR) (PsVNA)	% (n/N1) 95% CI	% (n/N1) 95% CI	Difference in Seroresponse Rate (%) 95% CI	Met Success Criteria[b]?
	100% (88/88) 95.9, 100.0	99.3% (292/294) 97.6, 99.9	0.7% -3.5, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; AU = arbitrary units; BD = booster dose; CI = confidence interval; GMC=geometric mean concentration; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least squares; nAb = neutralizing antibody; PPIS-neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status.

[a] The lower bound of GMR 95% confidence interval is > 0.667.

[b] The lower bound of SRR difference 95% confidence interval is > -10%.

N: the number of participants in PPIS-neg in P204, or Per-Protocol Immunogenicity Subset for primary series in P301.

N1: the number of participants who have nAb data available at the time point(s) for specific analysis.

The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulting LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation of GMC and GMR with 95% CIs.

SRR = Seroresponse rate at BD-Day 29 from baseline (pre-dose 1 of the primary series) is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse rate 95% CI is calculated using the Clopper-Pearson method. Seroresponse rate difference 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Neutralising antibody levels against an Omicron variant of SARS-CoV-2 (BA.1, VAC122 assay) were assessed among booster recipients as well (Table 21). In the P204 PPIS-Neg participants, booster administration resulted in a rise of GMC from 53.0 (95% CI: 45.3, 61.9) at Day 1 to 632.6 (95% CI: 546.7, 731.9) at Day 29, a GM fold-rise of 12.1, (95% CI: 9.7, 15.0). Among the pre-booster SARS-CoV-2 positive group, higher nAb titres measured at the Day 1 visit (1360.6, 95% CI: 939.5, 1970.4) were observed. In children with immunity both from mRNA-1273 priming as well as SARS-CoV-2 infection (hybrid immunity), Omicron nAb responses were higher at Day 29 (GMC 2362.9, 95% CI: 1778.0, 3140.4), with geometric mean fold rise 1.7 (95% CI, (1.3, 2.3) from administration of the booster dose.

Table 21. Serum nAb levels against Omicron SARS-CoV-2 (BA.1 PsVNA, "VAC122" assay) by Pre-booster SARS-CoV-2 Status among P204 (6 through 11 years) Booster Recipients in PPIS

P204, 6 through 11 years, boosted	Pre-booster SARS-CoV-2 Status		
Timepoint/Parameter	**Negative N=95**	**Positive N=27**	**Overall N=129**
Pre-Dose 1 Baseline GMC[a] (95% CI)	N1=50 8.6 (7.7, 9.6)	N1=19 7.2 (5.7, 9.1)	N1=70 8.2 (7.4, 9.1)
BD-Day 1 (pre-booster) GMC (95% CI)	N1=92 53.0 (45.3, 61.9)	N1=27 1360.6 (939.5, 1970.4)	N1=124 108.5 (82.4, 143.0)
BD-Day 29 GMC (95% CI)	N1=95 632.6 (546.7, 731.9)	N1=27 2362.9 (1778.0, 3140.4)	N1=129 860.6 (737.0, 1004.9)
GM fold-rise[b] (BD-Day 29/BD-Day 1) (95% CI)	N1=92 12.1 (9.7, 15.0)	N1=27 1.7 (1.3, 2.3)	N1=124 8.1 (6.5, 10.1)
Seroresponse rate (SRR) at BD-29 from pre-Dose 1 of primary series % (n/N1) (95% CI)	100% (50/50) (92.9, 100.0)	100% (19/19) (82.4, 100.0)	100% (70/70) (94.9, 100.0)

BD = booster dose; CI = confidence interval GMC = Geometric mean concentration of nAb (BA.1 PsVNA, "VAC122" assay); nAb = neutralizing antibody; PPIS = Per-Protocol Immunogenicity Subset for booster.

[a] Pre-dose Day 1 samples have been used previously for dose selection testing or primary analysis testing. Samples from those participants with available pre-dose 1 serum aliquots still remaining at the time of this Omicron testing were utilized.

[b] GM fold-rise refers to the fold rise in GMC at the two defined timepoints.

N: the number of participants in PPIS – pre-booster SARS-CoV-2 negative, positive or overall.

N1: the number of participants who have nAb data available at the time point(s) for specific analysis.

The t-distribution of the log-transformed values or the difference in the log-transformed values is used for the mean 95% CI calculation, then back transformed to the original scale for presentation of GMC or GM fold-rise 95% CI.

SRR = Seroresponse rate at BD-Day 29 from pre-Dose 1 of primary series is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.

7.4. Evaluator's conclusions on clinical efficacy

In the pivotal study P205 Part F, the sponsor sought to assess whether a single administration of mRNA-1273.222 50 µg as a second booster dose elicits a superior antibody response against Omicron BA.4/5 compared to a single booster dose of mRNA-1273 50 µg (Part F, Cohort 2) as a second booster dose.

As was the case with the previous bivalent SPIKEVAX vaccine (mRNA-1273.214, evaluated in PM-2022-02203-1-2), the current submission is without a dedicated study report for Study P205 Part H. As a result, the CER is based on the Clinical Overview and Clinical Study Protocol, which generally do not have the same level of details expected in a CSR.

The comparison between P205 Part H and Part F for the immune response against Omicron BA.4/BA.5 (in the PPIS-Neg population) showed that those who received mRNA-1273.222 demonstrated a much greater rise in the nAb titre, with the Day 29 GMFR (95% CI) of 26.4 (22.0, 31.9) and 3.6 (3.3, 4.0), respectively. The Omicron BA.4/BA.5 SRRs, using the pre-Dose 1/pre-primary vaccination values as baseline, were 98.1% (95.2, 99.5) and 86.4% (81.6, 90.3) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively.

As for the nAb against the ancestral SARS-CoV-2 D614G in the PPIS-Neg population, those who received mRNA-1273.222 showed a greater rise in the nAb titre compared to the pre-booster levels, with the Day 29 GMFR of 9.2 (7.9, 10.6) and 3.7 (3.4, 4.1), respectively. The SRRs against

the ancestral SARS-CoV-2 D614G, using the pre-Dose 1/pre-primary vaccination values as baseline were 100% (98.3, 100.0) and 100% (98.6, 100.0) 28 days after the mRNA-1273.222 and mRNA-1273 booster doses, respectively.

In the PPIS-Pos population (participants with evidence of prior SARS-CoV-2 infection) the post-booster GMTs and SRRs were higher compared to the PPIS-Neg group, but otherwise similar trend was observed. A lower Day 29 GMFR was observed against Omicron BA.4/BA.5 compared to PPIS-Neg (9.8 [8.4, 11.4] for Part H and 2.1 [1.8, 2.4] for Part F), but this is likely due to higher pre-booster level in the PPIS-Pos population.

A subgroup analysis in participants ≥ 18 to < 65 YOA and ≥ 65 YOA showed that the GMTs and GMFRs were largely similar between the two age groups for both Omicron BA.4/BA.5 and the ancestral SARS-CoV-2 D614.

A descriptive exploratory analysis on the cross-neutralisation ability of mRNA-1273.222 against the emerging Omicron variants BQ.1.1 and XBB.1 was also performed. This showed significant rise in the nAb titres at Day 29 against Omicron BQ.1.1 (19.6 [11.7, 32.8]) and Omicron XBB.1 (12.3 [7.4, 20.5]). The GMT-fold rise for Omicron BQ.1.1 and XBB.1 were less compared to Omicron BA.4/BA.5 (27.3 [15.9, 47.0]).

Study P205 Part H also counted the number of people with SARS-CoV-2 infections 14 days after the mRNA-1273.222 50 μg booster dose. However, the result was not meaningful in the absence of a contemporaneous comparator group.

Based on the immunogenicity findings, Study P205 Part H (along with P205 Part F as a comparator) has shown that mRNA-1273.222, when used as a booster in adults who have received a primary series and first booster with mRNA-1273, is able to elicit immune response against Omicron BA.4/BA.5 and the ancestral SARS-CoV-2 D614G. Demonstration of the superior immune response compared to those who received mRNA-1273 only (Part F) is consistent throughout people of older age (≥ 65 YOA) and in those with and without pre-booster SARS-CoV-2 infection. It should be noted however, that Study P205 Part H did not have a contemporaneous comparator, and there may be several confounders and biases as a result. For example, participants who received mRNA-1273.222 in Part H exhibited a greater rise in the nAb titre against the ancestral SARS-CoV-2 D614G than those who received mRNA-1273 in Part F. This may be, in part, due to the longer interval between the 1st and 2nd boosters in Part H, as it has previously demonstrated in the AZ vaccine that a longer dosing interval is associated with stronger immune response.[6] However, it is also noted that post mRNA-1273.222 booster vaccination, the GMFR for Omicron BA.4/BA.5 at Day 29 was much greater than that for the ancestral SARS-CoV-2 D614G (26.4 and 9.2, respectively), suggesting that mRNA-1273.222 is able to elicit somewhat selective immune response against the Omicron BA.4/BA.5 subvariants.

Overall, while one should carefully consider the impact of not having a contemporaneous comparator, Study P205 Part H has demonstrated a favourable immunogenicity data for mRNA-1273.222 against the ancestral SARS-CoV-2 D614G and Omicron BA.4/BA.5 subvariants in adults.

Other than the lack of a suitable comparator group, Study P205 Part H has several issues to consider. The study excluded several conditions, such as: unstable chronic diseases, immunosuppression (from disease or treatment), and history of myocarditis. While the rationale for some of these exclusions are understood, it should be noted that people with chronic diseases and immunosuppression will be the priority population for COVID-19 vaccination. The study also did not provide any paediatric clinical data.

[6] Pettini E, Pastore G, Fiorino F, Medaglini D, Ciabattini A. Short or Long Interval between Priming and Boosting: Does It Impact on the Vaccine Immunogenicity? *Vaccines (Basel)*. 2021 Mar 20;9(3):289. doi: 10.3390/vaccines9030289.

The cross-neutralisation data against the Omicron BQ.1.1 and XBB.1 subvariants is promising. Although the Day 29 nAb titre for these variants were numerically lower than for Omicron BA.4/BA.5, the assessment demonstrated significant rise for the emerging subvariants. However, there was no comparator for this analysis, and as such it is difficult to understand how mRNA-1273.222 compares to other existing SPIKEVAX vaccines. It is also not clear whether the cross-neutralisation method used has been validated and widely accepted.

It is emphasised that these immunogenicity data do not provide direct evidence of clinical protection against SARS-CoV-2 infection for mRNA-1273.222. Hence it is difficult to predict how the superior immunogenicity observed from mRNA-1273.222 will translate into clinical protection against SARS-CoV-2 infection in the current and future settings.

The sponsor has also provided clinical data for other studies to support the provisional registration of mRNA-1273.222. Study P205 Part G made an assessment of mRNA-1273.214 50 µg, but this product contains imelasomeran which is not a component of mRNA-1273.222. Study P203 Part C booster and Study P204 booster assessed the immunogenicity of mRNA-1273 when given to adolescents (12-17 YOA) and pre-adolescent children (6-11 YOA) as a booster. While these studies have delivered promising results for mRNA-1273 in individuals 6 to < 18 YOA, there is no clinical data involving mRNA-1273.222. As such their ability to support the use of mRNA-1273.222 in individuals <18 YOA is considered to be limited.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies included in the current submission provided evaluable safety data:

- **Study P205 Part H (mRNA-1273.222):** New bivalent boost data with mRNA-1273.222 in adults ≥18 YOA.
- **Study P205 Part G (mRNA-1273.214):** Re-provision of existing adult bivalent boost data for the Omicron bivalent vaccine mRNA-1273.214 (original/BA.1), previously evaluated by TGA (PM-2022-02203-1-2).
- **Study P203 Part C booster (mRNA-1273 prototype):** Re-provision of existing adolescent (12y-17y) data with mRNA-1273 prototype boost (SPIKEVAX original), previously evaluated by TGA (PM-2022-00685-1-2).
- **Study P204 booster (mRNA-1273 prototype):** New paediatric (6y-11y) data with mRNA-1273 prototype boost (SPIKEVAX original) from study P204.

8.2. Safety analyses from the main study

8.2.1. Study P204 booster (mRNA-1273 prototype)

8.2.1.1. Overview of safety

The safety information collected for Study P205 Part H (mRNA-1273.222 50 µg booster dose group) were as follows:

- Solicited local and systemic AEs during the 7-day follow-up period after vaccination. Solicited AEs that persisted beyond 7 days were also collected.
- Unsolicited AEs during the 28-day follow-up period after vaccination. This included any AE reported by the participant that was not specified as a solicited AE in the protocol or was specified as a solicited AE but starts at least 7 days after vaccination.
- SAEs, MAAEs, AEs leading to withdrawal and AESIs were collected throughout the study.

8.2.1.2. Solicited AEs

For reactogenicity assessments, participants recorded solicited local and systemic AEs in the eDiary on the day of vaccination and during the 7 days after vaccination (i.e. the day of injection and 6 subsequent days). Solicited local AEs assessed were injection site pain, injection site erythema, injection site swelling/induration, and axillary swelling or tenderness ipsilateral to the side of the injection. Solicited systemic AEs assessed were headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever. Any solicited AE that was ongoing beyond Day 7 was to be reported in the eDiary until it resolved.

Severity grading of solicited AEs occurred automatically based on participant entry into the eDiary according to the grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (CBER 2007)[7].

8.2.1.2.1. Solicited local AEs

In the P205 Part H, most participants had at least one solicited local AE (420/507 [82.8%]) (Table 22). The most common solicited local AE after the mRNA-1273.222 50 µg booster dose was injection site pain (418/507 participants [82.4%]), followed by axillary swelling or tenderness (106/507 participants [20.9%]). The majority of solicited local AEs were Grade 1 (329/507 participants [64.9%]) followed by Grade 2 (63/507 participants [12.4%]). Twenty-eight participants (28/507 [5.5%]) had a Grade 3 local AE and the most commonly reported term was injection site pain (20/507 participants [3.9%]). There were no Grade 4 local AEs. Local AEs were transient; the median duration was 3.0 days (range 1 to 22 days).

8.2.1.2.2. Solicited systemic AEs

Most participants in the Solicited Safety Set had at least one solicited systemic AE (372/508 [73.2%]). The most common systemic AE after the mRNA-1273.222 50 µg booster dose was fatigue (304/508 participants [59.8%]), followed by headache (249/507 participants [49.1%]), myalgia (235/507 participants [46.4%]), and arthralgia (177/507 participants [34.9%]) (Table 22). Most solicited systemic AEs were Grade 1 (172/508 [33.9%]) or Grade 2 (165/508 [32.5%]). Thirty-five participants (35/508 participants [6.9%]) had a Grade 3 systemic AE, the most common were myalgia (20/507 participants [3.9%]) and fatigue (17/508 participants [3.3%]). No Grade 4 solicited systemic AEs were reported. The median duration of systemic AEs was 3.0 days (range 1 to 38 days).

[7] Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov)

Table 22. Summary of Participants with Solicited Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.222 (Solicited Safety Set)

	P205 Part H
Solicited Adverse Reaction Category Grade	**mRNA-1273.222 50 µg (N=508) n (%)**
Solicited adverse reactions - N1	508
Any solicited adverse reactions	443 (87.2)
95% CI	84.0, 90.0
Grade 1	219 (43.1)
Grade 2	165 (32.5)
Grade 3	59 (11.6)
Grade 4	0
Solicited local adverse reactions - N1	507
Any solicited local adverse reactions	420 (82.8)
95% CI	79.3, 86.0
Grade 1	329 (64.9)
Grade 2	63 (12.4)
Grade 3	28 (5.5)
Grade 4	0
Pain - N1	507
Any	418 (82.4)
Grade 1	344 (67.9)
Grade 2	54 (10.7)
Grade 3	20 (3.9)
Grade 4	0
Erythema (redness)[a] - N1	507
Any	23 (4.5)
Grade 1	10 (2.0)
Grade 2	8 (1.6)
Grade 3	5 (1.0)
Grade 4	0
Swelling (hardness)- N1	507
Any	40 (7.9)
Grade 1	22 (4.3)
Grade 2	13 (2.6)
Grade 3	5 (1.0)
Grade 4	0
Axillary swelling or tenderness - N1	507
Any	106 (20.9)
Grade 1	86 (17.0)
Grade 2	19 (3.7)
Grade 3	1 (0.2)
Grade 4	0
Solicited systemic adverse reactions - N1	508
Any solicited systemic adverse reactions	372 (73.2)
95% CI	69.2, 77.0
Grade 1	172 (33.9)
Grade 2	165 (32.5)
Grade 3	35 (6.9)
Grade 4	0
Fever[b] - N1	507
Any	20 (3.9)
Grade 1	12 (2.4)
Grade 2	7 (1.4)
Grade 3	1 (0.2)
Grade 4	0
Headache - N1	507
Any	249 (49.1)
Grade 1	164 (32.3)
Grade 2	73 (14.4)
Grade 3	12 (2.4)
Grade 4	0
Fatigue - N1	508
Any	304 (59.8)
Grade 1	161 (31.7)
Grade 2	126 (24.8)
Grade 3	17 (3.3)
Grade 4	0
Myalgia - N1	507
Any	235 (46.4)
Grade 1	127 (25.0)
Grade 2	88 (17.4)
Grade 3	20 (3.9)
Grade 4	0
Arthralgia - N1	507
Any	177 (34.9)
Grade 1	108 (21.3)
Grade 2	60 (11.8)
Grade 3	9 (1.8)
Grade 4	0
Nausea/vomiting - N1	507
Any	71 (14.0)
Grade 1	56 (11.0)
Grade 2	14 (2.8)
Grade 3	1 (0.2)
Grade 4	0
Chills - N1	507
Any	112 (22.1)
Grade 1	60 (11.8)
Grade 2	48 (9.5)
Grade 3	4 (0.8)
Grade 4	0

Abbreviations: CI = confidence interval.

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method.

[a] Toxicity grade for erythema (redness) is defined as: Grade 1 = 25 – 50 mm; Grade 2 = 51 – 100 mm; Grade 3 = greater than 100 mm.

[b] Toxicity grade for fever is defined as: Grade 1 = 38 – 38.4 °C; Grade 2 = 38.5 – 38.9 °C; Grade 3 = 39 – 40 °C; Grade 4 = greater than 40 °C.

8.2.1.2.3. Solicited AEs by age category

Solicited AEs were analysed by age category (≥18 to <65 YOA and ≥65 YOA) and the results are presented below for solicited local and systemic AEs (Table 23).

Table 23. Summary of Participants with Solicited Adverse Reactions Within 7 Days After the Injection by Grade and by Age Category-2nd Booster Dose: mRNA-1273.222 (Solicited Safety Set)

	P205 Part H mRNA-1273.222 50 µg	
Solicited Adverse Reaction Category Grade	**≥18 to <65 Years of Age (N=403) n (%)**	**≥65 Years of Age (N=105) n (%)**
Solicited adverse reactions - N1	403	105
Any solicited adverse reactions	362 (89.8)	81 (77.1)
95% CI	86.5, 92.6	67.9, 84.8
Grade 1	172 (42.7)	47 (44.8)
Grade 2	141 (35.0)	24 (22.9)
Grade 3	49 (12.2)	10 (9.5)
Grade 4	0	0
Solicited local adverse reactions - N1	402	105
Any solicited local adverse reactions	347 (86.3)	73 (69.5)
95% CI	82.6, 89.5	59.8, 78.1
Grade 1	267 (66.4)	62 (59.0)
Grade 2	57 (14.2)	6 (5.7)
Grade 3	23 (5.7)	5 (4.8)
Grade 4	0	0
Pain - N1	402	105
Any	347 (86.3)	71 (67.6)
Grade 1	279 (69.4)	65 (61.9)
Grade 2	49 (12.2)	5 (4.8)
Grade 3	19 (4.7)	1 (1.0)
Grade 4	0	0
Erythema (redness)[a] - N1	402	105
Any	17 (4.2)	6 (5.7)
Grade 1	9 (2.2)	1 (1.0)
Grade 2	5 (1.2)	3 (2.9)
Grade 3	3 (0.7)	2 (1.9)
Grade 4	0	0
Swelling (hardness)- N1	402	105
Any	32 (8.0)	8 (7.6)
Grade 1	19 (4.7)	3 (2.9)
Grade 2	11 (2.7)	2 (1.9)
Grade 3	2 (0.5)	3 (2.9)
Grade 4	0	0
Axillary swelling or tenderness - N1	402	105
Any	91 (22.6)	15 (14.3)
Grade 1	72 (17.9)	14 (13.3)
Grade 2	18 (4.5)	1 (1.0)
Grade 3	1 (0.2)	0
Grade 4	0	0
Solicited systemic adverse reactions - N1	403	105
Any solicited systemic adverse reactions	307 (76.2)	65 (61.9)
95% CI	71.7, 80.3	51.9, 71.2
Grade 1	135 (33.5)	37 (35.2)
Grade 2	142 (35.2)	23 (21.9)
Grade 3	30 (7.4)	5 (4.8)
Grade 4	0	0
Fever[b] - N1	402	105
Any	16 (4.0)	4 (3.8)
Grade 1	9 (2.2)	3 (2.9)
Grade 2	6 (1.5)	1 (1.0)
Grade 3	1 (0.2)	0
Grade 4	0	0
Headache - N1	402	105
Any	210 (52.2)	39 (37.1)
Grade 1	135 (33.6)	29 (27.6)
Grade 2	64 (15.9)	9 (8.6)
Grade 3	11 (2.7)	1 (1.0)
Grade 4	0	0
Fatigue - N1	403	105
Any	243 (60.3)	61 (58.1)
Grade 1	119 (29.5)	42 (40.0)
Grade 2	110 (27.3)	16 (15.2)
Grade 3	14 (3.5)	3 (2.9)
Grade 4	0	0
Myalgia - N1	402	105
Any	197 (49.0)	38 (36.2)
Grade 1	103 (25.6)	24 (22.9)
Grade 2	77 (19.2)	11 (10.5)
Grade 3	17 (4.2)	3 (2.9)
Grade 4	0	0
Arthralgia - N1	402	105
Any	145 (36.1)	32 (30.5)
Grade 1	84 (20.9)	24 (22.9)
Grade 2	52 (12.9)	8 (7.6)
Grade 3	9 (2.2)	0
Grade 4	0	0
Nausea/vomiting - N1	402	105
Any	67 (16.7)	4 (3.8)
Grade 1	54 (13.4)	2 (1.9)
Grade 2	12 (3.0)	2 (1.9)
Grade 3	1 (0.2)	0
Grade 4	0	0
Chills - N1	402	105
Any	96 (23.9)	16 (15.2)
Grade 1	51 (12.7)	9 (8.6)
Grade 2	42 (10.4)	6 (5.7)
Grade 3	3 (0.7)	1 (1.0)
Grade 4	0	0

Abbreviations: CI = confidence interval.

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method.

a Toxicity grade for erythema (redness) is defined as: Grade 1 = 25 – 50 mm; Grade 2 = 51 – 100 mm; Grade 3 = greater than 100 mm.

b Toxicity grade for fever is defined as: Grade 1 = 38 – 38.4 °C; Grade 2 = 38.5 – 38.9 °C; Grade 3 = 39 – 40 °C; Grade 4 = greater than 40 °C.

8.2.1.2.4. Solicited Adverse Reactions by Pre-booster SARS-CoV-2 Status

In P205 Part H Solicited Safety Set, over half the participants had evidence of prior SARS-CoV-2 antibodies: 283/508 participants (55.7%) had a positive pre-booster SARS-CoV-2 status and 216/508 participants (42.5%) had a negative pre-booster SARS-CoV-2 status, while 9 participants had missing status (Table 24).

The frequency of solicited local AEs was similar among participants with a positive pre-booster SARS-CoV-2 status (229/282 [81.2%]) and participants with a negative pre-booster SARS-CoV-2 status (183/216 [84.7%]) (Table 24). The frequency of solicited systemic AEs was similar among participants with positive pre-booster SARS-CoV-2 status (197/283 [69.6%]) and participants with negative pre-booster SARS-CoV-2 status (167/216 [77.3%]). Grade 3 solicited local AEs was observed in 10/282 [3.5%] participants with positive pre-booster SARS-CoV-2 status and in 16/216 [7.4%] participants with negative pre-booster SARS-CoV-2 status. Grade 3 systemic AEs were similar in in frequency participants with positive pre-booster- SARS-CoV-2 status (19/283 [6.7%]) and negative pre-booster SARS-CoV-2 status (16/216 [7.4%]).

Table 24. Summary of Participants with Solicited Adverse Reactions Within 7 Days After the Injection by Grade and Pre-booster SARS-CoV-2 Status – 2nd Booster Dose: mRNA-1273.222 (Solicited Safety Set)

	P205 Part H mRNA-1273.222 50 µg	
	Pre-booster SARS-CoV-2 Status	
Solicited Adverse Reaction Category Grade	**Negative (N=216) n (%)**	**Positive (N=283) n (%)**
Solicited adverse reactions - N1	216	283
Any solicited adverse reactions	191 (88.4)	244 (86.2)
95% CI	83.4, 92.4	81.6, 90.0
Grade 1	88 (40.7)	129 (45.6)
Grade 2	74 (34.3)	87 (30.7)
Grade 3	29 (13.4)	28 (9.9)
Grade 4	0	0
Solicited local adverse reactions - N1	216	282
Any solicited local adverse reactions	183 (84.7)	229 (81.2)
95% CI	79.2, 89.2	76.1, 85.6
Grade 1	138 (63.9)	187 (66.3)
Grade 2	29 (13.4)	32 (11.3)
Grade 3	16 (7.4)	10 (3.5)
Grade 4	0	0
Pain - N1	216	282
Any	183 (84.7)	227 (80.5)
Grade 1	145 (67.1)	194 (68.8)
Grade 2	26 (12.0)	26 (9.2)
Grade 3	12 (5.6)	7 (2.5)
Grade 4	0	0
Erythema (redness)[a] - N1	216	282
Any	11 (5.1)	11 (3.9)
Grade 1	5 (2.3)	5 (1.8)
Grade 2	4 (1.9)	4 (1.4)
Grade 3	2 (0.9)	2 (0.7)
Grade 4	0	0
Swelling (hardness)- N1	216	282
Any	18 (8.3)	21 (7.4)
Grade 1	10 (4.6)	12 (4.3)
Grade 2	6 (2.8)	7 (2.5)
Grade 3	2 (0.9)	2 (0.7)
Grade 4	0	0
Axillary swelling or tenderness - N1	216	282
Any	46 (21.3)	58 (20.6)
Grade 1	37 (17.1)	47 (16.7)
Grade 2	8 (3.7)	11 (3.9)
Grade 3	1 (0.5)	0
Grade 4	0	0
Solicited systemic adverse reactions - N1	216	283
Any solicited systemic adverse reactions	167 (77.3)	197 (69.6)
95% CI	71.1, 82.7	63.9, 74.9
Grade 1	76 (35.2)	93 (32.9)
Grade 2	75 (34.7)	85 (30.0)
Grade 3	16 (7.4)	19 (6.7)
Grade 4	0	0
Fever[b] - N1	216	282
Any	9 (4.2)	10 (3.5)
Grade 1	5 (2.3)	6 (2.1)
Grade 2	3 (1.4)	4 (1.4)
Grade 3	1 (0.5)	0
Grade 4	0	0
Headache - N1	216	282
Any	116 (53.7)	126 (44.7)
Grade 1	75 (34.7)	84 (29.8)
Grade 2	36 (16.7)	35 (12.4)
Grade 3	5 (2.3)	7 (2.5)
Grade 4	0	0
Fatigue - N1	216	283
Any	144 (66.7)	154 (54.4)
Grade 1	77 (35.6)	83 (29.3)
Grade 2	57 (26.4)	64 (22.6)
Grade 3	10 (4.6)	7 (2.5)
Grade 4	0	0
Myalgia - N1	216	282
Any	109 (50.5)	121 (42.9)
Grade 1	58 (26.9)	66 (23.4)
Grade 2	40 (18.5)	46 (16.3)
Grade 3	11 (5.1)	9 (3.2)
Grade 4	0	0
Arthralgia - N1	216	282
Any	78 (36.1)	93 (33.0)
Grade 1	48 (22.2)	55 (19.5)
Grade 2	24 (11.1)	35 (12.4)
Grade 3	6 (2.8)	3 (1.1)
Grade 4	0	0
Nausea/vomiting - N1	216	282
Any	31 (14.4)	39 (13.8)
Grade 1	26 (12.0)	29 (10.3)
Grade 2	5 (2.3)	9 (3.2)
Grade 3	0	1 (0.4)
Grade 4	0	0
Chills - N1	216	282
Any	51 (23.6)	58 (20.6)
Grade 1	27 (12.5)	32 (11.3)
Grade 2	23 (10.6)	23 (8.2)
Grade 3	1 (0.5)	3 (1.1)
Grade 4	0	0

Abbreviations: CI = confidence interval; SARS-CoV-2 = severe acute respiratory infection coronavirus-2.

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method.

a Toxicity grade for erythema (redness) is defined as: Grade 1 = 25 – 50 mm; Grade 2 = 51 – 100 mm; Grade 3 = greater than 100 mm.

b Toxicity grade for fever is defined as: Grade 1 = 38 – 38.4 °C; Grade 2 = 38.5 – 38.9 °C; Grade 3 = 39 – 40 °C; Grade 4 = greater than 40 °C.

8.2.1.3. Unsolicited AEs

Unsolicited TEAEs were collected from Day 1 through Day 29 (median follow-up of 37 days) after the booster dose. Adverse events leading to discontinuation from study participation, SAEs, MAAEs, AESIs, and pregnancies were collected from Day 1 through the entire study period or until the last day of study participation. SAEs, MAAEs, AESIs, and pregnancies presented are as of the data cut-off, or as noted in the text.

8.2.1.3.1. Summary of unsolicited AEs

The incidence of unsolicited TEAEs in P205 Part H was similar for all types of events (TEAEs, SAEs, MAAEs, events considered by the investigator to be related to vaccination) (Table 25) to results in P205 Part F.

Unsolicited TEAEs within 28 days after the mRNA-1273.222 50 µg booster dose, regardless of relationship to study vaccination as assessed by the investigators, were reported for 116/511 participants (22.7%) (Table 25).

The most commonly reported unsolicited TEAEs, regardless of relatedness, within 28 days after the mRNA.222 50 µg booster dose were fatigue (22/511 [4.3%]); headache (15/511 [2.9%]); COVID-19 (11/511 [2.2%]); rhinovirus infection, upper respiratory tract infection (7/511 [1.4%] each); arthralgia, myalgia, and urinary tract infection (5/511 [1.0%] each). All other unsolicited TEAEs in P205 Part H were reported in < 1.0% of participants.

3 participants (0.6%) had 4 SAEs, and all were assessed by the investigator as not related to study vaccination. One SAE (0.2%) had a fatal outcome (subarachnoid haemorrhage), and the remaining 3 SAEs were reported in 2 participants (one participant had SAEs of anginal equivalent and syncope, and one participant had an SAE of anaemia) (Table 25). After the data cut-off date (23 September 2022), there was an additional fatal event (death of unknown cause) which occurred on Study Day 40. MAAEs were reported for 70/511 participants (13.7%), and all were assessed by the investigator as not related to study vaccination. No participants had TEAEs leading to study or vaccine discontinuation.

Table 25. Summary of Unsolicited TEAEs up to 28 Days After the Injection – 2nd Booster Dose: mRNA-1273.222 (Safety Set)

	P205 Part H
	mRNA-1273.222 50 µg (N=511) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination	
All	116 (22.7)
Serious	3 (0.6)
Fatal	1 (0.2)
Medically-attended	70 (13.7)
Leading to study discontinuation	0
Grade 3 or higher	5 (1.0)
At least 1 non-serious event [a]	115 (22.5)
Grade 3 or higher	2 (0.4)
Unsolicited TEAEs related to study vaccination	
All	40 (7.8)
Serious	0
Fatal	0
Medically-attended	0
Leading to study discontinuation	0
Grade 3 or higher	2 (0.4)
At least 1 non-serious event [a]	40 (7.8)
Grade 3 or higher	2 (0.4)

Abbreviation: SAE = serious adverse event;TEAE = treatment-emergent adverse event.
A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of participants in the Safety Set.
[a] Participants with at least one non-serious TEAE regardless of reporting any SAE or not.

Unsolicited TEAEs considered related to vaccination by the investigator were reported in 40/511 participants (7.8%), and most were consistent with symptoms or signs of reactogenicity, including: fatigue (22/511 [4.3%]), headache (15/511 [2.9%]), arthralgia and myalgia (5/511 [1.0%] each). All other treatment-related TEAEs were reported in < 1.0% of participants; these included injection site erythema (2 [0.6%] participants), injection site lymphadenopathy (3 [0.6%]), injection site pain and chills (2 [0.4%]), and injection site induration, injection site pruritus, dizziness and vomiting, each reported in 1 participant. Time to onset for all vaccine-related TEAEs was within 9 days of the booster dose; in 36 of the 40 participants, onset was within 7 days of the booster dose, and in 4 participants, onset was on Study Day 8.

Two participants experienced severe TEAEs that were considered related to vaccination. Both TEAEs were fatigue and were non-serious: a s47F -year-old s47F had severe fatigue that began on Study Day 2 and resolved on Study Day 28, and a s47F -year-old s47F had severe fatigue from Study Day 2 to Study Day 8. Neither event was medically attended.

8.2.1.3.2. Deaths

Case 1

At the time of the data cut-off one SAE with a fatal outcome was reported, and this case is summarised below (verbatim from the Clinical Overview).

- *Subarachnoid haemorrhage (Subject ID [redacted]: A [redacted]-year-old [redacted] with a medical history including [redacted] received 50 ug mRNA-1273.222 on Study Day 1 at 14:07 hours. Vital signs pre and [redacted] post vaccination were unremarkable. That evening, the participant's [redacted] reported the participant experienced tingling and described an "ant bite" sensation on the [redacted], and fatigue that resolved on Study Day 2. On Study Day 3, no symptoms were reported. On Study Day 4, in the evening, the participant developed a headache, nausea and vomiting. On Study Day 5, early in the morning, the participant called the emergency services due to a severe headache and [redacted] was transferred to the emergency room. [redacted] was started on [redacted] and [redacted] for headache, vomiting and elevated blood pressure. Soon thereafter the participant became unresponsive and was given [redacted] and [redacted] and was intubated. CT scan of head showed subarachnoid haemorrhage, and treatment was initiated with [redacted] and [redacted] The participant developed systolic BP in the [redacted]s, and treatment with [redacted] and [redacted] was stopped. A right frontal ventriculostomy revealed elevated pressure and blood-tinged cerebrospinal fluid. CT angiogram of head and neck showed normal blood vessels.*
  Treatment with [redacted] and [redacted] was initiated but the participant remained unresponsive. On Study Day 6, platelets were [redacted] (records indicate a previous platelet count of [redacted] in [redacted]). On Study Day 7, platelets were [redacted]. On the same day, the participant was transferred to palliative care and later that day [redacted] died. An autopsy and anti-platelet factor [redacted] (PF4) antibody assay were not performed. The investigator assessed the fatal event of [redacted] as not related to vaccination and more likely due to underlying disease.

Company assessment:

This report concerns a [redacted]-year-old [redacted] among other medications, who developed subarachnoid hemorrhage [redacted] days after receipt of a booster vaccination.

This report is heavily confounded by the participant's ongoing medical problems of [redacted] which are associated with an elevated risk for thromboembolic disease and brain hemorrhage, as well as the advanced age of the participant. Current and prior platelet levels were found to be low, which may suggest an additional risk factor. The investigator assessed the events as not related to the vaccine and considered that given the previous history of [redacted], it was unlikely the vaccination caused the [redacted]. The sponsor agreed with the investigator assessment and considered this event to be unlikely related to the vaccine, according to the WHO-UMC standardised case causality assessment (WHO 2013).

Case 2

After the data cut-off date one SAE with a fatal outcome was reported, and this case is further described as follows (verbatim from the Clinical Overview).

- *Death (unknown cause, Subject ID s47F): A s47F -year-old s47F with a medical history including s47F , received 50 ug mRNA-1273.222 on Study Day 1 and on Study Day 40 the participant died due to an unknown cause. Concomitant medications at study entry included s47F and s47F . According to the participant's s47F and the cause of death was not yet known as autopsy results were pending. s47F (not confirmed) and that the participant was taking s47F (not reported in clinical database), as well as other medications, and s47F . The study site has been unable to obtain any further information as they have not been able to reach the participant's s47F for further follow-up. At the time of this report, medical records associated with the death have been requested by the office of the participant's primary care physician. The investigator assessed the death as not related to vaccination and the sponsor agreed with this assessment based on available information and considering the time to onset and underlying illnesses.*

Evaluator's comment:

Based on the narratives, there is no outstanding features to establish causality between mRNA-1273.222 and the deaths.

8.2.1.3.3. Other Serious Adverse Events

In Study P205 Part H, SAEs were infrequent, and all were assessed by the investigator as unrelated to the booster dose. No new safety concerns were identified based on analysis of these SAEs.

As of the data cut-off, four SAEs in three participants were reported (Table 26). One SAE was associated with a fatal outcome, and this is described in Section 8.2.3.2. above. The remaining three SAEs occurred in two participants (one participant with angina and syncope, the other participant with anaemia). None of the SAEs were considered related to the vaccine booster.

Table 26. Participant Incidence of Serious TEAEs by System Organ Class and Preferred Term up to the Data Cut-off Date – 2nd Booster Dose: mRNA-1273.222

	P205 Part H
System Organ Class Preferred Term	mRNA-1273.222 50 µg (N=511) n (%)
Number of participants reporting serious AEs	3 (0.6)
Number of serious AEs	4
Blood and lymphatic system disorders	1 (0.2)
Anaemia	1 (0.2)
Nervous system disorders	2 (0.4)
Subarachnoid haemorrhage	1 (0.2)
Syncope	1 (0.2)
Cardiac disorders	1 (0.2)
Anginal equivalent	1 (0.2)

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

A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of participants in the Safety Set. MedDRA Version 23.0.

8.2.1.3.4. Medically Attended Adverse Events

A MAAE was defined as an AE that leads to an unscheduled visit to a healthcare practitioner. Per protocol, this included visits to a study site for unscheduled assessments (e.g. abnormal laboratory follow-up, and visits for COVID-19 surveillance) and/or visits to health care professionals external to the study site (e.g. urgent care, primary care physician). All confirmed COVID-19 cases were to be recorded as MAAEs.

In P205 Part H within 28 days after the booster dose, 70/511 participants (13.7%) had MAAEs. None of the MAAEs were considered related to vaccination by the investigator. No safety concerns were identified for mRNA-1273.222 based on MAAEs.

8.2.1.3.5. Adverse Events Leading to Discontinuation

No participants in the mRNA-1273.222 group discontinued due to a TEAE.

8.2.1.3.6. Adverse Events of Interest

An AESI was defined as an AE (serious or nonserious) of scientific and medical concern specific to the study vaccine.

Identification of AESIs for mRNA-1273.222 used overlapping strategies, including the investigator reporting and sponsor programmed MedDRA queries. Adverse events that were identified using these strategies were then medically reviewed by the sponsor.

The AESIs were collected using the following methods: Investigator-assessed AESIs, Programmed SMQs, and Supplemental CMQ (see below).

i) Investigator-assessed AESIs:

The study investigators reported TEAEs as AESIs based on pre-defined definitions. The investigators indicated at the time of reporting whether a TEAE was considered an AESI. In

addition to other AESIs, the investigators were to report all suspected cases of probable and confirmed myocarditis, pericarditis, or myopericarditis regardless of whether they met the CDC case definition.

No investigator-identified AESIs were reported at the time of data cut-off.

ii) Programmed SMQs:

All reported TEAEs were queried using MedDRA SMQs to identify AEs of interest up to 28 days after vaccination. The SMQs represented medical events that were considered by global experts and regulatory agencies as hypothetically relevant to an immune response to the vaccine. The SMQs included ischaemic heart disease, cardiac arrythmia, cardiac failure, cardiomyopathy, embolic and thrombotic events, central nervous system vascular disorders, hypersensitivity, angioedema, arthritis, hearing and vestibular disorders, convulsions, demyelinating disease of central nervous system, haematopoietic cytopenia, peripheral neuropathy, thrombophlebitis, and vasculitis.

In P205 Part H within 28 days after vaccination, no events were captured in the SMQs. No cases of myocarditis or pericarditis were reported.

Cases with PTs identified by SMQs are presented below. No safety concerns were identified by the sponsor.

- Ischemic Heart Disease SMQ:
  - Anginal equivalent (described in Section 8.2.1.3.3.)
- Cardiac arrhythmia SMQ:
  - Syncope (described in Section 8.2.1.3.3).
  - Bradycardia (Reported verbatim: *Transient bradycardia*) and Ventricular extrasystoles (Reported verbatim: *Asymptomatic premature ventricular complexes* [PVCS]): Transient bradycardia and asymptomatic PVCs were noted on Study Day 1 in a s47F-year-old s47F, which were both mild and non-serious, and medically attended. The bradycardia resolved on the same day and PVCs the next day without treatment. Concomitant medications at study entry included hydrochlorothiazide which is known to cause hypokalaemia, and chondroitin sulfate. The investigator assessed both events as not related to vaccination.
- CNS Vascular:
  - Subarachnoid haemorrhage (fatal; described in Section 8.2.1.3.2).
- Hypersensitivity SMQ:
  - Urticaria: A s47F-year-old s47F had urticaria on Study Day 13, described as Urticaria of face, which had not resolved at time of data cut-off (Study Day 36). The event was moderate in severity, was not medically attended, and no treatment was reported. The investigator assessed the event as not related to vaccination.
  - Mechanical urticaria (Reported verbatim: Dermatographia): A s47F-year-old s47F had mechanical urticaria on Study Day 16 to Study Day 32. Treatment included s47F, s47F and s47F. The event was moderate in severity and medically attended. The investigator assessed the event as not related to vaccination.
- Hearing and Vestibular Disorders:
  - Dizziness: A s47F-year-old s47F had dizziness on Study Day 1 to Study Day 3. The event was mild in severity and was not medically attended. The investigator assessed the event as related to vaccination. The participant also reported in the e-Diary that s47F had a grade 1 headache on Study Day 2 and pain

at the injection site on Study Day 2 to Study Day 3, which was treated with over-the-counter pain medications.

- Hematologic cytopenia:
  - Anaemia (described in Section 8.2.1.3.3).
- Arthritis SMQ:
  - Arthralgia was reported in 5 participants. All cases were non-serious and were assessed as mild or moderate in severity. Onset was within 7 days for all arthralgia cases; 2 on Study Day 2, 1 on Study Day 6 and 2 on Study Day 7. Duration ranged from 2 to 24 days. All cases were assessed as related to vaccination by the investigator.
- Peripheral Neuropathy SMQ:
  - Loss of Proprioception (Reported verbatim: Impaired proprioception): A s47F-year-old s47F of proprioception on Study Day 5 which was non-serious, moderate in severity, and was medically attended. The participant had been taking s47F since 2 months prior to vaccination for s47F and was started on s47F on the same day as the onset of this event. The event was ongoing at the time of data cut-off date (Study Day 43). The investigator assessed the event as not related to vaccination.
  - Dysesthesia: A s47F-year-old s47F had localised s47F (Study Day 9 to Study Day 16) and the s47F (Study Day 11 only). Both events were non-serious, mild and were not medically attended, and were considered not related to vaccination by the investigator.

iii) Supplemental CMQ:

Case detection for events potentially indicative of myocarditis and pericarditis was performed using a CMQ (based on the CDC working case definition[8]).

No events of potential myocarditis or pericarditis were identified with the CMQ for participants in Study P205 Part H.

8.2.1.3.7. Pregnancy

No pregnancies were reported in Study P205 Part H as of the data cut-off.

8.3. Safety analyses from other studies (not involving mRNA-1273.222)

8.3.1. Study P205 Part G (mRNA-1273.214)

8.3.1.1. Overview of safety

As previously highlighted, Study P205 Part G was previously evaluated by TGA to support the provisional registration of mRNA-1273.214 as a booster. As such, this CER discusses main safety points of the study. A detailed safety assessment of Study P205 Part G is provided in the CER for PM-2022-02203-1-2.

[8] Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices—United States, June 2021. Morbidity and Mortality Weekly Report 2021;70(27):977-82. doi: 10.15585/mmwr.mm7027e2.

Safety data was obtained from P205 Part G and P205 Part F over a short duration, with a median follow-up duration of 43 days (range 22 to 51 days) for Part G and 57 days (range 51 to 66 days) for Part F. This involved collection of solicited local and systemic AEs during 7-day follow-up period after vaccination, as well as unsolicited AEs during 28-day follow-up period after vaccination. SAEs, MAAEs, and AESIs were also collected until the data cut-off.

8.3.1.2. Solicited AEs

Most participants had at least one solicited local AE in both Part G and Part F (79.4% vs 79.5%, respectively). The most common solicited local AE was pain (77.3% vs 76.6%), followed by axillary swelling or tenderness (17.4% vs 15.4%). The majority of solicited local AEs were Grade 1 (66.6% vs 68.1%). Grade 3 local AE was seen in 3.4% of the Part G participants, with erythema being the most common AE (2.1%). In Part F, Grade 3 local AE was seen in 3.4% of the participants, with the most commonly reported AE being swelling (1.4%). In both parts, the median duration of local AEs was 2.0 days, and no Grade 4 local AE was reported.

Most participants had at least one solicited systemic AE in both Part G and Part F (70.3% vs 66.1%, respectively). The most common systemic AE after the mRNA-1273.214 50 µg booster dose was fatigue (54.9% vs 51.4%), followed by headache (43.9% vs 41.1%), myalgia (39.6% vs 38.6%), and arthralgia (31.1% vs 31.7%). The majority of solicited systemic AEs were Grade 1 (167/437 [38.2%]) followed by Grade 2 (116/437 [26.5%]). Grade 3 systemic AE was seen in 5.5% of the participants in Part G, with fatigue being the most commonly reported AE (3.4%). In Part F, 4.6% of the participants had a Grade 3 systemic AE, and the most commonly reported AE was myalgia (3.7%). In both parts, the median duration of systemic AEs was 2.0 days, and no Grade 4 solicited systemic AEs were reported.

A subgroup analysis was performed in those with negative and positive baseline SARS-CoV-2 status. In both Part G and Part F, the incidence of solicited AEs were largely similar between those with and without evidence of prior infection.

8.3.1.3. Unsolicited AEs

Unsolicited TEAEs regardless of relationship to study vaccination were reported for 18.5% of the Part G participants and 20.7% of the Part F participants. In Part G, 5.7% of the participants had a TEAE that was assessed to be related to study vaccination, and majority of these were consistent with known reactogenicity profile, with fatigue (2.1%), arthralgia (1.4%), and headache (1.4%) being the most common; there was one report of severe fatigue that spontaneously resolved. In Part F, 5.8% of the participants had a TEAE that was assessed by the investigator as related to study vaccination, of which fatigue (2.9%), arthralgia (1.6%) and myalgia (1.6%) were the most commonly reported; there were one case of severe fatigue and one case of severe myalgia, both of which spontaneously resolved.

In Part G, there were two cases of MAAE (fatigue and dermatitis) that were considered to be related to study vaccination. In Part F, there were two cases of MAAEs (hypertension and urticaria) thought to be related to study vaccination. There was no AESI that was related to myocarditis/pericarditis and thought to be related to study vaccination in Part G and Part F.

8.3.2. Study P203 Part C booster (mRNA-1273 prototype)

8.3.2.1. Overview of safety

Study P203 Part C booster investigated administration of a 50 µg mRNA-1273 booster dose to ongoing study participants from Study P203, which included healthy 12 to 17 years age group

who received a two-dose primary series with mRNA-1273 vaccine. This study has been previously assessed by TGA (PM-2022-00685-1-2).

Safety data were collected from start of the booster phase up to the data cut of 16 May 2022. Safety assessments included monitoring of solicited adverse reactions (collected for 7 days after the booster), collection of all unsolicited adverse events (up to 28 days) and collection of SAEs, MAAEs, AESIs, and AEs leading to discontinuation through the entire study period post-booster. Serum samples were collected for immunogenicity analysis at the pre-booster visit (Day 1) and again on Day 28 post-booster. Serum levels of SARS-CoV-2 specific antibody were measured.

Rates and profile of solicited AEs and unsolicited AEs reported after the booster were presented side-by-side with those reported after completion of the primary vaccine series to provide a context for evaluation of post-booster reactogenicity.

8.3.2.2. Solicited AEs

Solicited AEs were reported by most (95.1%) participants in the Booster group; 11.0% reported a Grade 3 solicited AE and none reported a Grade 4 solicited AE (Table 27). Most solicited AEs occurred within 1 to 2 days after the booster and generally persisted for a median of 3 days. Few participants (0.5%) reported solicited AEs with onset after Day 7.

Solicited local AEs were reported by 92.0% of participants in the Booster group; 4.3% reported Grade 3 local AEs. Pain was the most reported solicited local AE (91.1% of participants); 2.9% reported Grade 3 pain. Most solicited local AEs occurred within 1 to 2 days after the booster and generally persisted for a median of 3 days.

Solicited systemic AEs were reported by 76.6% of participants in the Booster group; 8.1% reported Grade 3 systemic AEs. Headache and fatigue were the most reported (57.2% and 58.7% of participants, respectively). Most solicited systemic AEs occurred within 1 to 2 days after the booster and generally persisted for a median of 2 days.

Overall, the Booster Dose group demonstrated lower (any) solicited adverse reactions compared with the primary series (95.1% and 99.2% post-booster and post-Dose 2, respectively).

Table 27. Summary of P203 Participants with Solicited Adverse Reactions within 7 Days After Booster and Primary Series – Solicited Safety Set (Part C, Booster Dose)

	mRNA-1273-Booster N = 1294 n (%)	Primary Series mRNA-1273 after any injection N = 2485 n (%)
Solicited Adverse Reactions – N1	1294	2485
Any solicited adverse reactions	1231 (95.1)	2466 (99.2)
Grade 3	142 (11.0)	626 (25.2)
Grade 4	0	3 (0.1)
Solicited Local Adverse Reactions – N1	1294	2485
Any solicited local adverse reactions	1191 (92.0)	2431 (97.8)
Grade 3	55 (4.3)	344 (13.8)
Grade 4	0	0
Pain – N1	1294	2485
Any	1179 (91.1)	2415 (97.2)
Grade 3	38 (2.9)	227 (9.1)
Grade 4	0	0
Erythema (Redness) – N1	1293	2485
Any	119 (9.2)	641 (25.8)
Grade 3	9 (0.7)	86 (3.5)
Grade 4	0	0
Swelling (Hardness) – N1	1293	2485
Any	174 (13.5)	688 (27.7)
Grade 3	9 (0.7)	80 (3.2)
Grade 4	0	0
Axillary Swelling or Tenderness – N1	1293	2484
Any	363 (28.1)	859 (34.6)
Grade 3	3 (0.2)	16 (0.6)
Grade 4	0	0
Solicited Systemic Adverse Reactions – N1	1293	2485
Any	990 (76.6)	2284 (91.9)
Grade 3	105 (8.1)	411 (16.5)
Grade 4		3 (0.1)
Fever – N1	1279	2484
Any	78 (6.1)	340 (13.7)
Grade 3	8 (0.6)	54 (2.2)
Grade 4	0	1 (< 0.1)
Headache – N1	1293	2485
Any	739 (57.2)	1947 (78.4)
Grade 3	28 (2.2)	160 (6.4)
Grade 4	0	1 (< 0.1)
Fatigue – N1	1293	2485
Any	759 (58.7)	1868 (75.2)
Grade 3	52 (4.0)	210 (8.5)
Grade 4	0	0
Myalgia – N1	1293	2484
Any	523 (40.4)	1349 (54.3)
Grade 3	44 (3.4)	143 (5.8)
Grade 4	0	0
Arthralgia – N1	1293	2484
Any	311 (24.1)	859 (34.6)
Grade 3	17 (1.3)	66 (2.7)
Grade 4	0	0
Nausea/Vomiting – N1	1293	2484
Any	231 (17.9)	728 (29.3)
Grade 3	2 (0.2)	4 (0.2)
Grade 4	0	1 (<0.1)
Chills – N1	1293	2484
Any	396 (30.6)	1219 (49.1)
Grade 3	7 (0.5)	13 (0.5)
Grade 4	0	0

Abbreviations: N1 = Number of exposed participants who submitted any data for the event.
Any = Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for erythema (redness) is defined as: Grade 1 = 25–50 mm; Grade 2 = 51–100 mm; Grade 3 ≥100 mm. Toxicity grade for fever is defined as Grade 1 = 38–38.4 C; Grade 2 = 38.5–38.9 C; Grade 3 = 39–40 C; Grade 4 = ≥40 C.

8.3.2.3. Unsolicited Adverse Events

8.3.2.3.1. Summary of unsolicited AEs

Unsolicited AEs were collected within 28 days after Booster Dose.

SAEs, MAAEs, AESIs, and AEs leading to discontinuation were collected throughout the study period. A total of 191 participants in the Booster group (14.2%) reported any unsolicited AE, of which 55 (4.1%) were considered treatment related (Table 28). Those assessed by the investigator as related to study treatment were reported by 4.1% of participants. These event rates were lower than those in the primary series (after any injection) where unsolicited AEs occurred in 510/2486 participants (20.5%) and 312/2486 participants (12.6%) were considered treatment related. There were 3 (0.3%) severe events in the Booster group, 2 of which were considered related by the investigator and both of which were reactogenicity events (an event of vomiting diagnosed as viral gastroenteritis and an event of fatigue).

There were no SAEs, AESI or AEs leading to discontinuation from vaccine or study reported in the Booster phase of the study.

Table 28. Summary of Unsolicited TEAEs up to 28 Days After Booster Dose

	mRNA-1273-Booster N = 1346 n (%)	
Category, n (%)	**Any AE**	**Related to Injection**
All	191 (14.2)	55 (4.1)
Serious	0	0
Fatal	0	0
Medically Attended AEs	104 (7.7)	2 (0.1)
Leading to Discontinuation - Vaccine	0	0
Leading to Discontinuation - Study	0	0
Grade 3/Severe	3 (0.2)	2 (0.1)
AESI of MIS-C	0	0
AESI other	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MIS-C = multisystem inflammatory syndrome in children; TEAE = treatment-emergent adverse event.
Percentages are based on the number of safety participants in Part 1C-1 (N).

Unsolicited TEAEs by SOC and PT reported for ≥ 2 participants up to 28 days after the mRNA-1273 Booster group are presented in Table 29.

Participants reported unsolicited events most commonly in the infections and infestations SOC (7.6%) followed by the general disorders and administration site conditions SOC (3.2%). The most commonly reported unsolicited AE was COVID-19 (3.0%) followed by other respiratory-related infections including asymptomatic COVID-19 (1.3%). Other commonly reported events were reactogenicity-related events.

Table 29. Overall Unsolicited TEAE by MedDRA System Organ Class and Preferred Term (≥2 participants) up to 28 Days After Booster Dose Safety Set

System Organ Class Preferred Term	mRNA-1273-Booster N = 1294 n (%)
Number of participants reporting unsolicited adverse events	191 (14.2)
Number of unsolicited adverse events	263
Infections and infestations	102 (7.6)
COVID-19	41 (3.0)
Asymptomatic COVID-19	17 (1.3)
Upper respiratory tract infection	16 (1.2)
Nasopharyngitis	7 (0.5)
Pharyngitis	6 (0.4)
Viral infection	4 (0.3)
Influenza	3 (0.2)
Psychiatric Disorders	6 (0.4)
Anxiety	2 (0.1)
Nervous system disorders	26 (1.9)
Headache	26 (1.9)
Respiratory, thoracic, and mediastinal disorders	11 (0.8)
Nasal congestion	3 (0.2)
Cough	2 (0.1)
Dyspnoea	2 (0.1)
Oropharyngeal pain	2 (0.1)
Rhinorrhea	2 (0.1)
Gastrointestinal disorders	10 (0.7)
Vomiting	3 (0.2)
Abdominal pain	3 (0.2)
Skin and subcutaneous tissue disorders	12 (0.9)
Acne	4 (0.3)
Urticaria	4 (0.3)
Musculoskeletal and connective tissue disorders	13 (1.0)
Myalgia	7 (0.5)
Arthralgia	5 (0.4)
General disorders and administration site conditions	43 (3.2)
Fatigue	23 (1.7)
Injection site pain	9 (0.7)
Pyrexia	5 (0.4)
Injection site induration	4 (0.3)
Chills	3 (0.2)
Injection site lymphadenopathy	2 (0.1)
Pain	2 (0.1)
Injury, poisoning, and procedural complications	14 (1.0)
Ligament sprain	5 (0.4)
Hand fracture	2 (0.1)

Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities
A treatment-emergent adverse event was defined as any event not present before exposure to study injection or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of safety participants in Part 1C-1 (N).
MedDRA version 23.0

8.3.2.3.2. Unsolicited Medically Attended Adverse Events

At least 1 MAAE was reported by 12.2% of Booster group participants throughout the duration of the safety follow up. Throughout the Booster phase, the most reported AEs were in the infections and infestations SOC (9.4%); within the SOC, COVID-19 was the most reported event (68 participants, 5.1%), followed by other respiratory-related infections, symptoms, and reactogenicity-related events. No new trends or safety concerns were identified.

No unsolicited TEAEs leading to discontinuation from study vaccine or study participation were reported after Booster Dose. No SAEs were reported after Booster Dose.

8.3.2.3.3. Adverse Events of Special Interest

No AESI (including multisystem inflammatory syndrome in children [MIS-C]) were reported within 28 days after the booster dose.

Hypersensitivity events

Nine participants experienced Hypersensitivity events. Four participants experienced events of urticaria and one participant each experienced an event of: asthma, dermatitis, hypersensitivity/allergic reaction, rash, and rhinitis allergic. None of the events reported by single participants (asthma, dermatitis, rash, and rhinitis allergic) were considered related to vaccine. Two of the urticaria events were considered not related (starting on post-booster Days 15 and 17) and both resolved within 24 hours. The other 2 events of urticaria were considered treatment-related events following administration of mRNA-1273-booster. A brief summary of these events are as follows:

- A [redacted]-year-old [redacted] experienced mild urticaria (verbatim *urticaria on bilateral posterior hands*) [redacted] days after receiving the booster. Relevant medical history included seasonal allergies. The event was resolved the following day. No medical treatment or other concurrent AEs were reported. The participant had no previous events of urticaria or hypersensitivity reactions with the previous vaccinations.
- A [redacted]-year-old [redacted] experienced mild urticaria [redacted] days after receiving the booster. There was no contributory medical history and no prior or concurrent AEs. The participant was treated with [redacted] as needed for the event. The event was ongoing (recovering/resolving) as of the cut-off date (16 May 2022).

Cases of clinical interest based on MedDRA Cardiomyopathy SMQs

As a supplemental measure to search for unrecognised myocarditis/pericarditis cases, as per the sponsor the safety dataset was interrogated for AEs compatible with signs, symptoms, laboratory investigations or procedural findings that might indicate unrecognised cases. Since these event terms were not specific for myocarditis and pericarditis, each of the identified cases was evaluated. Events were filtered for those occurring within 28 days of the most recent vaccine dose.

There were 4 participants in total in the mRNA-1273 booster group who reported events included within the cardiomyopathy SMQ, both narrow and broad. Three events of dyspnoea and 1 event of arrhythmia were reported.

One event of arrythmia, nonserious, was reported in 1 participant:

- A [redacted]-year-old [redacted] experienced mild cardiac arrythmia [redacted] days after receiving the booster dose. The participant had an ongoing medical condition of environmental allergy and asthma at the time of study entry and was being treated with [redacted] and

s47F. A concurrent AE of COVID-19 was reported. The participant began experiencing intermittent palpitations following symptomatic COVID-19 but did not seek medical attention. Approximately 1 month after the event, a physical examination by the site investigator noted irregular heartbeat but the participant was otherwise asymptomatic, no work-up was conducted and no specific follow-up planned. The event was ongoing as of the cut-off date (16 May 2022). The investigator considered the events not related to mRNA-1273-booster. After the data cut-off, the investigator updated the AE to 'Irregular heart rate'. On the follow-up visit of 14 Jul 2022, the rhythm was noted by the investigator to be regular, and the AE was considered resolved.

Three events of dyspnoea, all nonserious, occurred in 3 participants:

- A s47F-year-old s47F experienced mild dyspnoea starting on the day of the booster dose. Potentially relevant medical history included s47F and s47F. The site reported that the participant experienced mild shortness of breath on s47F of the booster dosing and the day after which resolved without medical intervention or medication. There was no associated chest pain and no other concurrent AEs reported. The event was considered resolved the day following the booster dose. The investigator considered the event related to mRNA-1273-booster.
- A s47F-year-old s47F experienced mild dyspnoea (shortness of breath) s47F days after receiving the booster. A concurrent AE of COVID-19 was reported. According to the investigator, the event of dyspnoea was associated with a confirmed diagnosis of symptomatic COVID-19. The event was ongoing as of the cut-off date (16 May 2022). The investigator considered the event not related to mRNA-1273-booster.
- A s47F-year-old s47F experienced mild dyspnoea (shortness of breath) s47F days after receiving the booster. Potential contributory medical history included anxiety. No other AEs were reported concurrently, and no further details were available. The event was ongoing as of the cut-off date (16 May 2022) and was considered resolved on 19 May 2022. The investigator considered the event not related to mRNA-1273-booster.

Additional analysis of myocarditis and pericarditis

There were no additional AEs reported within the myocarditis/pericarditis algorithm.

8.3.3. Study P204 booster (mRNA-1273 prototype)

8.3.3.1. Overview of safety

Study P204 assessed the safety of mRNA-1273 25 µg when given as a booster in children 6 through 11 YOA, administered from 6 months post-Dose 2 of the primary series (mRNA-1273, 50 µg).

Safety data were presented from the time of the booster administration up to the data cut of 23-May-2022.

Safety assessment included the following:

- Solicited local and systemic ARs that occurred during the 7 days following the booster, recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following the booster (i.e. the day of injection and 27 subsequent days).

- AEs leading to discontinuation from dosing and/or study participation from Day 1 of the booster through the last day of study participation.
- SAEs and MAAEs from the booster on Day 1 through the entire study period.
- AESI from the booster on Day 1 through the entire study period, including: acute myocarditis or pericarditis and MIS-C. Symptoms suggestive of potential myocarditis or pericarditis were sought from participants during safety calls (7 days following each injection and subsequent safety calls).

8.3.3.2. Solicited AEs

Local and systemic AEs were solicited in the 7 days after the booster vaccination. Assessed local AEs included pain, erythema, swelling, and axillary swelling or tenderness. Systemic AEs included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills.

Solicited AEs were mostly Grade 1 (45.9%) or Grade 2 (39.4%) and had an overall median onset within 1 day after vaccination and median duration of 3 days. A total of 7.9% of participants reported a Grade 3 solicited AR. Fatigue was the most common Grade 3 solicited AE (3.7% of participants), followed by pain (1.9%), and headache (1.7%). One Grade 4 systemic AE of fever (>40˚C) was reported 4 days post-booster in a participant who had COVID-19 concurrently.

Pain was the most reported solicited local AE (90.1% of participants), and fatigue was the most reported solicited systemic AE (48.9%) following the booster administration. Fever was reported in 9.5% of participants following the booster.

The incidence and severity of solicited AEs reported after the booster are displayed side-by-side with solicited AEs from the primary series reported after receipt of any primary dose (Table 27, rates after "any" dose were utilised to allow for a more balanced representation). Lower incidences of solicited AEs were reported after the booster for all categories except for axillary (or groin) swelling or tenderness compared to that reported after primary vaccination. Axillary (or groin) swelling or tenderness was similar after the booster and after primary dose. The differential between the the booster and primary series was particularly evident for Grade 2 and Grade 3 AEs.

Few solicited AEs persisted beyond 7 days. Solicited local AEs persisting beyond 7 days after the booster administration were reported in 1.3% of participants and most common events were axillary (or groin) swelling or tenderness (0.7%) and pain (0.5%). Solicited systemic AEs persisting beyond 7 days after the booster administration were reported in 2.0% of participants and most common events were fatigue (1.3%) and headache (1.0%).

The incidence of any solicited AEs was higher among participants who were SARS-CoV-2 negative at baseline prior to the booster (95.8% of 757 participants) compared with participants who were SARS-CoV-2 positive at baseline prior to the booster (89.5% of 428 participants).

Table 30. Summary Solicited AEs After 25 µg Booster or 50 µg Primary Series (any injection), Solicited Safety Set by Grade (6 through 11 years)

Solicited Adverse Reaction Category Grade	mRNA-1273 25 µg – Booster N=1280 n (%)	mRNA-1273 50 µg Primary Series N=3386 n (%)
Solicited Adverse Reactions – N1	1280	3386
Any solicited Adverse Reactions	1193 (93.2)	3358 (99.2)
95% CI [a]	91.7, 94.5	98.8, 99.4
Grade 1	587 (45.9)	902 (26.6)
Grade 2	504 (39.4)	1888 (55.8)
Grade 3	101 (7.9)	568 (16.8)
Grade 4	1 (<0.1)	0
Solicited Local Adverse Reaction – N1	1279	3386
Any Solicited Local Adverse Reactions	1165 (91.1)	3333 (98.4)
95% CI [a]	89.4, 92.6	98.0, 98.8
Grade 1	722 (56.5)	1510 (44.6)
Grade 2	410 (32.1)	1642 (48.5)
Grade 3	33 (2.6)	181 (5.3)
Grade 4	0	0
Pain[b] – N1	1279	3386
Any	1152 (90.1)	3325 (98.2)
Grade 1	778 (60.8)	1777 (52.5)
Grade 2	350 (27.4)	1437 (42.4)
Grade 3	24 (1.9)	111 (3.3)
Grade 4	0	0
Erythema (Redness) – N1 [c]	1279	3386
Any	137 (10.7)	818 (24.2)
Grade 1	67 (5.2)	410 (12.1)
Grade 2	66 (5.2)	355 (10.5)
Grade 3	4 (0.3)	53 (1.6)
Grade 4	0	0
Swelling (Hardness) - N1 [c]	1279	3386
Any	139 (10.9)	767 (22.7)
Grade 1	83 (6.5)	469 (13.9)
Grade 2	52 (4.1)	256 (7.6)
Grade 3	4 (0.3)	42 (1.2)
Grade 4	0	0
Axillary (or Groin) Swelling or Tenderness – N1 [d]	1279	3386
Any	355 (27.8)	883 (26.1)
Grade 1	245 (19.2)	693 (20.5)
Grade 2	106 (8.3)	184 (5.4)
Grade 3	4 (0.3)	6 (0.2)
Grade 4	0	0
Solicited Systemic Adverse Reactions – N1[e]	1280	3386
Any Solicited Systemic Adverse Reactions	823 (64.3)	2917 (86.1)
95% CI [a]	61.6, 66.9	84.9, 87.3
Grade 1	414 (32.3)	1005 (29.7)
Grade 2	331 (25.9)	1464 (43.2)
Grade 3	77 (6.0)	448 (13.2)
Grade 4	1 (<0.1)	0
Fever – N1 [f]	1276	3386
Any	108 (8.5)	861 (25.4)
Grade 1	59 (4.6)	451 (13.3)
Grade 2	32 (2.5)	271 (8.0)
Grade 3	16 (1.3)	139 (4.1)
Grade 4	1 (<0.1)	0

Headache - N1	1280	3384
Any	489 (38.2)	2094 (61.9)
Grade 1	275 (21.5)	989 (29.2)
Grade 2	192 (15.0)	957 (28.3)
Grade 3	22 (1.7)	148 (4.4)
Grade 4	0	0
Fatigue – N1	1279	3384
Any	625 (48.9)	2458 (72.6)
Grade 1	340 (26.6)	1011 (29.9)
Grade 2	238 (18.6)	1201 (35.5)
Grade 3	47 (3.7)	246 (7.3)
Grade 4	0	0
Myalgia – N1	1280	3384
Any	269 (21.0)	1168 (34.5)
Grade 1	147 (11.5)	628 (18.6)
Grade 2	103 (8.0)	451 (13.3)
Grade 3	19 (1.5)	89 (2.6)
Grade 4	0	0
Arthralgia – N1	1279	3384
Any	160 (12.5)	700 (20.7)
Grade 1	102 (8.0)	468 (13.8)
Grade 2	46 (3.6)	202 (6.0)
Grade 3	12 (0.9)	30 (0.9)
Grade 4	0	0
Nausea/Vomiting – N1	1279	3384
Any	168 (13.1)	979 (28.9)
Grade 1	126 (9.9)	736 (21.7)
Grade 2	36 (2.8)	217 (6.4)
Grade 3	6 (0.5)	26 (0.8)
Grade 4	0	0
Chills – N1	1279	3384
Any	179 (14.0)	1136 (33.6)
Grade 1	118 (9.2)	649 (19.2)
Grade 2	57 (4.5)	464 (13.7)
Grade 3	4 (0.3)	23 (0.7)
Grade 4	0	0

Abbreviations: CI = Confidence intervals; G = Severity grade; N1 = Number of exposed participants who submitted any data for the event. Any = Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Data cut-off for BD data = 23 May 2022. Data cut-off for primary series data = 10 Nov 2021.
[a] 95% CI is calculated using the Clopper-Pearson method.
[b] Pain for participants age 6 through 11 years is injection site pain or tenderness/injection site pain.
[c] Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants age 37 months to <12 years is defined as: G1 = 25 - 50 mm; G2 = 51 - 100 mm; G3>100 mm; G4 = Necrosis or exfoliative dermatitis.
[d] Toxicity grade for Groin or underarm swelling or tenderness for Axillary swelling or tenderness for participants age 37 months to < 12 years is defined as: G1 = No interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization.
[e] Toxicity grades for systemic adverse reactions other than Fever are defined as: G1 = no interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization.
[f] Toxicity grade for Fever for participants age 37 months to <12 years is defined as: G1 = 38 - 38.4°C; G2 = 38.5 - 38.9°C; G3 = 39 - 40 °C; G4 = >40°C.

8.3.3.3. Unsolicited AEs

The reported incidence of any unsolicited AE after the booster was 13.1% (Table 28). The incidence of unsolicited AEs after the booster assessed by the investigator as related to study treatment was 4.0%. These event rates were lower than those in the primary series (after any injection) where unsolicited AEs occurred in 891 of 3007 participants (29.6%) of which 319 (10.6%) were considered treatment related.

The most commonly reported unsolicited AEs were injection site reactions, fatigue and headache, which are consistent with the known reactogenicity profile of the vaccine. Most other AEs were reported in few participants and no specific safety trends were identified. A total of 96 participants (7.4%) experienced an MAAE within 28 days after the mRNA-1273 BD. Ten

(<1%) participants experienced an MAAE assessed by the investigator as related to study treatment.

One SAE was reported. Seven (0.5%) participants reported severe (Grade 3 or higher) events (Table 8); the majority of these represented reactogenicity-related events, e.g. headache, myalgia, injection site pain, and chills. Six of these events were considered by the investigator to be vaccine related. Similarly, 12 of 3007 participants (0.4%) reported severe events in the primary series, 9 (0.3%) of which were considered related by the investigator and were also primarily representative of reactogenicity.

No unsolicited AEs caused discontinuation from study participation. One AESI was reported, which is described further in Section 2.5.5.5. It was determined by the investigator to be potentially related to vaccination.

Table 31. Summary of Unsolicited AE up to 28 Days After 25 µg the booster Safety Set (6 through 11 years)

	mRNA-1273 25 µg - Booster N=1294 n (%)
Unsolicited AEs Regardless of Relationship to Study Vaccination	
All	169 (13.1)
Serious	1 (<0.1)
Fatal	0
Medically-Attended AEs	96 (7.4)
Leading to Discontinuation - Vaccine	0
Leading to Discontinuation from Participation in the Study	0
Grade 3/Severe	7 (0.5)
Non-Serious [a]	168 (13.0)
Grade 3/Severe	6 (0.5)
At Least 1 Non-serious [b]	169 (13.1)
Grade 3/Severe	6 (0.5)
Special Interest (AESI)	1 (<0.1)
MIS-C	0
Other	1 (<0.1)
Unsolicited AEs Related to Study Vaccination	
All	52 (4.0)
Serious	0
Fatal	0
Medically Attended	10 (0.8)
Leading to Discontinuation from Study Vaccine	0
Leading to Discontinuation from Participation in the Study	0
Grade 3/Severe	6 (0.5)
Non-Serious [a]	52 (4.0)
Grade 3/Severe	6 (0.5)
At Least 1 Non-Serious [b]	52 (4.0)
Grade 3/Severe	6 (0.5)
Special Interest (AESI)	1 (<0.1)
MIS-C	0
Other	1 (<0.1)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BD = booster dose; MIS-C = multisystem inflammatory syndrome in children.
An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of safety participants in BD analysis.
Solicited adverse reactions with toxicity Grade = 0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
[a] Participants who reported at least one non-serious AE and did not report any serious AE are included in the summary.
[b] Participants who reported at least one non-serious AE regardless of reporting any serious AE or not are included in the summary.

Unsolicited AEs by SOC and PT

Unsolicited AEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) reported for >1 participant up to 28 days after the booster administration are presented in Table 29.

The most common SOCs represented by unsolicited AEs were of Infections and infestations (n=80, 6.2%), General disorders and administration site conditions (n=34, 2.6%), and

Respiratory, thoracic and mediastinal disorders (n=23, 1.8%). The most commonly reported unsolicited AE PT was COVID-19 (25 participants, 1.9%). Other unsolicited AE PTs were expected for this age group or known aspects of the reactogenicity profile of the vaccine. No new safety concerns were identified.

Table 32. Unsolicited AE by System Organ Class and Preferred Term (>1 participant) up to 28 Days after 25 µg the booster Safety Set (6 through 11 years)

MedDRA version 23.0 System Organ Class Preferred Term	mRNA-1273 25 µg - Booster N=1294 n (%)
Number of participants reporting unsolicited adverse events	169 (13.1)
Number of events	238
Infections and Infestations	80 (6.2)
COVID-19	25 (1.9)
Upper respiratory tract infection	17 (1.3)
Asymptomatic COVID-19	6 (0.5)
Respiratory tract infection viral	5 (0.4)
Ear infection	4 (0.3)
Influenza	4 (0.3)
Gastroenteritis	3 (0.2)
Otitis media	3 (0.2)
Gastroenteritis viral	2 (0.2)
Nasopharyngitis	2 (0.2)
Viral infection	2 (0.2)
Immune System Disorder	5 (0.4)
Seasonal allergy	3 (0.2)
Metabolism and nutrition disorder	2 (0.2)
Decreased appetite	2 (0.2)
Psychiatric disorders	5 (0.4)
Attention deficit hyperactivity disorder	3 (0.2)
Nervous System Disorder	15 (1.2)
Headache	15 (1.2)
Respiratory, thoracic and mediastinal disorders	23 (1.8)
Cough	6 (0.5)
Oropharyngeal pain	6 (0.5)
Rhinorrhoea	6 (0.5)
Nasal congestion	5 (0.4)
Gastrointestinal disorders	12 (0.9)
Vomiting	8 (0.6)
Abdominal pain	2 (0.2)
Abdominal pain upper	2 (0.2)
Skin and subcutaneous tissue disorders	13 (1.0)
Urticaria	7 (0.5)
Mechanical urticaria	2 (0.2)
Musculoskeletal and connective tissue disorders	9 (0.7)
Arthralgia	4 (0.3)
Myalgia	3 (0.2)
General disorders and administration site conditions	34 (2.6)
Fatigue	13 (1.0)
Pyrexia	10 (0.8)
Injection site lymphadenopathy	9 (0.7)
Injection site pain	5 (0.4)
Chills	2 (0.2)
Injection site erythema	2 (0.2)
Injury, poisoning, and procedural complications	8 (0.6)
Ligament sprain	3 (0.2)
Arthropod bite	2 (0.2)

Abbreviations: AE = adverse event; BD = booster dose; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.

An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.

Percentages are based on the number of safety participants in BD analysis.

8.3.3.3.1. Unsolicited Medically Attended Adverse Events

There were no new trends or patterns observed for MAAEs following the booster administration as compared with the primary series. A total of 116 (9.0 %) participants experienced at least one MAAE after the booster (Study P204 Table 14.3.1.19.6.2). Two participants (0.2%) reported 4 MAAEs that were considered severe: abdominal pain (n=1, <0.1%), myalgia (n=1, <0.1%), chills (n=1, <0.1%), and fatigue (n=1, <0.1%). Ten (0.8%) participants had MAAEs considered by the investigator to be related to mRNA-1273.

The MedDRA SOCs in which the highest numbers of participants had MAAEs were Infections and infestations (n=82, 6.3%) comprised predominantly of respiratory tract infections. Reporting of MAAEs may be artificially high as respiratory symptoms often required an illness visit at the site for COVID-19 testing and severity assessment. Given the overlap with COVID-19 symptoms, other respiratory tract infections were thus classified as MAAEs even if they would not have normally prompted a visit to a medical provider. The most commonly reported MAAE in the Infections and infestations SOC was COVID-19 in 24 (1.9%) participants.

8.3.3.3.2. Serious Adverse Events

There was one SAE of abdominal pain in a participant who received a 25 µg mRNA-1273 booster dose. s47F after receiving the booster, a s47F-year-old s47F developed severe abdominal pain and vomiting. Magnetic resonance imaging and abdominal ultrasound ruled out appendicitis, hernia, and bowel obstruction, and a COVID-19 test was negative. The participant was admitted and started on s47F and s47F.

By the next day s47F was tolerating oral intake and discharged from the hospital. No definitive diagnosis was determined; the event was recorded as "stomach inflammation" and was considered not related to study vaccination by the investigator.

8.3.3.3.3. Discontinuation from study

One participant discontinued the study due to withdrawal of consent. Withdrawal for this participant was not related to AEs. No unsolicited AEs caused discontinuation from study participation.

8.3.3.3.4. Adverse Events of Special Interest

There was one event categorised by the investigator as an AESI although it did not meet protocol-defined definition of an AESI. This was an event of chest pain in a s47F-year-old s47F and s47F participant (s47F) who, s47F days after receiving the BD, experienced mild chest pain. A cardiac workup was completed including an electrocardiogram, which was normal, as well as normal values for high sensitivity troponin 1, erythrocyte sedimentation rate, and C-reactive protein. Given these results, the event was considered to be non-cardiac chest pain of unknown aetiology by the investigator. The chest pain resolved within the same day. Given the temporal association, this event was considered by the investigator to be related to study vaccination. No other AESIs were reported during the study period.

Hypersensitivity events

Twenty-four (1.9%) participants reported hypersensitivity events after the booster according to the narrow and broad SMQ of hypersensitivity. The most commonly reported event was urticaria, occurring in 8 (0.6%) participants. The only other event occurring in more than one

participant was seasonal allergy (n=3, 0.2%). Three participants experienced events that were considered related to study vaccination by the investigator, including one event of serum sickness-like reaction and 2 events of urticaria. None of these 3 participants had previous similar reactions during the primary series. A brief summary of these cases follows:

- An s47F or s47F experienced a mild serum sickness-like reaction s47F days after receiving the booster. Symptoms included generalised pruritis that progressed to urticaria on trunk and bilateral thighs as well as arthralgia, myalgia, chills, and nausea. There was no fever or upper respiratory infection symptoms.
  There were no new medications or change in food/soap, lotion or detergents and s47F Medical treatment included s47F, s47F, and s47F No concurrent AEs were reported, and the event was recovering/resolving at the time of the data cut-off.
- A s47F-year-old s47F experienced moderate urticaria (*verbatim urticarial rash, nonpapular, diffuse*) s47F days after receiving the booster. Medical treatment included oral antihistamines and topical hydrocortisone. There was a concurrently reported AE of moderate, generalised arthralgia which resolved in 3 days. The event of urticaria was unresolved at the time of the data cut-off (duration of which was s47F days from date of AE onset to data cut-off date).
- A s47F-year-old s47F experienced moderate urticaria (*verbatim generalised urticarial rash*) s47F days after receiving the booster. Medical treatment included oral antihistamine. There were no concurrently reported AEs and the event resolved in 51 days. The causality assessment for this AE was changed to not related to the vaccination by the investigator after the data lock point.

Cases of clinical interest based on MedDRA Cardiomyopathy SMQs

As a supplemental measure to search for unrecognised myocarditis/pericarditis cases, the safety dataset was interrogated for AEs compatible with signs, symptoms, laboratory investigations or procedural findings that might indicate unrecognised cases. Since these event terms are not specific for myocarditis and pericarditis, each of the identified cases was evaluated. Events were filtered for those occurring within 28 days of the most recent vaccine dose.

There were 2 events in the cardiomyopathy SMQ. One was the AESI of chest pain described discussed above. The other event occurred in a s47F-yearold s47F who experienced a mild episode of dyspnoea s47F days after the booster that resolved the same day. No other concurrent AEs were reported. The event was considered by the investigator to be related to study vaccination.

Autoimmune event

There was a case of juvenile rheumatoid arthritis (JRA).

A s47F-year-old s47F with a medical history of s47F and s47F received the mRNA-1273 50 µg primary series on s47F and s47F . s47F experienced an SAE of post-viral s47F, s47F months and s47F days after Dose 2 of the primary series. s47F which was treated with s47F. Overnight s47F awoke with severe pain, unable to ambulate, and was admitted to the hospital. Magnetic resonance imaging showed fluid accumulation around both hip joints. Parents informed hospital staff of their family history which includes s47F with s47F, in an attempt for them to rule these out at that time. A COVID-19 test taken at the time was negative and all laboratory

studies were reported as normal. Although [redacted] had not been ill or diagnosed with a viral infection recently, the diagnosis of post-viral transient synovitis was assigned given the negative work-up. [redacted] was treated with [redacted] and sent home with [redacted] and a referral for physical therapy. The event was reported as resolved on [redacted].

At a regularly scheduled 3-month follow-up appointment following discharge from the hospital, the practitioner noted on the participant's physical exam that the fingers on both [redacted] hands were swollen, and [redacted] had decreased grip strength bilaterally. Given the family history of [redacted] and the recent hip pain hospital admission, the provider checked autoimmune laboratory studies again, which then came back elevated. [redacted] was then seen by Rheumatology and received the diagnosis of JRA on [redacted]. [redacted] was prescribed [redacted] injections biweekly and has been doing well since. Prior to the diagnosis of JRA, the participant was asymptomatic. [redacted] hip pain had resolved and there had been no complaints of finger pain. After the practitioner drew attention to the decreased strength in [redacted] hands, [redacted]

The participant received [redacted] the booster on [redacted]. On [redacted], the date of [redacted] Rheumatology appointment, an AE of JRA (hips and hands predominant, non-serious, moderate) was recorded. As described above, there was no change in clinical status, just confirmation of the diagnosis from the ongoing work-up. Neither AEs of post-viral transient synovitis nor JRA were considered by the investigator to be related to study vaccination.

8.4. Post marketing experience

SPIKEVAX Bivalent mRNA-1273.222 (Original/BA.4/5) received emergency use authorisation in the US for use as a booster dose in individuals 18 years of age and older on August 31, 2022. Cumulatively as of 18 October 2022 (Monthly Safety Summary Report 16); a total of 36,729,950 doses of SPIKEVAX Bivalent mRNA-1273.222 (Original/BA.4/5) had been delivered to the US. A limited number of cases have been reported to the MAH and are summarised in a consolidated manner. Monthly Summary Safety reports are submitted to relevant regulatory agencies by the sponsor.

Cumulatively, as of 18 October 2022, 677 cases (1,922 events) involving SPIKEVAX Bivalent mRNA-1273.222 (Original/BA.4/5) booster were reported to the MAH. Of the 677 cases (1,922 events) reported, 376 cases were medically confirmed, 37 cases (69 events) were serious, and 2 cases were reported with a fatal outcome. The mean age was 60.3 years (SD 20.1 years) with a median age of 67.0 years. Most of the cases were reported in females (295 cases, 43.6%) compared to males (183 cases, 27.0%), and 199 (29.4%) cases had missing sex information. The majority of cases were non-serious (640 nonserious cases, 94.5%). Cumulatively, the most frequently reported clinical events associated with mRNA-1273.222 booster included pyrexia (2.7%), fatigue (2.3%), vaccination site pain (2.3%), chills (2.2%), and pain in extremity (2.2%). Events coded as "No adverse event" (18.0% of all events) were often associated with events involving product administration errors (e.g. accidental underdose (9.4%), wrong product administered (2.2%), etc.).

The 2 events (0.1%) with a reported fatal outcome, were both consumer reports and included a female of an unknown age with no medical history reported, and no other information provided by the reported, including vaccine dose, time to onset, clinical course and cause of death. The second fatal case was reported by a consumer that only mentioned she talked to a gentleman that ended dying and who seems to have blood clot problems. No other information was provided.

Upon further review of the report, it was determined the death occurred before emergency use authorisation of SPIKEVAX Bivalent .222; the case is be corrected and coded to the original SPIKEVAX vaccine (mRNA-1273).

Routine pharmacovigilance monitoring is being continued.

Myocarditis and pericarditis

As of 18 October 2022, for SPIKEVAX Bivalent mRNA-1273.222 (Original/BA.4/5) there was one reported case of pericarditis concerning a male of unknown age who had a family history of atrial fibrillation and heart rate increased. According to the WHO-UMC standardised case causality assessment (WHO 2013), this case was assessed as "unassessable" due to important missing information including exposure information, time to onset, laboratory values, medical history and clinical course.

8.5. Evaluator's overall conclusions on clinical safety

In the current submission, the sponsor has presented interim safety data from the pivotal study P205 Part H, which consists of summaries of adverse events following mRNA-1273.222 as a second booster in adults ≥ 18 YOA.

For the solicited AEs, most participants (87.2%) had at least one event. Grade 3 AEs were less common (11.6%) and no Grade 4 AE was identified. The most common solicited local AE was pain, followed by axillary swelling or tenderness. The most common solicited systemic AE was fatigue (59.8%), followed by headache (49.1%), myalgia (46.4%), and arthralgia (34.9%). Fever was relatively uncommon, reported in only 3.9% of the participants, with one (0.2%) reporting a Grade 3 fever (39-40°C) and no report of Grade 4 fever (>40°C). The incidence of solicited AEs between 18 to <65 YOA and ≥65 YOA were largely comparable or slightly lower in the latter age group. There was generally slightly lower incidence of solicited local and systemic AEs in those with evidence of previous SARS-CoV-2 infection compared to those without any evidence of the infection, however the two subgroups had comparable AE profiles overall.

As for the unsolicited AEs, 22.7% of the participants had reported adverse reactions. The most commonly reported unsolicited TEAEs regardless of relatedness were fatigue (4.3%); headache (2.9%); COVID-19 (2.2%); rhinovirus infection, upper respiratory tract infection (1.4% each); arthralgia, myalgia, and urinary tract infection (1.0% each). 7.8% of the participants reported unsolicited TEAEs that were considered to be related to mRNA-1273.222, none of which were serious or required medical attendance. Two (0.4%) participants reported fatigue that were considered to be severe (Grade 3 or higher) on Day 2, and both resolved within 28 days from the booster vaccination.

Study P205 Part H did not have a comparator for the safety assessment. Therefore, it is challenging to draw a meaningful conclusion from the provided safety data. While not ideal, comparisons can be made with provisionally approved SPIKEVAX products (mRNA-1273 and mRNA-1273.214). When the abovementioned solicited and unsolicited AE figures for Study P205 Part H are compared with those from Study P205 Part F (mRNA-1273) and Study P205 Part G (mRNA-1273.214), all three studies appear to have largely comparable safety statistics.

In Study P205 Part H, 3 participants (0.6%) had 4 SAEs, and all were assessed by the investigator as not related to study vaccination. One of these was a fatal outcome with subarachnoid haemorrhage in a 70 year-old male. The other three SAEs included angina with syncope, and anaemia. There was one further case of death outside the data cut-off date in a 68 year-old female on Day 40, which was due to an unknown cause but considered to be unrelated to the study vaccine. 13.7% of the participants had MAAEs, none of which was considered to be

related to the study vaccine. AESIs were largely sporadic and did not establish a concerning pattern in terms of safety. No case of myocarditis or pericarditis was identified.

Overall, the safety profile of mRNA-1273.222 are consistent with the known reactogenicity of mRNA-1273 and mNRA-1273.214, and no particular safety concern is raised. While the safety outcomes for Study P205 Part H are promising, there are certain limitations that should be considered. The safety data was obtained over a short duration, in a small number of participants that would be unable to reliably detect rare AEs such as myocarditis and pericarditis. Additionally, Study P205 Part H did not allow individuals that were immunocompromised or have unstable chronic disease, who are the priority populations in the community.

Considering the proposed target population of ≥6 YOA, a major shortcoming in the current submission is that there is no paediatric data for mRNA-1273.222. While the sponsor has provided Study P203 Part C booster (12-17 YOA) and Study P204 booster (6-11 YOA) to support the use of mRNA-1273.222 in children, these studies are without davesomeran and therefore do not provide any direct clinical data to support the proposed indication in children.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

<table>
<tr><td colspan="2">Indication: “As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.”</td></tr>
<tr><th>Benefits</th><th>Strengths and Uncertainties</th></tr>
<tr><td>Based on the Day 29 interim analysis of Study P205 Part H, administration of mRNA-1273.222 as a second booster is associated with a greater immune response against the Omicron BA.4/5 subvariants when compared to mRNA-1273.</td><td rowspan="2">Individuals who received mRNA-1273.222 in Study P205 Part H demonstrated a greater rise in the nAb titres compared to the mRNA-1273 counterpart (Part F). However, it should be noted that the two study groups were not contemporaneous and there were significant differences identified at baseline. As such, the comparison between these two groups should be interpreted with a caution.

It is unclear how the immunogenicity result will translate into protection against SARS-CoV-2 infection. In addition, no immunogenicity information is available on people who are immunosuppressed or have unstable chronic diseases.

Only short-term immunogenicity data is available for mRNA-1273.214. The longevity of the immunogenicity and clinical protection are unclear.

The presented immunogenicity data is based on nAb only. It is unclear how mRNA-1273.222 affects other types of immunity.</td></tr>
<tr><td>Ability to elicit neutralising response against the wild-type reference strain appears to be largely preserved in mRNA-1273.222.</td></tr>
</table>

	Immunogenicity has been studied as a second booster only, whereas the proposed indication is for any booster dose. It is unclear if the clinical data presented can be extended to other booster doses. The optimal timing for booster with mRNA-1273.222 is unknown. No data is available regarding heterologous boosting with mRNA-1273.222. The sponsor proposes the vaccine to be used in children as young as 6 YOA, however there is no clinical data with mRNA-1273.222 in individuals ≤ 18 YOA.
mRNA-1273.222 is shown to have a greater cross-neutralisation ability against the Omicron BQ.1.1 and XBB.1 subvariants.	It is unclear how well the immunogenicity testing for BQ.1.1 and XBB.1 variants is validated/accepted. It is unclear how effective mRNA-1273.222 will be for other emerging variants.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
Based on Study P205 Part H, Part G and Part F, the safety profile of mRNA-1273.222 appears to be consistent with mRNA-1273 and mRNA-1273.214. There was no new safety concern that was raised for mRNA-1273.222.	The safety data is based on a small sample set, and therefore unable to reliably detect rare adverse events. The safety data is based on short term follow-up only. No long-term information is available. No safety information is available on individuals with unstable chronic diseases or immunosuppression, or those with recent COVID-19 infection (as per exclusion criteria). **Most importantly, no safety information is available for individuals <18 YOA.** Safety has been studied as a second booster only. No safety information on co-administration with other vaccines (e.g. flu vaccine).

9.3. First round assessment of benefit-risk balance

Studies P205 Part H and Part F have shown that mRNA-1273.222 is able to generate greater neutralising immune response when given as a second booster in adults who have received a primary series and a booster dose with mRNA-1273. Higher immune responses were observed against Omicron BA.4/5 and ancestral SARS-CoV-2 strain (primary endpoints) as well as other

emerging subvariants including Omicron BQ.1.1 and XBB.1 (exploratory endpoints). While such results are promising, it should be noted that the supporting data are not without shortcomings, as summarised in Section 9.2.

A major issue that needs a further discussion is the proposed use in individuals 6 to <18 YOA. The sponsor has provided certain paediatric data based on mRNA-1273 to support this indication. While it is acknowledged that mRNA-1273 has been well characterised in children, extrapolation of mRNA-1273's data to mRNA-1273.222 in individuals 6 to <18 YOA requires an assumption that davesomeran and elasomeran has comparable immunogenicity (hence efficacy) and reactogenicity in this age group. While there may be no strong reason to reject this claim, one has to be mindful of the fact that there is no direct clinical data to support it either.

Other issues include that mRNA-1273.222 has only been studied as a second booster only. The optimal timing for its use (i.e. interval from primary series or previous booster dose) is also unclear.

On balance, the evaluator considers that the benefit-risk assessment in individuals ≥18 YOA to be favourable. As for individuals <18 YOA, this will require a further discussion at the ACV.

10. First round recommendation regarding authorisation

Based on the evaluation of the clinical data presented by the sponsor, the evaluator recommends approval of SPIKEVAX BIVALENT BA.4-5 (elasomeran/davesomeran) *as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in* ***individuals 18 years of age and older*** *who have previously received at least a primary vaccination course against COVID-19.*

As for deciding a lower age limit of the target group, the evaluator would like to defer the decision to the delegate and ACV.

The Sponsor is requested to address the comments to the proposed PI/CMI changes and clinical questions summarised in Sections 11 and 12.2 of this CER, respectively.

11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

The PI comments below are based on the draft PI supplied in Sequence 0004 (PI v1.2, 07Dec22). The proposed PI is largely in line with the PI of SPIKEVAX and SPIKEVAX BIVALENT (BA.1).

PI Comment 1: (Section 4, page 2)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 (elasomeran/davesomeran) COVID-19 Vaccine has **provisional approval** for the indication below:

As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.

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

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

Evaluator's comment:

The lower age limit for SPIKVAX BA.4-5 is to be decided at a later date.

PI Comment 2: (Section 4.2, page 2)

Paediatric population

The safety and efficacy of SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 in children less than 6 years of age have not yet been established. No data are available.

Evaluator's comment:

The comment above implies that safety and efficacy of SPIKEVAX BA.4-5 is established in children 6 YOA and older, which is not the case. The comment will need to be revised.

PI Comment 3: (Section 4.6, page 8)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in females.

In a combined fertility and developmental toxicity study, 100 micrograms of mRNA (elasomeran) and other ingredients included in a single human dose of SPIKEVAX (original) was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in dams from prior to mating to the end of the study on lactation day 21 as well as in fetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryofetal or offspring development or postnatal development. No data are available on SPIKEVAX (original), SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) or SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 vaccine placental transfer or excretion in milk. The effect on male fertility has not been determined.

Evaluator's comment:

This section should have a comment that currently there is no data regarding fertility, pregnancy and lactation for SPIKEVAX BA.4-5.

PI Comment 4: (Section 4.8, page 9)

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 booster dose

The safety, reactogenicity, and immunogenicity of a bivalent booster dose of SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 511 participants received the SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 50 microgram booster dose, and 376 participants received the SPIKEVAX (original) 50 microgram booster dose.

The SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 booster had a reactogenicity profile similar to that of the SPIKEVAX (original) booster given as a second booster dose. The frequency of adverse reactions after immunisation with SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 was also similar or lower relative to that of a first booster dose of SPIKEVAX (original) (50 micrograms) and relative to the second dose of the SPIKEVAX (original) primary series (100 micrograms). No new safety signals were identified.

Evaluator's comment:

This section should mention that the safety data is based on an interim analysis. It should also mention the median follow-up duration.

PI Comment 5: (Section 4.8, page 11)

The study protocol was amended to include an open-label booster dose phase that included 1,294 participants 6 years through 11 years of age who received a booster dose of SPIKEVAX (original) at least 6 months after the second dose of the primary series. No additional adverse reactions were identified in the open-label portion of the study.

Evaluator's comment:

The last sentence is slightly confusing, potentially implying that there was no adverse reaction in Study P204 booster. It is suggested that the phrase "adverse reaction" is changed to "safety concern" or equivalent.

PI Comment 6: (Section #.#, page #)

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

SPIKEVAX (original) (elasomeran) and SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) (elasomeran/imelasomeran) both contain mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After

Evaluator's comment:

For clarity, it is suggested that the first sentence in the "Mechanism of action" paragraph contain SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.4-5) along with the other two SPIKEVAX vaccines.

PI Comment 7: (Section 5.1, page 17)

SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1)

Immunogenicity in participants 18 years of age and older – after SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) booster dose (0.5 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a bivalent booster dose of SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) 50 microgram booster dose, and 377 participants received the SPIKEVAX (original) 50 microgram booster dose.

Evaluator's comment:

The clinical data for SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) is included as a supportive data for SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.4-5). However, SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) contains imelasomeran which is not included in SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.4-5). Therefore, it is suggested that this section presents the primary finding in texts only, and remove Table 7 from the PI. The data in Table 8 (immunogenicity for Omicron BA.4/5) is an exploratory endpoint for SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1) and does not need to be in the current PI; this information is already available in the PI for SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.1).

PI Comment 8: (Section 5.1, page 26)

Elderly population

SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 was assessed in 511 individuals 18 years of age and older (P205 Part H). A total of 105 of the 511 participants (20.5%) were ≥ 65 years of age.

Evaluator's comment:

It is suggested that an additional sentence is added to this paragraph to state that the immunogenicity results (Omicron BA.4/5 and ancestral SARS-CoV-2) were consistent between 12-64 and ≥65 years age groups.

11.2. First round comments on draft CMI (clinical aspects)

The draft CMI for SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 is largely similar to those of the previous SPIKEVAX vaccines. This is considered to be acceptable.

The CMI is intended for individuals ≥6 YOA. This may need to be revised depending on the ACV and delegate's decision.

The sponsor is requested to respond to the query raised below.

CMI Comment 1: (Section 6, page 5)

Serious side effects

Serious side effects	What to do
• Feeling faint or light-headed • Changes in your heartbeat • Shortness of breath • Wheezing • Swelling of your lips, face, or throat • Hives or rash • Nausea or vomiting • Stomach pain • Decreased sense of touch or sensation • Tingling, pricking or pins and needles feeling	**Call your doctor, pharmacist, or nurse straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.**

Evaluator's comment:

The list of serious side effects for SPIKEVAX BIVALENT ORIGINAL/OMICRON (BA.4-5) as shown above does not contain erythema multiforme, which is included in the CMI for SPIKEVAX ORIGINAL. Please explain why this is.

11.3. First round comments on draft RMP (Summary of Safety Concerns)

11.3.1. EU Risk Management Plan

The sponsor has submitted a EU Risk Management Plan (RMP) v6.1 (dated 30/10/2022) in Sequence 0003. The Summary of Safety Concerns is shown in Table 33.

Table 33. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Myocarditis Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast-feeding Long-term safety Use in immunocompromised subjects Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders

11.3.2. Australia-Specific Annex

Australia-Specific Annex (ASA) v1.1 (dated 07/12/2022) has been presented in Sequence 0004.

The sponsor has stated in the ASA that there are "*no additional safety concerns for Spikevax Bivalent Original/Omicron BA.4-5 in Australia*", and that "*There are no Australia-specific additional pharmacovigilance activities for Spikevax Bivalent Original/Omicron BA.4-5*".

Evaluator's comments: The Summary of Safety Concerns in the draft RMP is consistent with those of SPIKEVAX and SPIKEVAX ORIGINAL/OMICRON (BA.1). This is considered to be appropriate. The evaluator agrees that there is no additional safety concern specific to Australia.

12. Clinical questions

12.1. Clinical questions with the sponsor's response

On 20 December 2022, two clinical questions were sent to the sponsor at the request of the clinical evaluator. The sponsor's response was received on 22 December 2022 in a PDF file titled "*22-12-22 Moderna - Response to Clinical Questions received 20-12-22 PM-2022-048 24-1-2 mRNA1273.222*".

Question 1: Does the sponsor have any clinical efficacy/safety data on individuals <18 YOA for davesomeran? If not, what is the sponsor's justification for lowering the age limit to 6 YOA?

Sponsor's response:

Clinical study efficacy (immunogenicity) and safety data with mRNA-1273.222 (Original +Omicron BA.4/BA.5 bivalent) administered as a booster dose is only available in adults from Study P205 Part H (subject of this respective application (PM-2022-04824-1-2)). No clinical data are available on davesomeran as a monovalent vaccine.

In Australia, Spikevax (mRNA-1273) is authorized as a primary series in individuals 6 months and above and as a booster dose in individuals 12 years and above. The bivalent vaccine mRNA-1273.214 (Original + Omicron BA.1) has been authorized as a booster dose in 18 years and above.

Given the following, the Sponsor believes that the appropriateness of extrapolation from adults to <18 years of age is reinforced and that mRNA-1273.222 can be used by persons > 6 years of age for the prevention of COVID-19:

1. Clinical data from the mRNA-1273-P203 study in adolescents indicated non-inferior antibody responses of mRNA-1273 in adolescents compared to adults and previously supported the authorization of mRNA-1273 in individuals <18 years-old, and

2. Immunogenicity and safety data from the booster phase of mRNA-1273-P204 support the administration of mRNA-1273 booster to children 6 through 11 years, and

3. Data from mRNA-1273-P205 part H indicated superior antibody responses against Omicron BA.4/BA.5 with mRNA-1273.222 as a booster compared to mRNA-1273.

Additionally, clinical data from the original vaccine mRNA-1273 booster dose is intended to support authorization of mRNA-1273 booster formulations most relevant to prevailing public health needs, including Omicron-containing formulations.

Evaluator's comments:

The sponsor's response does not include any new data or explanation to support the proposed use in individuals as young as 6 YOA. This is to be further discussed at the ACV.

<u>Question 2</u>: Are there further trenches of clinical data expected for the current submission?

Sponsor's response:

No further clinical efficacy or safety data are expected for mRNA-1273.222 for the current submission.

Evaluator's comment:

The sponsor's response is acknowledged.

12.2. Clinical questions to be answered by the sponsor

Question 1:

Is there a formal study (either ongoing or planned) to assess mRNA-1273.222 in individuals <18 YOA?

Question 2:

For US/EU/Canada, were the approvals based on evaluation of clinical data with mRNA-1273.222 (i.e. Study P205 Part H)?

Question 3:

The sponsor should submit a summary of major protocol violations/deviations for Study P205 Part H.

13. First round evaluation errata

13.1. Minor editorial changes

Pending.

13.2. Minor errors of fact

Pending.

13.3. Significant errors of fact

Pending.

14. Second round evaluation

Pending.

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

Pending.

15.2. Second round assessment of risks

Pending.

15.3. Second round assessment of benefit-risk balance

Pending.

16. Second round recommendation regarding authorisation

Pending.

17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

Pending.

17.2. Second round comments on draft CMI (clinical aspects)

Pending.

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

Pending.

18. References

See footnotes in relevant section.

Therapeutic Goods Administration

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

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Risk Management Plan Evaluation Report
Provisional Approval Pathway

Elasomeran/ davesomeran (Spikevax Bivalent Original/Omicron BA.4-5)

Submission No: PM-2022-04824-1-2

Sponsor: Moderna Australia Pty Ltd

Round 1: 29 November 2022
Round 2: 10 January 2023
Post ACV report: 17 February 2023

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TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type:	New biological entity
Sponsor:	Moderna Australia Pty Ltd
Generic name:	**Elasomeran/Davesomeran**
Trade name:	**Spikevax bivalent Original/ Omicron BA.4-5**
Dose form and strength:	Suspension for injection; 0.1 mg/ml in multidose vial and pre-filled syringe
Drug class:	Active immunisation to prevent COVID-19 disease (mRNA vaccine)
Submission No; eSubmission ID:	PM-2022-04824-1-2; e006836 - (0003)
RMP file No:	E22-629663
TRIM reference:	D22-6157126
EU-RMP Version:	Round 1– version 6.1; dated 30 October 2022; DLP 12 September 2022 Round 2 – version 6.3; dated 6 December 2022; DLP 17 September 2022.
ASA Version:	Round 1– version 1.0; dated 22 November 2022 Round 2 – version 1.1; dated 7 December 2022 and version 1.2; dated 20 December 2022
Evaluator:	s22 [redacted]
Peer Reviewer:	
Date authorised:	29 November 2022 [Round 1] 10 January 2023 [Round 2] 17 February 2023 [Post ACV report]
RMP referral to ACV:	Not referred to ACV from RMS
Pharmacovigilance activities:	Routine Follow-up questionnaires Clinical Trial Observational Studies Other: Clinical study plan
Risk minimisation Activities	Routine Other: Risk minimisation measures implemented by the Australian/State Governments
Black Triangle Scheme:	Yes, provisional registration
PSUR review issues:	No

SUMMARY

- Moderna Australia Pty Ltd has applied to register a new biological entity, elasomeran/davesomeran (Spikevax Bivalent Original/ Omicron BA.4-5), through the Provisional Approval Pathway. Spikevax Bivalent Original/ Omicron BA.4-5, is proposed to be used as a booster dose for active immunisation to prevent coronavirus disease 2019 in individuals 6 years and older. The proposed dosing regimen involves one intramuscular injection of 0.5 ml (50 mcg), for individuals ≥ 12 years of age, or 0.25 ml (25 mcg), for individuals between 6 years and < 12 years of age, of elasomeran/ davesomeran, given at least 3 months following a primary series and/ or previous booster dose.

- Moderna Australia Pty Ltd has submitted EU-RMP version 6.1 (dated 30 October 2022; DLP 12 September 2022) and ASA version 1.0 (dated 22 November 2022) in support of this application.

- At round 2, sponsor has provided EU-RMP version 6.3 (dated 6 December 2022; DLP 17 September 2022) and ASA version 1.1 (dated 7 December 2022) and version 1.2 (dated 20 December 2022).

- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Myocarditis	✓[1]	✓[2]	✓	–
	Pericarditis	✓[1]	✓[2]	✓	–
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)	✓[1]	✓[2]	–	–
Missing information	Use in pregnancy and while breastfeeding	✓	✓[3]	✓	–
	Long-term safety	✓	✓[2]	–	–
	Use in immunocompromised subjects	✓	–	✓	–
	Interaction with other vaccines	✓	–	✓	–
	Use in frail subjects with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders)	✓	✓[2]	✓	–
	Use in subjects with autoimmune or inflammatory disorders	✓	✓[2]	✓	–

[1]Specific adverse reaction follow-up questionnaires
[2]Clinical trials
[3]Observational Studies – mRNA-1273-P905 and mRNA-1273-P919

- The summary of safety concerns is the same as that most recently evaluated and deemed acceptable for Spikevax Bivalent Original/ Omicron BA.1. This summary of safety concerns is acceptable from an RMP perspective.

- Sponsor has proposed routine pharmacovigilance for all safety concerns which includes specific adverse reaction follow-up questionnaires for the important identified and potential risks. Sponsor was requested to clarify the updates to the additional

pharmacovigilance activities in the ASA in the form of clinical trials and in the s31 response, has provided adequate justification for the changes. The pharmacovigilance plan is acceptable at round 2. A clinical study plan has been provided and the acceptability of this plan is for the Delegate to consider.

- Only routine risk minimisation measures are proposed by the sponsor. This approach was deemed acceptable during the previous evaluations as there are risk minimisation measures implemented by the Australian Government Department of Health. The changes proposed by the current submission are not expected to require additional risk minimisation measures as part of the RMP.

NEW AND OUTSTANDING RECOMMENDATIONS - ROUND 2

The recommendations made in the round 1 evaluation, along with consideration of the sponsor response, are located in Section 5.1 (Recommendations 1 to 4).

There are no outstanding or new recommendations for this submission.

Other advice to the Delegate

Diarrhoea and erythema multiforme have been removed as adverse reactions from the proposed Australian PI but remain in the SmPC. This discrepancy is raised to the attention of the Delegate for consideration.

No clinical and non-clinical evaluation reports are available for the RMP evaluator to incorporate into the Round 2 RMP evaluation report.

The delegate is expected to include the conditions of registration with regards to the clinical study plan.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The SPIKEVAX BIVALENT ORGINAL/ OMICRON BA.4-5 EU-Risk Management Plan (RMP) (version 6.3, dated 6 December 2022, data lock point 17 September 2022), with Australian Specific Annex (version 1.2, dated 20 December 2022), included with submission PM-2022-04824-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less*

frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of 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. Each report must have been prepared within ninety calendar days of the data lock point for that report.

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

As SPIKEVAX BIVALENT ORIGINAL/ OMICRON BA.4-5 is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

SPIKEVAX BIVALENT ORIGINAL/ OMICRON BA.4-5 (elasomeran/davesomeran to be included in the Black Triangle Scheme. The PI and CMI for SPIKEVAX BIVALENT ORIGINAL/ OMICRON BA.4-5 must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.

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MAIN BODY

1. BACKGROUND

Moderna Australia Pty Ltd has applied to register a new biological entity, elasomeran/davesomeran (Spikevax Bivalent Original/ Omicron BA.4-5), through the Provisional Approval Pathway. Spikevax Bivalent Original/ Omicron BA.4-5, is proposed to be used as a booster dose for active immunisation to prevent coronavirus disease 2019 in individuals 6 years and older. The proposed dosing regimen involves one intramuscular injection of 0.5 ml (50 mcg), for individuals > 12 years of age, or 0.25 ml (25 mcg) for individuals between 6 years and < 12 years of age, of elasomeran/ davesomeran, given at least 3 months following a primary series and/ or previous booster dose.

Moderna Australia Pty Ltd has submitted EU-RMP version 6.1 (dated 30 October 2022; DLP 12 September 2022) and ASA version 1.0 (dated 22 November 2022) in support of this application.

At round 2, sponsor has provided EU-RMP version 6.3 (dated 6 December 2022; DLP 17 September 2022) and ASA version 1.1 (dated 7 December 2022) and version 1.2 (dated 20 December 2022).

1.1. INDICATION

The proposed indication is:

> As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals ~~6~~ 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Post ACV, the proposed indication has been updated to increase the age limit from 6 to 12 years as stated above, in line with advice from ACV and requested by the Delegate.

The following information on the emergence of the omicron variant in Australia has been provided in the ASA[1]:

> Since the emergence of the Omicron variant in Australia, there have been three distinct waves of transmission. In early July 2022, BA.5 (including sub-lineages) became the predominant subvariant in Australia which was responsible for the third wave of transmission and peaked in the week ending 24 July 2022. After that, cases continued to decrease and at the end of August 2022, became the lowest observed since December 2021. Importantly, case numbers reported since January 2022 are an underestimate due to probable cases not being systematically reported from all jurisdictions.
>
> As at 26 October 2022, there have been 10,332,884 total confirmed cases of COVID-19 and 14,853 total deaths in Australia reported to WHO.
>
> In Australia, as at 28 October 2022, there were 7 provisionally approved vaccines against COVID-19 and 5 of these were in use in Australia.

[1] ASA version 1.0 (dated 22 November 2022).

1.2. DOSAGE AND ADMINISTRATION

Intramuscular injection of 0.5 ml (for individuals 12 years and older) or one dose of 0.25 ml (for individuals 6 years to < 12 years) of elasomeran/ davesomeran given at least 3 months following a primary series and/or previous booster dose with Spikevax (original), Spikevax Bivalent (original/Omicron BA.1) or another approved COVID-19 vaccine.

It is noted that the pre-filled syringe contains a dose of 0.5ml and the PI states that this cannot be used to administer a partial dose of 0.25ml.

See proposed PI for more details.

1.3. OVERSEAS REGULATORY STATUS

Sponsor states that Spikevax Bivalent Original/ Omicron BA.4-5, was approved under Emergency Use Authorisation in the USA on 31 August 2022 for use in individuals 18 years of age and older and on 12 October 2022 for use in individuals 6 years to <18 years of age. It is noted that the proposed indication for Australia is for use in individuals 6 years of age and older, similar to that approved in the USA.

Spikevax Bivalent (Original/ Omicron BA.4-5), has been approved in Canada and Japan for use in individuals 18 years of age and older on 4 November 2022 and 1 November 2022 respectively.

In the EU, positive EC decision was received on 20 October 2022 for use in individuals 12 years and older.

1.4. QUALITY OF THE SUBMISSION

EU-RMP and ASA provided are in the recommended format and these are acceptable for evaluation.

2. SAFETY SPECIFICATION

2.1. NONCLINICAL ADVICE ON SAFETY SPECIFICATION

The Toxicology area of the Scientific Evaluation Branch (SEB) of the TGA is assessing the nonclinical section of the RMP. This evaluation will further inform the adequacy and completeness of the summary of the safety concerns as specified by the sponsor.

The sponsor should be aware that safety considerations may be raised by the nonclinical evaluator through the consolidated section 31 request and/or the nonclinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

2.2. CLINICAL ADVICE ON SAFETY SPECIFICATION

The Prescription Medicines Authorisation Branch (PMAB) of the TGA is assessing this section of the RMP. This evaluation will further inform the adequacy and completeness of the summary of the safety concerns as specified by the sponsor.

The sponsor should be aware that safety considerations may be raised by the clinical evaluator through the consolidated section 31 request and/or the clinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

2.3. PROPOSED SUMMARY OF SAFETY CONCERNS - ROUND 1

The sponsor has proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	Myocarditis
	Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding
	Long-term safety
	Use in immunocompromised subjects
	Interaction with other vaccines
	Use in frail subjects with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	Use in subjects with autoimmune or inflammatory disorders

The above summary of safety concerns is the same as that most recently evaluated and deemed acceptable for Spikevax Bivalent Original/ Omicron BA.1. This summary of safety concerns continues to be acceptable from an RMP perspective.

2.4. SUMMARY OF KEY CHANGES TO SAFETY SPECIFICATION - ROUND 2

No changes to the summary of safety concerns were requested and sponsor has not proposed any updates. Summary of safety concerns continues to be acceptable from an RMP perspective.

3. PHARMACOVIGILANCE PLAN

3.1. PROPOSED PHARMACOVIGILANCE PLAN – ROUND 1

The sponsor has proposed routine pharmacovigilance for all safety concerns. This includes specific adverse reaction follow-up questionnaires:

- COVID-19/Vaccine failure Questionnaire - for the risk of 'Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)'.
- Myocarditis/ Pericarditis Questionnaire – for the risks of 'Myocarditis' and 'Pericarditis'.

Table 3 in the ASA lists Ongoing and planned additional pharmacovigilance activities.

Since the last evaluation, study 20-0003 and mRNA-1273-P201 have been completed and removed from the ASA. This is acceptable.

It is noted that mRNA-1273-P301, mRNA-1273-P901 and mRNA-1273-P304 have been removed from the ASA but continue to be included in the EU-RMP.

Clinical study plan has been provided. The acceptability of this plan is for the Delegate to consider.

Spikevax Bivalent Original/ Omicron BA.4-5 contains a new biological entity for which the safety and efficacy is yet to be fully characterised. As such, the sponsor should note that monthly summary safety reports, for the first 6 months post registration and thereafter at intervals specified by the TGA, will be included as a condition of registration.

3.2. ADEQUACY OF PROPOSED PHARMACOVIGILANCE PLAN

The proposed pharmacovigilance plan is as above. The specific adverse reaction follow-up questionnaires were found to be acceptable during previous evaluations and continue to be acceptable for this product.

The pharmacovigilance plan has been evaluated during the previous evaluations of Spikevax (monovalent) vaccine and Spikevax Bivalent Original/ Omicron BA.1. The following changes have been made to the plan:

- study 20-0003 and mRNA-1273-P201 have been completed and removed from the ASA. This is acceptable.
- In section 3.2 of the ASA, sponsor states that there are no differences in the additional pharmacovigilance activities in the EU-RMP and ASA. However, mRNA-1273-P301, mRNA-1273-P901 and mRNA-1273-P304 have been removed from the ASA but continue to be included in the EU-RMP. Sponsor is requested to provide justification for this discrepancy.

3.3. PLANNED STUDIES

Planned studies have not been updated since the previous evaluation. See Table 3 in the ASA for the list Ongoing and planned additional pharmacovigilance activities.

3.4. SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN - ROUND 2

In the s31 response, sponsor states that mRNA-1273-P301, mRNA-1273-P901 and mRNA-1273-P304 have been removed from ASA as these do not pertain to Spikevax Bivalent Original/ Omicron BA.4-5. Sponsor's justification is acceptable. At round 2, the pharmacovigilance plan is acceptable from an RMP perspective.

Sponsor has updated the information on the requirement for SSR in the ASA. This is acceptable.

It is noted that the clinical study plan has been updated with changes to the study status for a completed milestone. This is raised to the Delegates notice as the final acceptability of the clinical study plan is for the Delegate to consider.

4. RISK MINIMISATION PLAN

4.1. PLANNED RISK MINIMISATION ACTIVITIES - ROUND 1

Only routine risk minimisation measures have been proposed, similar to the Spikevax monovalent vaccine and Spikevax Bivalent Original/ Omicron BA.1.

4.1.1. Product labelling

4.1.1.1. Product Information

Diarrhoea and erythema multiforme have been removed as adverse reactions from the proposed Australian PI but remain in the SmPC. This discrepancy is raised to the attention of the Delegate for consideration.

Spikevax Bivalent Original/ Omicron BA.4-5, contains a new biological entity, and as such meets the inclusion criteria for the Black Triangle Scheme. The Black Triangle symbol and statement have been correctly added to the top of the first page of the PI. This is acceptable.

As a provisionally registered vaccine, the sponsor has included a statement in the PI explaining that the vaccine and indication are provisional. This is acceptable from an RMP perspective.

4.1.1.2. Consumer medicine information

The proposed CMI should be amended in line with any changes to the PI.

The Black Triangle symbol and statement have been correctly added to the top of the first page of the CMI. This is acceptable.

As a provisionally registered vaccine, the sponsor has correctly included a statement in the CMI explaining that the vaccine and indication are provisional. This is acceptable.

Sponsor is recommended to combine the information in paragraphs 1 and 2 in section 2 of the summary page, to limit the summary page to one page.

4.1.2. Additional risk minimisation activities

Currently there are no additional risk minimisation measures implemented by the sponsor for the Spikevax monovalent vaccine or for Spikevax Bivalent Original/ Omicron BA.1. There are risk minimisation measures implemented for COVID-19 vaccines by the Department of Health and Aged Care and State Governments. The introduction of this bivalent vaccine is not expected to require additional risk minimisation measures as part of the RMP.

4.1.3. Evaluation of effectiveness of additional risk minimisation activities

As there are no additional risk minimisation measures for this product, this section is not applicable for this submission.

4.2. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN - ROUND 2

At round 2 sponsor has updated ASA stating that the proposed PI will contain information on the risk of use in frail subjects with unstable health conditions and co-morbidities. This approach is acceptable.

In the s31 response sponsor has also provided assurance that CMI will be updated in line with any changes to PI and that the summary page of the CMI will be reduced to one page. This is acceptable.

4.3. SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN – POST ACV

After round 2, sponsor has provided an amended CMI in line with the response to recommendation 3 and 4 (see section 5.1 of this report for the commitment and the updated CMI with sponsor's response is in TRIM: D23-5092076). CMI is acceptable.

Both draft PI and CMI have been updated in line with updated indication to increase age limit from 6 to 12 years. This is acceptable.

5. ROUND 2 EVALUATION

5.1. RECONCILIATION OF ROUND 1 RECOMMENDATIONS

Sponsor response is in TRIM: D22-6232156

Recommendation 1: Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
Sponsor's response: The Sponsor will address any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications in a revised Australian RMP/Australia-Specific Annex.
RMP evaluator comment: Sponsor's response is noted.
Recommendation 2: In section 3.2 of the ASA, sponsor states that there are no differences in the additional pharmacovigilance activities in the EU-RMP and ASA. However, mRNA-1273-P301, mRNA-1273-P901 and mRNA-1273-P304 have been removed from the ASA but continue to be included the EU-RMP. Sponsor is requested to provide justification for this discrepancy.
Sponsor's response: Whilst ASA v1.0 covers Spikevax Bivalent Original/Omicron BA.4-5 only, it is aligned with EU-RMP v6.1 which includes information for Spikevax, Spikevax Bivalent Original/Omicron BA.1 and Spikevax Bivalent Original/Omicron BA.4-5. In the ASA, studies mRNA-1273-P301, mRNA-1273-P901 and mRNA-1273-P304 have not been included as additional pharmacovigilance activities since the objectives of these studies do not currently include, or are planned to include, the evaluation of the safety, reactogenicity or effectiveness of Spikevax Bivalent Original/Omicron BA.4-5 (mRNA-1273.222).
RMP evaluator comment: Sponsor's justification is acceptable.
Recommendation 3: The proposed CMI should be amended in line with any changes to the PI.
Sponsor's response: The Sponsor will amend the proposed CMI in line with any changes to the PI that impact the CMI.
RMP evaluator comment: Sponsor's commitment is noted.
Recommendation 4: In the CMI, sponsor is recommended to combine the information in paragraphs 1 and 2 in section 2 of the summary page, to limit the summary page to one page.
Sponsor's response: The Sponsor will consider combining relevant information in the CMI to limit the summary page to one page. An updated CMI will be provided after the clinical evaluation.
RMP evaluator comment: Sponsor's commitment is noted.

5.2. ACV ADVICE

The ACV advised that extension of the indication to individuals 6 years and older was not supported while acknowledging there is a limited but unmet need for a booster dose in the 6–12 year group. The ACV advised that there were insufficient data, including no immunogenicity data, presented by the sponsor to support use in the 6-12 years age group.

Minutes from the ACV is in TRIM: D23-5121140

The proposed indication has been updated to increase the age limit from 6 to 12 years as per the request from Delegate and advice from ACV. The proposed indication is:

> SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5 (elasomeran/davesomeran) COVID-19 Vaccine has **provisional approval** for the indication below:
>
> As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.
>
> The use of this vaccine should be in accordance with official recommendations.
>
> The decision has been made on the basis of immunogenicity and short-term safety data. Continued approval depends on the evidence of longer-term benefits and safety from ongoing clinical trials and post-market assessment.

APPENDIX 1 – LIST OF ACRONYMS

AE	Adverse Event
ACM	Advisory Committee on Medicines
ASA	Australian Specific Annex
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
PI	Product Information
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
SEB	Scientific Evaluation Branch
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration
USA	United States of America
VAED	Vaccine-associated enhanced disease (VAED)
VAERD	Vaccine associated enhanced respiratory disease (VAERD)

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: tozinameran and famtozinameran

Product name: COMIRNATY Original/Omicron BA.4-5 COVID-19 VACCINE

Sponsor: Pfizer Australia Pty Ltd

Submission number: PM-2022-05306-1-2

eSubmission number: e006875 (0000)

Date of first round report: 9/01/2023

Date of second round report: 16/02/2023

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 Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, 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>.

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List of abbreviations

Abbreviation	Meaning
ACIP	Advisory Committee on Immunization Practices
ACV	TGA's Advisory Committee for Vaccines
AE	adverse event
AESI	adverse event of special interest
anti-N	anti-nucleocapsid protein
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ATC	anatomical therapeutic chemical
aVE	absolute vaccine effectiveness
B.1.1.529	the Omicron variant of SARS-CoV-2
B.1.1.7	the Alpha variant of SARS-CoV-2
B.1.617.2	the Delta variant of SARS-CoV-2
BMI	body mass index
BNT162b2 30 µg	used interchangeably with the tradename COMIRNATY Original
BNT162b2 bivalent (WT/OMI BA.1) 30 µg	used interchangeably with COMIRNATY Original/Omicron BA.1
BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg	used interchangeably with COMIRNATY Original/Omicron BA.4-5
BNT162b2 OMI	where sublineage not specified, this refers to Omicron modified vaccine BNT162b2 OMICRON (B.1.1.529) BA.1
BNT162b2 OMI BA.1	Omicron modified vaccine BNT162b2 OMICRON (B.1.1.529) BA.1
BNT162b2 OMI BA.4/BA.5	Omicron modified vaccine BNT162b2 OMICRON (B.1.1.529) BA.4/BA.5
$BNT162b2_{SA}$	the beta variant vaccine formulation of BNT162b2

Abbreviation	Meaning
CDC	United States Centers for Disease Control and Prevention
CER	clinical evaluation report
CI	confidence interval
CMI	consumer medicines information
CMS	Center's for Medicare & Medicaid Services
CO	Clinical Overview
COMIRNATY Original/Omicron BA.1	used interchangeably with BNT162b2 bivalent (WT/OMI BA.1) 30 µg
COMIRNATY Original/Omicron BA.4-5	used interchangeably with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg
COVID-19	coronavirus disease 2019
CRF	case record form
CSR	clinical study report
DCO	data cutoff
DNA	deoxyribonucleic acid
eCTD	electronic common technical document
ED	emergency department
e-diary	electronic diary
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EU	European Union
EUA	emergency use authorization
EvQ	Evaluator's question
FDA	US Food and Drug Administration
FFRNT	fluorescent focus reduction neutralization test
GCP	good clinical practice

Abbreviation	Meaning
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titre
HIV	human immunodeficiency virus
ICATT	Increasing Community Access to Testing program (USA)
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular
IP	investigational product
IRC	internal review committee
IRT	interactive response technology
ITT	intention to treat
LLOQ	lower limit of quantitation
LNP	liquid nanoparticle
MEC	minor editorial change
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A/MIS-C	multisystem inflammatory syndrome in adults/children
mITT	modified intention to treat
mRNA	messenger ribonucleic acid
N	SARS-CoV-2 nucleoprotein
NAAT	nucleic acid amplification test
NIAID	National Institute of Allergy and Infectious Diseases
NT	neutralising titre
NT50	50% neutralising titre

Abbreviation	Meaning
OMI	Omicron
OMI BA.4/BA.5	Omicron B.1.1.529 sublineage BA.4/BA.5
OR	odds ratio
P2 S	SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein
PCR	polymerase chain reaction
PD	protocol deviation
PI	product information
PRNT	plaque reduction neutralisation test
PSUR	periodic safety update report
PT	preferred term for an adverse event using the MedDRA classification
RAT	rapid antigen test
reference strain	wild type or ancestral strain (Wuhan-Hu-1; USA WA1/2020)
RMP	risk management program
RNA	ribonucleic acid
rVE	relative vaccine effectiveness
RWE	real world evidence
S glycoprotein, S	spike glycoprotein
SA	South African
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SmPC	summary of product characteristics
SMQ	standardised MedDRA queries

Abbreviation	Meaning
SOC	system organ class for an adverse event using the MedDRA classification
SSD	substudy D
SSE	substudy E
TGA	Therapeutic Goods Administration
Tris	tris(hydroxymethyl)aminomethane
UC	urgent care
US/USA	United States of America
VAED	vaccine-associated enhanced disease
VAERD	vaccine enhance respiratory disease
VE	vaccine effectiveness
VOC	variant of concern
VSD	Vaccine Safety Datalink
WHO	World Health Organization
WT	wild type or ancestral strain (Wuhan-Hu-1; USA WA1/2020), also called reference strain
YOA	years of age

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Figure 24. Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.617.2) - Reactogenicity Set – Part 2....162

1. Submission details

1.1. Identifying information

Submission number	PM-2022-05306-1-2
eSubmission number	e006875
eSubmission sequences covered in this report	0000-0003, 0005
Sponsor	Pfizer Australia Pty Ltd
Trade name	COMIRNATY Original/Omicron BA.4-5 COVID-19 VACCINE
Active substance	tozinameran and famtozinameran

1.2. Submission type

Category 1 type A (i.e. 'new chemical/biological entity' to provisionally register the new active substance famtozinameran) AND Category 1 type B (i.e. 'new fixed combination medicine' of the previously provisionally registered active substance tozinameran with famtozinameran).

This is an eCTD submission. The new PI is substantially based on the existing PI for the Sponsor's existing bivalent COVID-19 vaccine (i.e. COMIRNATY Original/Omicron BA.1 [tozinameran and riltozinameran]) and has been annotated to reflect the substitution of famtozinameran into the new fixed combination vaccine, including with pertinent safety and immunogenicity data.

Evaluator's comments: The submission types A and B are appropriate.

1.3. Drug class and therapeutic indication

COMIRNATY Original/Omicron BA.4-5 is a COVID-19 vaccine that contains mRNA encapsulated in lipid nanoparticles and belongs to the WHO ATC groups: Vaccines; Viral vaccines; Other viral vaccines; COVID-19 vaccines (ATC code J07BX03). It induces active immunity to the spike protein of SARS-CoV-2, which is the virus that causes COVID-19.

The newly proposed vaccine is a fixed combination product that is bivalent (i.e. in containing active substances of the mRNAs encoding spike proteins for the reference strain of SARS-CoV-2 as well PLUS the Omicron BA.4/5 sublineage of the Omicron variant of concern). This is similar in concept to the Sponsor's existing bivalent vaccine COMIRNATY Original/Omicron BA.1 (active substances tozinameran and riltozinameran). It has the same total dose of 30 μg mRNA that is present in the monovalent COMIRNATY original (i.e. BNT162b2) and COMIRNATY Original/Omicron BA.1.

The proposed therapeutic indication is the same as for COMIRNATY Original/Omicron BA.1 but with a lower age limit (i.e. ≥ 12 YOA for COMIRNATY Original/Omicron BA.4-5 vs ≥ 18 YOA for COMIRNATY Original/Omicron BA.1):

4.1 Therapeutic indications

COMIRNATY Original/Omicron BA.4/BA.5 Vaccine has **provisional approval** for the indication below:

As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.

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

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

Source: Module 1.3.1.2, Product information – annotated

Evaluator's comments: The COMIRNATY Original/Omicron BA.4-5 vaccine appears very similar to the Sponsor's previously provisionally approved COMIRNATY Original/Omicron BA.1 vaccine; however, they are seeking a lower age limit of ≥ 12 YOA compared to ≥ 18 YOA respectively.

1.4. Dosage forms and strengths

COMIRNATY Original/Omicron BA.4-5 is presented in a 2 mL clear multidose vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal. There are 2 pack sizes, 10 vials and 195 vials.

Each vial (2.25 mL of product) contains 6 doses of 0.3 mL. One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of famtozinameran (embedded in lipid nanoparticles).

1.5. Dosage and administration

The proposed dosage is presented in the PI as follows:

4.2 Dose and method of administration

Dosage

Booster dose in individuals 12 years of age and older

A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older.

COMIRNATY Original/Omicron BA.4-5 may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another COVID-19 vaccine.

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

Source: Module 1.3.1.2, Product information - annotated

Each 0.3 mL dose contains 15 µg of tozinameran and 15 µg of famtozinameran, making a total **dosage** of 30 µg of the active substances. This is similar to the 15 µg of tozinameran and 15 µg of riltozinameran that constitute each provisionally registered dose of COMIRNATY Original/Omicron BA.1. It is also similar to the 30 µg of tozinameran that constitutes each provisionally registered dose of COMIRNATY Original.

'COMIRNATY Original/Omicron BA.4-5 should be **administered** intramuscularly. The preferred site of administration is the deltoid muscle of the upper arm.'

Evaluator's comments: The dosage aspects (including the total dose of 30 µg mRNA) are very similar to the Sponsor's 2 previous vaccines that have been provisionally approved (i.e. COMIRNATY Original and COMIRNATY Original/Omicron BA.1).

There is some confusion created by potentially contradictory advice in the first 2 paragraphs in this section of the PI. The first paragraph allows for administration of COMIRNATY Original/Omicron BA.4-5 as a booster to individuals ≥ 12 YOA who have previously received '…a COVID-19 vaccine primary series…' and is agnostic to the type of vaccine previously received, whether BNT162b2 30 µg or another vaccine; however, the second paragraph appears to restrict COMIRNATY Original/Omicron BA.4-5 to individuals ≥ 18 YOA where that primary series was '…another COVID-19 vaccine.', which would potentially include BNT162b2 30 µg as well as other Sponsors' vaccines. There is no comment about administration of COMIRNATY Original/Omicron BA.4-5 to individuals who have previously received a booster, which is now a sizeable proportion of the Australian population. The Evaluator would like this clarified.

EvQset3: In the proposed PI section '**4.2 Dose and method of administration / Dosage / Booster dose in individuals**', the first paragraph facilitates administration of COMIRNATY Original/Omicron BA.4-5 as a booster to individuals ≥ 12 YOA who have previously received '…a COVID-19 vaccine primary series…' and is agnostic to the type of vaccine previously received, whether BNT162b2 30 µg or another vaccine. However, the second paragraph appears to restrict COMIRNATY Original/Omicron BA.4-5 to individuals ≥ 18 YOA where that primary series was '…another COVID-19 vaccine.', which would potentially include primary series of BNT162b2 30 µg as well as other Sponsors' vaccines. There is no advice regarding use of COMIRNATY Original/Omicron BA.4-5 after a previous booster dose. The CMI is worded similarly. In contrast, the advice provided from the US EUA amendment (Module 1.11.1) states clearly that 'Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in individuals 12 years of age and older as a single booster dose administered at least 2 months after either: completion of primary vaccination with any authorized or approved monovalent1 COVID-19 vaccine, or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.' Please rewrite this section of the PI (and corresponding sections of the CMI) so it is clear what the intentions are in relation to: (1) lower age limit(s) and whether they differ in different circumstances; (2) the use of COMIRNATY Original/Omicron BA.4-5 after booster vaccination; (3) the type of vaccine previously administered for the primary series and/or booster; (4) the time between the most recent dose of primary series or booster and the booster dose of COMIRNATY Original/Omicron BA.4-5.

1.6. Proposed changes to the product documentation

The proposed PI is most similar to the existing PI for COMIRNATY Original/Omicron BA.1.[1] The main differences include vaccine-specific sections in relation to the headings/subheadings:

- Qualitative and quantitative composition.
- Summary of safety profile.

[1] Version: pfpcodii11122, date of first approval 28/10/2022, last updated 14/11/2022.

- Immunogenicity.

Of note, two updates made to the latest version of the PI for COMIRNATY Original/Omicron BA.1 in relation to post-marketing experience (i.e. non-sexually acquired genital ulceration and dizziness) have been included in the proposed PI for COMIRNATY Original/Omicron BA.4-5. An update was also made in relation to a safety update on 'Myocarditis and pericarditis' and the PI for COMIRNATY Original/Omicron BA.1 includes a statement:

> 'The risk of myocarditis after a booster dose of COMIRNATY or COMIRNATY Original/Omicron BA.1 has not yet been characterised.'

A similar statement *does not* appear in the proposed PI for COMIRNATY Original/Omicron BA.4-5.

Evaluator's comments: The Evaluator notes the general consistency between the proposed PI for COMIRNATY Original/Omicron BA.4-5 and the existing PI for COMIRNATY Original/Omicron BA.1; however, is unclear why the statement about myocarditis risk (that was quoted above) has been deleted. This is further addressed in section 11.1.

2. Background

2.1. Information on the condition being treated

COVID-19 is the disease caused by infection with the pandemic virus SARS-CoV-2, which was first recognised internationally in late 2019 and in Australia by early 2020. It is manifest by respiratory, systemic and other organ-related manifestations.

Disease severity is mainly related to respiratory manifestations and increases with age. Mortality in unvaccinated individuals with untreated disease is rare in childhood but increases steeply beyond 60 years of age.

In the absence of highly effective prophylactic or therapeutic medicines, active immunisation through vaccination represents the best means of preventing hospitalisation and deaths at an individual level and controlling the pandemic at a societal level.

Emerging mutated SARS-CoV-2 variants of concern pose challenges for current vaccination strategies, which until recently had been based on inducing immunity to the non-mutated spike protein that was sequenced in the original wild-type virus.

2.2. Current treatment options

Provisionally approved treatments for COVID-19 are shown in Table 1.

Table 1. COVID-19 treatments that have been provisionally approved by the TGA

Effective date	Sponsor	Name
a. 24 February 2022	AstraZeneca Pty Ltd	tixagevimab and cilgavimab (EVUSHELD) a. For pre-exposure prophylaxis in individuals 12 years and over
18 January 2022	Merck Sharp & Dohme (Australia) Pty Ltd	molnupiravir (LAGEVRIO)
18 January 2022	Pfizer Australia Pty Ltd	nirmatrelvir + ritonavir (PAXLOVID)
6 December 2021	Celltrion Healthcare Australia Pty Ltd	regdanvimab (REGKIRONA)
1 December 2021	Roche Products Pty Ltd	tocilizumab (ACTEMRA)
15 October 2021	Roche Products Pty Ltd	casirivimab + imdevimab (RONAPREVE)
20 August 2021	GlaxoSmithKline Australia Pty Ltd	Sotrovimab (XEVUDY)
a. 10 July 2020 b. 6 May 2022	Gilead Sciences Pty Ltd	remdesivir (VEKLURY) a. For treatment of COVID-19 in adults and adolescents (aged 12 years and weighing at least 40 kg) with pneumonia, requiring supplemental oxygen. b. For treatment of: • adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2, who require supplemental oxygen • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19

Source: Accessed from https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-registrations on 21/11/2022 (last updated 23/09/2022).

Provisionally approved vaccines for COVID-19 that are marketed in Australia by the Sponsor are shown in Table 2 and by other Sponsors in Table 47.

Of note, in relation to the current submission, the only vaccines provisionally approved as booster doses for individuals 12 to < 18 YOA are COMIRNATY (tozinameran) and SPIKEVAX (elasomeran). NUVAXOVID (NVX-CoV2373) is only approved in this age group for use in the primary series. Those 3 vaccines are based on the original wild-type strain of SARS-CoV-2.

There are 2 vaccines provisionally approved as booster doses for individuals ≥ 18 YOA that induce specific immunity to both the wild-type and Omicron BA.1 strain, COMIRNATY Original/Omicron BA.1 (tozinameran and riltozinameran) and SPIKEVAX Bivalent Original/Omicron (elasomeran and imelasomeran).

There are presently no provisionally approved vaccines designed to specifically induce active immunity to the spike protein of the Omicron BA.4/5 spike protein.

Table 2. Sponsor's related COVID-19 vaccines that have been provisionally approved by the TGA

Effective date	Sponsor	Name	Type
a. 25 January 2021 b. 22 July 2021 c. 26 October 2021 d. 3 December 2021 e. 27 January 2022 f. 7 April 2022 g. 20 September 2022 h. 29 September 2022	Pfizer Australia Pty Ltd	COMIRNATY (tozinameran) a. For individuals aged 16 years and over b. For individuals aged 12 years and over c. Booster dose for individuals aged 18 years and over d. For individuals aged 5 years and over e. Booster dose for individuals aged 16-17 years old f. Booster dose for individuals aged 12-15 years old g. Booster dose for individuals aged 5-11 years old h. For individuals aged 6 months and over	mRNA
27 October 2022	Pfizer Australia Pty Ltd	COMIRNATY Original/Omicron BA.1 (tozinameran and riltozinameran) Booster dose for individuals aged 18 years and over	mRNA

Source: Accessed from https://www.tga.gov.au/products/covid-19/covid-19-vaccines/covid-19-vaccine-provisional-registrations on 21/11/2022 (last updated 28/10/2022).

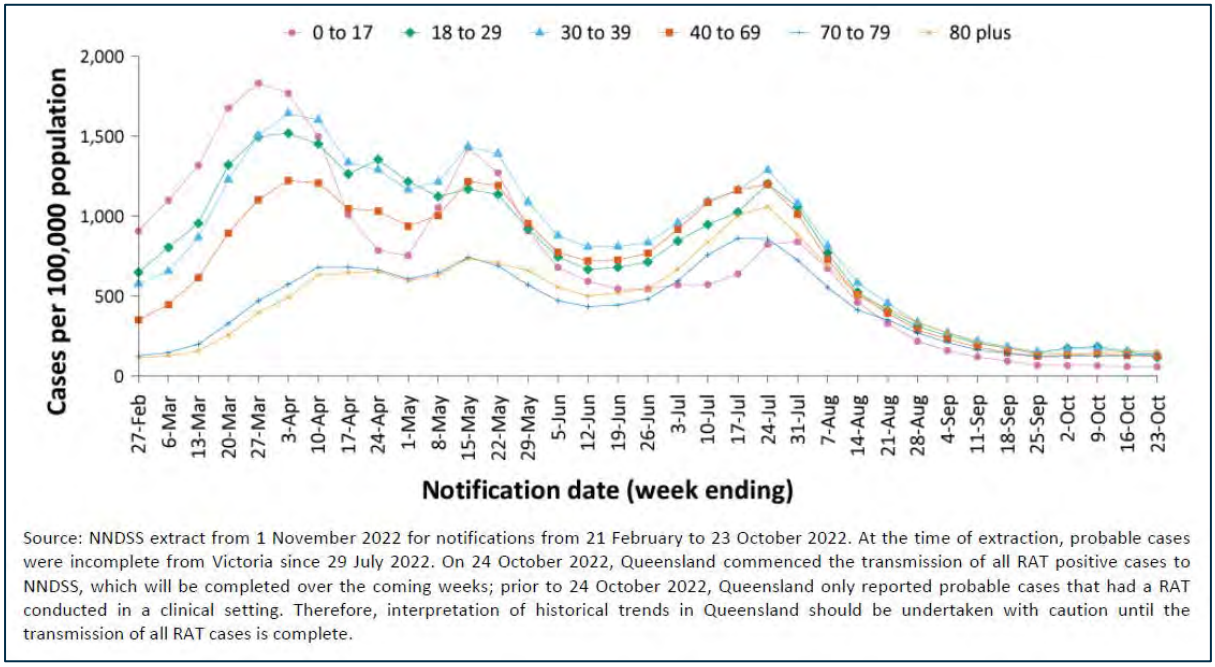
Evaluator's comments: There are currently no provisionally approved variant-specific vaccines available to adolescents 12-17 YOA. The only currently provisionally approved variant-specific vaccines for adults ≥ 18 YOA target Omicron BA.1 rather than the more recently observed Omicron BA.4/5 sublineages.

2.3. Clinical rationale

Real-world data (quoted by the Sponsor) '…have shown that after the initial booster dose of BNT162b2, in the presence of the now-predominant Omicron variant, vaccine effectiveness against symptomatic COVID-19 is lower and wanes more quickly post-Dose 3 compared to prior variants.' This has led the Sponsor to develop variant vaccine constructs, including the previously provisionally approved COMIRNATY Original/Omicron BA.1 vaccine and the present COMIRNATY Original/Omicron BA.4-5 vaccine.

The Sponsor has stated in the Cover Letter that there is an '…unmet need for the bivalent Omicron-modified vaccine in Australia…' and quoted data showing 4,636,110 PCR-confirmed and 4,332,525 RAT probable COVID-19 cases from 15/12/2021 through 23/10/2022 (i.e. Omicron era). Case rates for all age groups are shown in Figure 1.

Figure 1. PCR-confirmed and RAT probable COVID-19 case rates for all ages by week, Australia, 27 February – 23 October 2022

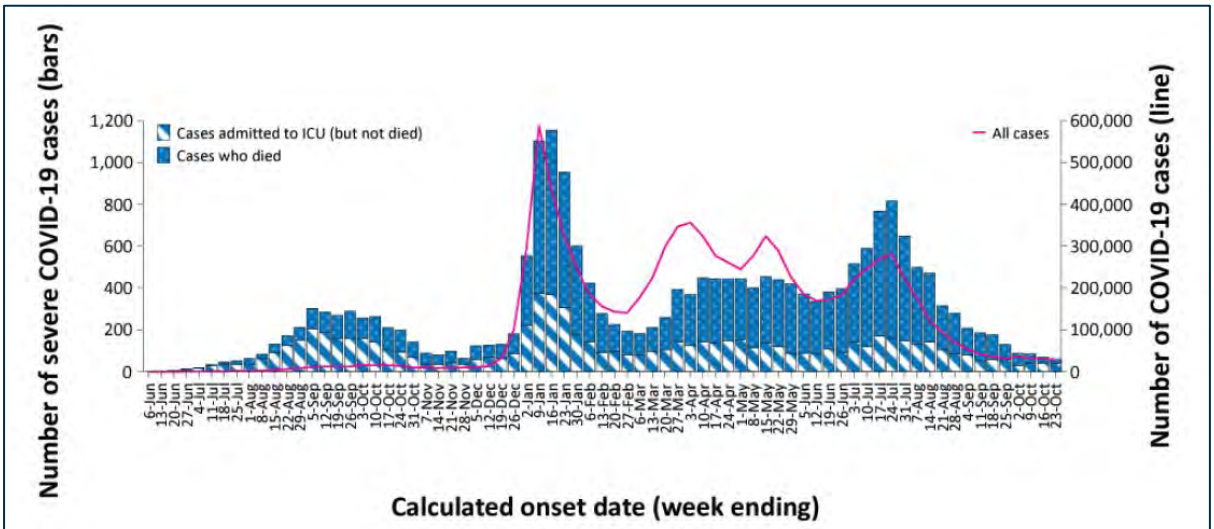


Source: NNDSS extract from 1 November 2022 for notifications from 21 February to 23 October 2022. At the time of extraction, probable cases were incomplete from Victoria since 29 July 2022. On 24 October 2022, Queensland commenced the transmission of all RAT positive cases to NNDSS, which will be completed over the coming weeks; prior to 24 October 2022, Queensland only reported probable cases that had a RAT conducted in a clinical setting. Therefore, interpretation of historical trends in Queensland should be undertaken with caution until the transmission of all RAT cases is complete.

Source: Module 1.0.1, Cover Letter.

The Sponsor also presented data showing ongoing occurrence of severe cases in Australia as shown in Figure 2. Further, 'During the Omicron wave to date, the overall notification rate of severe cases in Aboriginal and Torres Strait Islander people was 54.0 per 100,000 population, compared to 16.3 per 100,000 population during the Delta wave.'

Figure 2. COVID-19 cases, deaths and ICU admissions, Australia, by date of onset, Australia, 31 May 2021 to 23 October 2022



Source: NNDSS extract from 1 November 2022 for notifications to 23 October 2022. At the time of extraction, probable cases were incomplete from Victoria since 29 July 2022. On 24 October 2022, Queensland commenced the transmission of all RAT positive cases to NNDSS, which will be completed over the coming weeks; prior to 24 October 2022, Queensland only reported probable cases that had a RAT conducted in a clinical setting. Therefore, interpretation of historical trends in Queensland should be undertaken with caution until the transmission of all RAT cases is complete. The shaded bars at the right represent the most recent two reporting weeks and should be interpreted with caution, as cases with an illness onset in these weeks may not have yet developed severe disease.

Source: Module 1.0.1, Cover Letter.

In this context, the Sponsor has reasoned that:

> '…a variant-adapted vaccine that improves immune responses to currently circulating variants may help restore higher levels of protection against infection, and thus transmission, similar to that observed at earlier stages in the pandemic. Preventing infection may also help reduce long-term COVID-19 sequelae, and although effectiveness against omicron-related severe disease remains high in the general population among those who recently received a booster dose, the long-term durability of the vaccine against severe endpoints remains unknown and may be starting to wane in some high-risk populations. A variant-adapted vaccine administered would help ensure high levels of protection against severe illness.'

Evaluator's comments: The clinical rationale for a variant-specific COVID-19 vaccine targeting the Omicron BA.4/5 sublineage has been adequately established in the Australian context; however, it is unclear how long Omicron BA.4/5 may remain a prevalent circulating variant, noting the recent emergence of Omicron XBB.1.5 and other subvariants.

2.4. Formulation

2.4.1. Formulation development

COMIRNATY Original/Omicron BA.4-5 (tozinameran and famtozinameran) is a bivalent vaccine containing two active substances embedded in LNPs. Tozinameran comprises mRNA encoding the viral spike protein of wild-type SARS-CoV-2 ('Original'). Famtozinameran comprises mRNA encoding the viral spike protein of the Omicron BA.4/5 subtype of SARS-CoV-2 ('Omicron BA.4/5'). Both are produced using a cell-free *in vitro* transcription method from the

corresponding DNA templates. The active substances are mixed in a 1:1 ratio prior to the LNP formation and stabilisation step.

Each dose of 30 µg mRNA contains 15 µg of each active ingredient in a 0.3 mL injection volume. It is manufactured using identical methods as for the original vaccine, at previously authorised/licensed Pfizer/BioNTech sites.

It is formulated in a Tris/Sucrose buffer as per the original COMIRNATY vaccine and the Sponsor has confirmed there are no expected changes to the physiochemical properties or stability.

2.4.2. Excipients

- ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
- 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
- 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
- cholesterol
- trometamol
- trometamol hydrochloride
- sucrose
- water for injections.

Evaluator's comments: The COMIRNATY Original/Omicron BA.4-5 vaccine appears to differ from the COMIRNATY Original/Omicron BA.1 vaccine in the mRNA sequence for the sublineage-specific spike protein. The size of the mRNA transcript and/or LNP could potentially vary between vaccines and lead to different clinical characteristics. This will likely be further assessed by the non-clinical evaluators.

2.5. Regulatory history

2.5.1. Australian regulatory history

COMIRNATY (tozinameran) was first included on the register (provisional registration) on 25/01/2021 (ARTG ID 346290), for primary vaccination of individuals ≥ 16 YOA. Key dates in the subsequent rollout of COMIRNATY to other age groups and for booster doses is shown in Table 2.

The newly formulated variant vaccine COMIRNATY Original/Omicron BA.1 (tozinameran and riltozinameran) was included on the register on 28/10/2022 (ARTG ID 394890).

2.5.2. Orphan drug designation

Not applicable.

2.5.3. Related submissions

Not applicable.

2.5.4. Overseas regulatory history

In relation to COMIRNATY Original, the Sponsor has advised that, 'At present, BNT162b2 has received temporary authorization for emergency use, conditional marketing authorization approval, or full approval in more than 100 countries globally.'

A summary of applications for registration of COMIRNATY Original/Omicron BA.4-5 in other jurisdictions was presented by the Sponsor in Module 1.1.11, Foreign Regulatory Status as shown in Table 3. The Sponsor stated that, 'A similar applications [sic] has not been deferred, withdrawn or rejected in any of the below countries/jurisdictions.'

Table 3. Foreign Regulatory Status of COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran) COVID-19 Vaccine

Country/Jurisdiction	Submission Date	Status	Approved Indications
United States of America	Only Quality and non-clinical data submitted to FDA for EUA amendment	EUA Amendment: 31 Aug 2022 and 12 Oct 2022	Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in individuals 12 years of age and older as a single booster dose administered at least 2 months after either: • completion of primary vaccination with any authorized or approved monovalent1 COVID-19 vaccine, or • receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.
European Union (centralised procedure)	Only Quality and non-clinical data submitted to EMA	Approved: 12 Sept 2022	Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1). The use of this vaccine should be in accordance with official recommendations.
New Zealand	3 October 2022 Initial submission included only Quality and non-clinical data. Rolling submission of clinical data.	Under evaluation	-
Canada	Rolling submission from 2 Sept 2022	Approved: 7 Oct 2022	The Pfizer-BioNTech Comirnaty Original and Omicron BA.4/BA.5, bivalent COVID-19 vaccine is approved as a booster for people who are 12 years of age and older. Its safety and effectiveness in younger people has not yet been established.
Singapore	1 Sept 2022 Submission based on US EUA	Approved: 11 Oct 2022	Per US EUA
Switzerland	15 Sept 2022 Initial submission included only Quality and non-clinical data. Rolling submission of clinical data.	Under evaluation	-

Source: Module 1.11.1, Foreign Regulatory Status. [1]Monovalent refers to any authorized or approved COVID-19 vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2.

By way of update, the Sponsor advised that, 'On 10 November 2022, the 10 µg dose of the COMIRNATY Original/Omicron BA.4-5 vaccine was approved for use in individuals 5 through 11 years of age by the **EMA**.'

Evaluator's comments: The Evaluator notes that the initial approvals in the USA and EU were given prior to the availability of specific immunogenicity data for COMIRNATY Original/Omicron BA.4-5 or reporting of specific reactogenicity or safety outcomes (earliest DCO for those data was 12/09/2022).

2.6. Guidance

The evaluator referred to the following TGA guidance:

- Guidance 8: Product information.
- Form for providing product information.
- Reformatting product information: frequently asked questions.

The evaluator referred to the following TGA-adopted guidance:

- ACCESS Consortium: Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines (14/09/2021).
- ACCESS Consortium: Points to consider for strain changes in authorised COVID-19 vaccines in an ongoing SARS-CoV-2 pandemic (5/03/2021).
- ACCESS Consortium: Access consortium statement on COVID-19 vaccines evidence (4/12/2020).
- EMEA: Guidelines on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005) (18/10/2006).
- EMEA: Points to Consider on Applications with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99) (31/05/2002).
- EMEA: Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99) (27/07/2000).

The evaluator referred to the following additional guidance:

- US FDA: Emergency use authorization for vaccines to prevent COVID-19: guidance for industry (25/05/2021).
- WHO: Evaluation of COVID-19 vaccine effectiveness (interim guidance) (17 March 2021).
- EMA: EMA considerations on COVID-19 vaccine approval (EMA/592928/2020) (16/11/2020).
- US FDA: COVID-19: developing drugs and biological products for treatment or prevention: guidance for industry (February 2021).
- US FDA: Development and licensure of vaccines to prevent COVID-19: guidance for industry (June 2020).
- WHO: Guidelines on clinical evaluation of vaccines: regulatory expectations, Annex 9 (2017).
- US FDA: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: Guidance for Industry (September 2007).
- WHO: Design of vaccine efficacy trials to be used during public health emergencies – points of consideration and key principles (not dated).

2.7. Evaluator's commentary on the background information

The background information is satisfactory.

3. Contents of the clinical dossier

The initial eCTD submission was received on 15/12/2022 with a Cover Letter dated the same day. The Sponsor advised by email (D22-6232175) that, 'Due to timing of the eCTD sequence publishing, the following did not make it into the sequence.':

- 'Updated clinical data – full 18+ groups Immunogenicity (15/15 micrograms) emailed on 12 Dec 2022
- RMP ASA (v 0.7) emailed on 14 Dec 2022
- Section 14 exemption application emailed on 15 Dec 2022
- Response to query on 4 AE (still under preparation)'[2]

Evaluator's comments: The first, second and fourth of these documents are relevant to this CER and the Evaluator acknowledges that the first and second had been received in non-eCTD format among 4 tranches of documents leading up to the electronic submission (see section 3.1.4).

3.1. Scope of the clinical dossier

The following documents were those most relevant to the clinical evaluation.

3.1.1. Module 1 of the eCTD submission

- Cover letter.
- Application forms, pre-submission details and tracking table.
- Clean and annotated versions of the proposed PI and CMI.
- Label mock-ups and specimens.
- Risk management plan (i.e. Clinical study plan).
- Foreign regulatory status.
- Foreign product information (EU SmPC).
- Data similarities and differences.
    - Supportive studies submitted in this application included:[3]
        - Study C4591031 Substudy D.
        - Study C4591031 Substudy E (> 55 YOA).
        - Study C4591031 Substudy E (18-55 YOA).
        - Study C4591001.

3.1.2. Module 2 of the eCTD submission

- 2.3 Quality overall summary.
- 2.4 Non-clinical overview.
- 2.5 Clinical Overview:
    - COVID-19 Vaccine 2.5 Clinical Overview – Safety VOC Vaccines – MAA – August 2022, dated 15/08/2022.
    - Bivalent (Original/Omicron BA.4/BA.5) COVID-19 Vaccine (BNT162b2; PF-07302048): 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2, dated 23/11/2022.
    - Study C4591044 Cohort 2-Additional Variant Neutralization Data, dated 15/11/2022.

[2] This is in response to question 1 from clinical questions set no. 2 (see section 12.1.1.2).
[3] The Sponsor noted that, 'All of the supportive studies, except for one [i.e. C4591031 Substudy E (18-55 years], have already been evaluated by the TGA for the registration of Omicron BA.1 variant adapted bivalent vaccine.' The CER for that evaluation is available at Trim: D22-5946058.

  - Study C4591044 Cohort 2-7 Day Post Dose_Safety Data, dated 29/09/2022.
  - Study C4591044 Cohort 2-7 Day Post Dose_lmmunogenicity Data, dated 12/10/2022.
- 2.7.1. Summary of Biopharmaceutic studies and Associated Analytical Methods.

3.1.3. Module 5 of the eCTD submission

- 5.2 Tabular Listing of all Clinical Studies.
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.
- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.
  - CSRs (and associated documents) were included for Studies C4591001 (month 6), C4591031 (Substudy D and Substudy E; month 1).
  - Study C4591044 Cohort 2 was provided in the form of the associated Clinical Overviews listed in section 3.1.2 of the CER, along with safety and immunogenicity data bundles (i.e. tables, figures and other listings) in this Module of the electronic submission.

3.1.4. Non-eCTD only (Round 1 CER)

The following documents were provided in non-eCTD format prior to the eCTD submission but weren't provided in the initial eCTD submission and therefore weren't available prior to finalisation of the Round 1 CER:

- 'Study C4591044 Cohort 2- 1 Month Post Dose_lmmunogenicity Data-Groups 2 and 4-December 2022', dated 7/12/2022, received by email 12/12/2022.
- RMP ASA (Version: 0.7), received by email 14/12/2022.
- 2.5 Clinical Overview_VOC Safety Summary (Alpha and Delta Variant) -Omicron BA.4-BA.5 Modified Vaccine (C4591031 SSE)_MAA_August 2022, dated 24/08/2022.
- Document titled: 'AN INTERVENTIONAL, RANDOMIZED, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BIVALENT BNT162b RNA-BASED VACCINE CANDIDATES AS A BOOSTER DOSE IN COVID-19 VACCINE-EXPERIENCED HEALTHY INDIVIDUALS', dated 24/08/2022. Document name: 'C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022'.

These documents were subsequently provided in eCTD format prior to the completion of the Round 2 CER.

3.1.5. Round 2 CER

The following documents were provided first in non-eCTD format but subsequently in eCTD format between preparation of the Round 1 and Round 2 CERs:

- 1.3 Medicine information and labelling/
  - Product information – annotated (version: 'proposed-pi-ba45-16-Jan-23').
  - Consumer medicines information – annotated.
- 2.5 Clinical Overview.
  - Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years)_1MPD_lmmunogenicity Data.
  - Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_lmmunogenicity and Safety Data
- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.
  - Interim Report – Cohort 2 – 1-Month Analysis: An Interventional, Randomized, Active-controlled, Phase 2/3 Study to Investigate the Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals (including associated documents).

3.2. Paediatric data

The submission includes data to support used in adolescents 12-17 YOA but not in younger children. The Sponsor indicated that they have submitted a Paediatric Investigation Plan for the EU (first report due July 2024).

3.3. Good clinical practice

Each of the submitted Clinical Study Reports includes a statement that the study was conducted in compliance with good clinical practice guidelines.

3.4. Evaluator's commentary on the clinical dossier

Round 1 CER:

To facilitate rapid assessment of the submission, the Sponsor provided documents in advance of the eCTD submission (received on 15/12/2022) in non-eCTD format. By 19/12/2022, the Evaluator was still awaiting the formal electronic submission of those documents listed at the start of section 3 of this CER; however, notes they were previously made available in non-eCTD format. The Evaluator is also awaiting an updated version of the annotated proposed PI that includes immunogenicity data (and possibly some other data) that weren't included in the initial electronic submission or in non-eCTD format. The version of the proposed PI available on 19/12/2022 was not suitable for evaluation as it was incomplete and missing essential data; however, the Evaluator notes that the Sponsor has undertaken to make an update available as soon as possible (see section 11.1 and Table 65).

One document that was provided in non-eCTD format (listed in section 3.1.4) does not appear to be part of the formal submission and the Evaluator is unclear if it was intended to be evaluated as supportive data. **EvQset3**: The document titled, '2.5 Clinical Overview_VOC Safety Summary (Alpha and Delta Variant) -Omicron BA.4-BA.5 Modified Vaccine (C4591031 SSE)_MAA_August 2022', dated 24/08/2022, was provided in non-eCTD format along with the first tranche of data that were emailed to the TGA on 17/11/2022; however, the Evaluator could not locate it in the eCTD submission. Please clarify whether that document is intended to be part of the formal submission.

Notwithstanding the awaited update of the proposed PI and clarification of whether then Alpha and Delta Variant CO (above) is intended for evaluation, the Evaluator thought the eCTD and non-eCTD submissions (combined) were suitable and sufficient for evaluation.

Round 2 addendum:

The clinical dossier was satisfactory for evaluation.

4. Pharmacokinetics

Not applicable to vaccines.

5. Pharmacodynamics

The immunogenicity of COMIRNATY Original/Omicron BA.4-5

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

Not applicable.

6.2. Phase II dose finding studies

The dose of BNT162b2 30 µg that is provisionally approved for adolescents and adults in the primary series and as a booster dose is based on the Phase 1 component of Study C4591001 and available non-clinical data.

Study C4591044 Cohort 2 (Phase 2/3) investigates BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg as a second booster (i.e. 4th) dose in participants ≥ 12 YOA, and also 60 µg doses in participants ≥ 18 YOA only.

The higher dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg used in a subset of adults in Cohort 2 was informed by experience in a subset of Study C4591031 Substudy E participants who received BNT162b2 bivalent (WT/OMI BA.1) 60 µg as a 4th dose. Participants > 55 YOA from Substudy E who received monovalent or bivalent Omicron-modified BA.1 at the 60 µg dose experienced more reactogenicity than those at the 30 µg dose level.

6.3. Phase III pivotal studies investigating more than one dose regimen

Not applicable.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The choice of the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg dose across all ages ≥ 12 YOA is supported by previous experience with BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg. The addition of the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg dose is reasonable given the possibility that the 30 µg dose could be insufficient, and also that BNT162b2 bivalent (WT/OMI BA.1) 60 µg was reasonably tolerated in Study C4591031 Substudy E (albeit with higher reactogenicity in those > 55 YOA). Restricting the higher dose to adults only seems reasonable.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

7.2. Pivotal or main efficacy studies

7.2.1. Study C4591044: An Interventional, Randomized, Active-Controlled, Phase 2/3 Study To Investigate The Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals

The purpose of this study (Cohorts 2 and 3) is to evaluate the '…safety, tolerability, and immunogenicity of BNT162b2 bivalent (Original + Omicron BA.4/BA.5) vaccine in individuals ≥ 12 years of age.'

7.2.1.1. Study design, objectives, locations and dates

Design

Study C4591044 is a randomized, active-controlled study. As the vaccines being studied were bivalent vaccines similar to the bivalent vaccine being studied in Study C4591031 Substudy E (i.e. BNT162b2 bivalent [WT/OMI BA.1]) in which there had been no identified safety concerns, Study C4591044 was conceived as a Phase 2/3 study divided into multiple cohorts:

- **Cohort 1** evaluated bivalent COVID-19 vaccines not relevant to this evaluation and hence, is not further considered in this CER. These vaccines were BNT162b5 bivalent (WT/OMI BA.2) 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg. Participants were 18-55 YOA.
- **Cohort 2** participants (n ~ 500; Phase 2 study) received either a 30 µg (i.e. 15 µg/15 µg) or 60 µg (i.e. 30 µg/30 µg) dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) (Table 4).
    - Participants **12-17 YOA** who had received 3 prior doses of BNT162b2 30 µg, with the most recent dose being 150 to 365 days prior to Day 1, received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg as a booster (Dose 4) dose (**open-label**).
    - Participants **18-55 YOA** and > **55 YOA** who had received 3 prior doses of BNT162b2 30 µg prior to Day 1 were randomised 1:1 within each age group to received either BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg as a booster (Dose 4) (**observer-blind**).
- **Cohort 3** participants (n ~ 400; Phase 3 study) received a 30 µg dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) (Table 5). The purpose of Cohort 3 was to combine with and expand the numbers of participants in the 18-55 and > 55 YOA groups of Cohort 2 to approximately 300 participants in each, to allow examination of additional safety and immunogenicity objectives, including a formal superiority analysis (to be reported in February 2023).
    - Participants ≥ 18 YOA who had received 3 prior doses of BNT162b2 30 µg, with the most recent dose being 150 to 365 days prior to Day 1, received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg as a booster (Dose 4) dose (open-label).

Table 4. Study C4591044 Cohort 2 Design

Cohort 2: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	**Participant Age Group**	**Prior Doses of BNT162b2**	**Time Since Last Dose**	**Study Dose**	**Number of Participants**	**Randomization / Blind**
1	12-17 years	3	150-365 days	30 µg	100	Open-label
2	18-55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
3	18-55 years	3	150-365 days	60 µg	100	
4	>55 years	3	150-365 days	30 µg	100	Randomize 1:1 Observer-blind
5	>55 years	3	150-365 days	60 µg	100	

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

Table 5. Study C4591044 Cohort 3 Design

Cohort 3: BNT162b2 Bivalent (WT/OMI BA.4/BA.5)						
Group	Participant Age Group	Prior Doses of BNT162b2	Time Since Last Dose	Study Dose	Number of Participants	Randomization / Blind
1	18-55 years	3	150-365 days	30 µg	200	Open-label
2	>55 years	3	150-365 days	30 µg	200	Open-label

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

A control group was selected from Study C4591031 Substudy E to aid in the evaluation of the immunogenicity objectives for Study C4591044 Cohort 2 and Cohorts 2/3 combined (Table 49, Table 50 and Table 51). This was to comprise a subset of ~ 100 participants from each age group (18-55 YOA and > 55 YOA) and dose group (30 µg and 60 µg) from the C4591031 Substudy E expanded cohort who received BNT162b2 bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose (Table 6). When feasible, the control group from Substudy E was to include a similar proportion of baseline SARS-CoV-2 positive participants as those in Cohort 2.

Table 6. Cohort 2 Immunogenicity Control Groups From C4591031 Substudy E

C4591031 Substudy E Subset			
Participant Age Group	Vaccine Group	Dose	Number of Participants
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
18-55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	30 µg	100
>55 years	Bivalent BNT162b2 (WT/OMI BA.1)	60 µg	100

Note: Vaccine group name in C4591031 Substudy E is "Bivalent BNT162b2 and BNT162b2 OMI".

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

Evaluator's comments: The study design for Cohort 2 is appropriate for a descriptive study and restricting the higher 60 µg dose to adult participants seems reasonable (see section 6.4).

Objectives

The study objectives, estimands and endpoints for Study C4591044 Cohorts 1, 2 and 3 are shown in Table 48 (primary safety), Table 49 (primary immunogenicity), Table 50 (secondary immunogenicity) and Table 51 (exploratory).

Locations

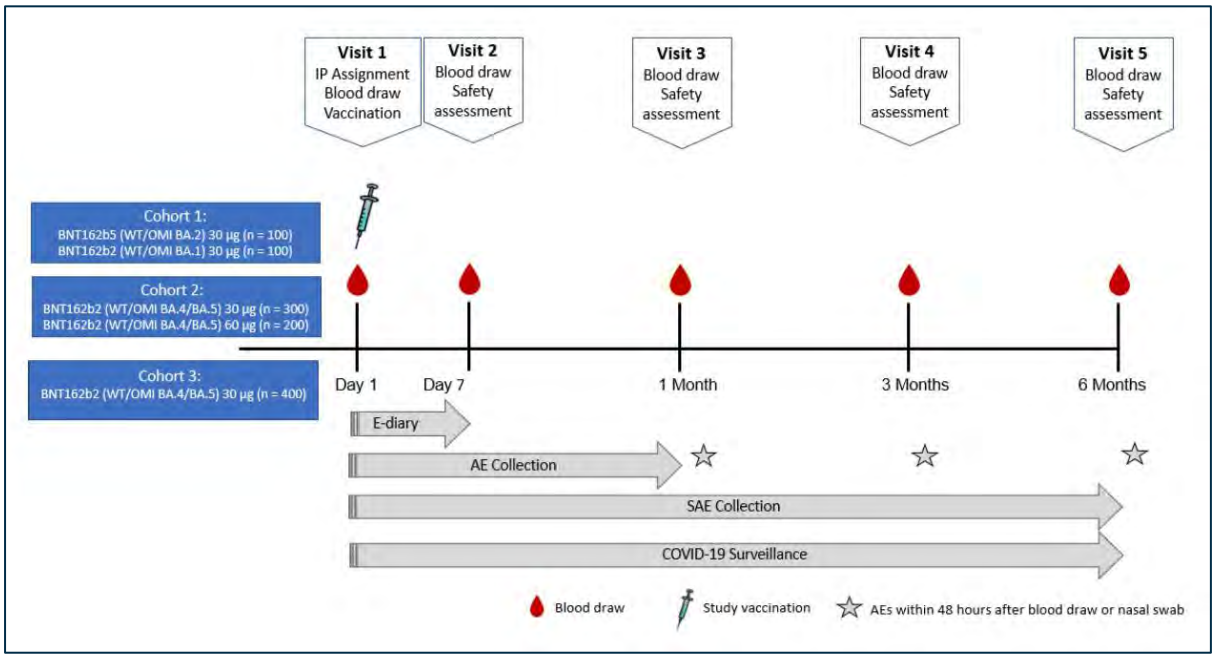
There were up to 31 study locations, all within the US.[4]

Dates and time scheme

The study duration for each participant is intended to be approximately 6 months. The study was designed so that cohorts could be studied in a staggered or parallel manner, as required by the clinical plan. A study schema is shown in Figure 3.

[4] See https://clinicaltrials.gov/ct2/show/NCT05472038, (accessed 19/12/2022).

Figure 3. Study C4591044 - Overall Schema



Source: 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report of November 2022 (data cutoff 12/10/2022).

Evaluator's comments: The Evaluator notes the use of historical controls rather than randomised controls. The potential biases this introduces will be further considered in the Evaluator's commentary on immunogenicity and safety.

7.2.1.2. Inclusion and exclusion criteria

It was intended to enrol participants in alignment with the Census-based US population distribution for age in the age group studied. It was recognised a priori that there may be less representation with respect to race, ethnicity and geographic location given the relatively small size of the study.

The ages for participants in each cohort were as follows:

- Cohort 1: 18-55 YOA at randomization.
- Cohort 2: ≥ 12 YOA at Visit 1.
- Cohort 3: ≥ 18 YOA at Visit 1.

Inclusion criteria

Notable features regarding the inclusion criteria were:

- Healthy participants as determined by the Investigator, inclusive of those with stable pre-existing disease.
- **Cohort 1**: Documented confirmation of prior receipt of 1 booster dose of a US-authorised COVID-19 vaccine at least 90 or more days prior to Visit 1 (Day 1).
- **Cohorts 2 and 3**: Documented confirmation of prior receipt of 3 prior doses of BNT162b2 30 µg, with the last dose being 150-365 days before Visit 1 (Day 1).

Exclusion criteria

Notable features regarding the exclusion criteria were:

- Severe adverse reaction to a vaccine.

- Severe allergy to any component of the IP.
- Bleeding diathesis.
- Immunocompromising condition or therapy.
- Pregnancy or breastfeeding.
- Unwillingness to use contraception during the study period.
- At-risk psychiatric condition or laboratory abnormality.
- Recent use of antibody products that could interfere with vaccine immunity.

Enrolment could be delayed, to ensure:

- No positive SARS-CoV-2 test within 28 days.
- No febrile illness within 48 hours.
- No receipt (or intended receipt) of an influenza vaccine within 14 days pre/post Visit 1 or any other non-study vaccine within 28 days pre/post Visit 1.
- No short-course systemic corticosteroids within 28 days (longer course steroids were an exclusion criteria).

Evaluator's comments: The inclusion and exclusion criteria seem fit for purpose and are in line with previous studies of the Sponsor's vaccines. The decision to enforce contraception seems reasonable given the experimental nature of the new bivalent vaccines relative to the well-established BNT162b2, which has been shown to be relatively safe in pregnancy and breastfeeding.

7.2.1.3. Study treatments

All study treatments were administered IM in the deltoid muscle. The BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg vaccine comprised 15 µg BNT162b2 Wild Type and 15 µg BNT162b2 Omicron (B.1.1.529 sublineage BA.4/5). Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020) and is also referred to in this CER as the 'reference strain'. Dosages were doubled for the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg vaccine.

The study arms for Cohort 2 are shown in Table 7.

Table 7. Study C4591044 Cohort 2 - Study Arms

Study Arms – Cohort 2					
Arm Title	Group 1: 12-17 years, 30 µg	Group 2: 18-55 years, 30 µg	Group 3: 18-55 years, 60 µg	Group 4: >55 years, 30 µg	Group 5: >55 years, 60 µg
Arm Type	Experimental	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg at Visit 1	Participants will receive BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg at Visit 1
Associated Intervention Label	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) (BNT162b2 Wild Type[a] and BNT162b2 OMICRON [B.1.1.529 sublineage BA.4/BA.5])				

a. Wild Type refers to the ancestral strain (Wuhan-Hu-1; USA-WA1/2020), also referred to in this protocol as the reference strain.

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

7.2.1.4. Efficacy variables and outcomes

The study objectives, estimands and endpoints for Study C4591044 Cohorts 1, 2 and 3 are shown in Table 48 (primary safety), Table 49 (primary immunogenicity), Table 50 (secondary immunogenicity) and Table 51 (exploratory).

7.2.1.5. Randomisation and blinding methods

For the Study C4591044 Cohort 2 participants who were **randomised** to either BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg, randomisation was performed using an IRT system on a 1:1 basis within each age group (i.e. 18-55 YOA and > 55 YOA). All participants 12-17 YOA in Cohort 2 were **open-label**, as were all participants ≥ 18 YOA in Cohort 3 (the expansion subset).

Participants 18-55 YOA and > 55 YOA in Cohort 2 were observer and participant-blinded at the site level with respect to study intervention allocation but were open-label to most Pfizer staff (with the reason given being 'To facilitate rapid review of data in real time…').

Evaluator's comments: The randomisation and blinding methods seemed fit for purpose, noting that this was not a placebo-controlled trial and there was a need to rapidly analyse data. All of Cohort 2 was open-label.

7.2.1.6. Analysis populations

The analysis sets were defined as shown in Table 8 and more information about the participants included in each analysis population is given in section 7.2.1.9 'Participant Flow'.

Table 8. Study C4591044 - Analysis Sets

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized/assigned	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All eligible randomized/assigned participants who receive the study intervention to which they are randomized/assigned, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
All-available immunogenicity (mITT)	All randomized/assigned participants who receive the study intervention with a valid and determinate immunogenicity result after vaccination.
Safety	All participants who receive the study intervention.

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

7.2.1.7. Sample size

For the **immunogenicity** analyses conducted separately for Cohorts 1 and 2 the sample size was not based on any formal hypothesis testing and it was intended that all statistical analyses would be descriptive.

In relation to the **safety** analyses, Table 9 shows the probability of observing at least one AE for a given true event rate of a particular AE.

Table 9. Probability of Observing at Least 1 AE by Assumed True Event Rate

Assumed True Event Rate of an AE	N=100	N=200	N=300
0.1%	0.10	0.18	0.26
0.3%	0.26	0.45	0.59
0.5%	0.39	0.63	0.78
0.8%	0.55	0.80	0.91
1%	0.63	0.87	0.95
2%	0.87	0.98	>0.99
3%	0.95	>0.99	>0.99
4%	0.98	>0.99	>0.99
5%	0.99	>0.99	>0.99

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

7.2.1.8. Statistical methods and study procedures

Statistical methods

'GMTs and GMFRs with their 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ. Seroresponse was defined as achieving a ≥4-fold rise from baseline (or postvaccination assay result ≥4 × LLOQ if the baseline measurement was below LLOQ). The exact 95% CI for percentage of participants with seroresponse was computed using the F distribution (Clopper-Pearson method).'

Study procedures

Blood samples and assays

The Sponsor stated that, 'Immunogenicity results were based on **validated assays** for 50% SARS-CoV-2 neutralizing titers against Omicron BA.4/BA.5, Omicron BA.1 and the reference strain (USA-WA-1/2020) titers from before study vaccination (dose 4) to 1 month after study vaccination…' An N-binding antibody test was also performed at each visit to establish prior exposure to SARS-CoV-2.

It was also intended to collect blood samples ~ 130 mL from a subset of ~ 30 participants per group (≥ 18 YOA only) within Cohort 2 for B and T-cell responses to Omicron and the reference strain. An additional 5 mL was to be collected for HLA typing.

Evaluator's comments: The Evaluator notes that the assays used in Study C4591044 were validated.

Surveillance for COVID-19 and MIS-C

Participants were instructed to contact the Investigator in the event of acute respiratory illness for an in-person or telehealth visit that would facilitate RT-PCR testing for SARS-CoV-2 at a central laboratory (as well as review other results). Local NAAT results could also be used if they met criteria. **COVID-19 (study definition)** was defined on the basis of at least 1 listed symptom plus a positive NAAT for SARS-CoV-2, during or within 4 days pre/post the symptomatic period. Alternate **FDA** and **CDC COVID-19 definitions** were applied separately.

Surveillance for **MIS-C** occurred in participants < 21 YOA based on the CDC MIS-C definition.

Collection of safety data

There was an 'active collection period' for all AEs (including SAEs) that began at the time of informed consent and ran through Visit 3 (1 month post-vaccination). Additionally, any AE occurring up to 48 hours after a blood draw or nasal swab was monitored. SAEs were collected from the time of informed consent through Visit 5 (6 months post-vaccination). Myocarditis and pericarditis were designated as AESIs and in addition, the Sponsor monitored other AEs of clinical interest from a dynamic list of MedDRA AE terms during clinical safety data review and signal detection.

7.2.1.9. Participant flow

Study C4591044 Cohort 2 – Safety Population (data cutoff 12/10/2022)

This was the Safety Population that contributed data to the analysis of reactogenicity (up to 7 days) and of all unsolicited AEs up to 1 month post-vaccination. There were 528 participants ≥ 12 YOA who received a booster (Dose 4) dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg Table 10. One participant in the 12-17 YOA BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group was excluded from the safety population as they didn't provide informed consent. There was one participant 18-55 YOA who was randomised to BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg but not vaccinated; they were not included in the safety analysis (shown in Table 9 of the 1 Month Post Dose Safety and Immunogenicity [Sentinel] Data, Study C4591044 Cohort 2 report).

Median **follow-up time** was 1.6 months (1.5 months for the 12-17 YOA age group [30 µg] vs 1.6 months in the 18-55 and > 55 YOA groups [including both 30 µg and 60 µg strata). All but 1 participant in the 18-55 YOA group (60 µg stratum) had ≥ 1 month of follow-up. The minimum follow-up was 0.6 months and maximum was 1.8 months. Follow-up was shown in Table 8 of the 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report.

Table 10. Safety Population – Cohort 2 (1-month visit)

	Vaccine Group (as Administered)					
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
	12-17 Years	18-55 Years		>55 Years		
	30 µg n[a]	30 µg n[a]	60 µg n[a]	30 µg n[a]	60 µg n[a]	Total n[a] (%)
Randomized[b]						530
Vaccinated	108	103	110	106	102	529 (99.8)
Safety population	107	103	110	106	102	528 (99.6)
HIV-positive	0	1	2	0	2	5 (0.9)
Excluded from safety population						2 (0.4)
Reason for exclusion						
Participant did not receive study intervention						1 (0.2)
Did not provide informed consent	1	0	0	0	0	1 (0.2)

a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.

Source: Table 7, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report, DCO 12/10/2022.

Overall, all but 1 (99.8%) participant completed the 7-day post-dose vaccination visit and all but 9 (98.3%) participants completed the 1-month post-dose vaccination visit (Table 11) (noting that 1-month follow-up data were available for 527/528 [99.8%] of participants as per Table 8 of the 1 Month Post Dose Safety and Immunogenicity [Sentinel] Data, Study C4591044 Cohort 2 report).

Table 11. Disposition of All Participants – Cohort 2 – Randomized Population

	Vaccine Group (as Randomized)					
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
	12-17 Years	18-55 Years		>55 Years		
	30 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)	30 µg n[a] (%)	60 µg n[a] (%)	Total n[a] (%)
Randomized[b]	108 (100.0)	104 (100.0)	110 (100.0)	106 (100.0)	102 (100.0)	530 (100.0)
Not vaccinated	0	1 (1.0)	0	0	0	1 (0.2)
Vaccinated	108 (100.0)	103 (99.0)	110 (100.0)	106 (100.0)	102 (100.0)	529 (99.8)
Completed 7-day post–study vaccination visit	108 (100.0)	103 (99.0)	110 (100.0)	106 (100.0)	102 (100.0)	529 (99.8)
Completed 1-month post–study vaccination visit	108 (100.0)	101 (97.1)	106 (96.4)	105 (99.1)	101 (99.0)	521 (98.3)
Withdrawn from the study	0	0	1 (0.9)	0	0	1 (0.2)
Reason for withdrawal						
Physician decision	0	0	1 (0.9)	0	0	1 (0.2)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.

Source: Table 10, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Study C4591044 Cohort 2 – Immunogenicity Population – descriptive immunogenicity analysis (data cutoff 2/12/2022)

'The immunogenicity analysis included approximately 100 randomized participants per vaccine group (Table 12). All participants 18 to 55 and > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg groups from Study C4591044 Cohort 2 were included. Approximately 100 participants in each of the 18 to 55 and > 55 years of age groups in C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg were selected as the reference group.'

'To achieve a similar balance of participants with or without prior SARS-CoV-2 infection, the reference group included all evaluable participants who had evidence of prior SARS-CoV-2 infection before study vaccination (baseline positive) and randomly selected additional participants without evidence of prior infection (baseline negative) from the corresponding groups in C4591031 Substudy E. Because of substantially lower prior infection rate in C4591031 Substudy E, the subset selected still has a lower baseline infection rate than the groups in C4591044 Cohort 2.'

'Most exclusions from the evaluable immunogenicity population were due to lack of at least 1 valid and determinate immunogenicity result within 28 to 42 days after the study vaccination.'

Table 12. Immunogenicity Populations – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort

	Vaccine Group (as Randomized)			
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg	
	18-55 Years n[a] (%)	>55 Years n[a] (%)	18-55 Years n[a] (%)	>55 Years n[a] (%)
Randonized[b]	104 (100.0)	106 (100.0)	100 (100.0)	100 (100.0)
All-available immunogenicity population	97 (93.3)	105 (99.1)	100 (100.0)	100 (100.0)
Excluded from all-available immunogenicity population	7 (6.7)	1 (0.9)	0	0
Reason for exclusion[d]				
Participant did not receive study intervention	1 (1.0)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after study vaccination	7 (6.7)	1 (0.9)	0	0
Evaluable immunogenicity population	95 (91.3)	102 (96.2)	100 (100.0)	100 (100.0)
Participants without evidence of infection up to 1 month after the study vaccination[c]	32 (30.8)	40 (37.7)	67 (67.0)	64 (64.0)
Excluded from evaluable immunogenicity population	9 (8.7)	4 (3.8)	0	0
Reason for exclusion[d]				
Did not meet eligibility and randomization criteria	5 (4.8)	0	0	0
Participant did not receive study intervention as randomized	1 (1.0)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination	9 (8.7)	4 (3.8)	0	0
Had other important protocol deviation	5 (4.8)	0	0	0

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
c. Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
d. Participants may have been excluded for more than 1 reason.

Source: Table 1, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: The Evaluator is unclear what process was used to randomly select the controls from among the population of Study C4591031 Substudy E. **EvQset4**: Please outline in detail the process that was used to randomly select baseline negative controls from Study C4591031 Substudy E into the reference group for the immunogenicity population described in section 3.2 of the 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, dated 7/12/2022.

7.2.1.10. Major protocol violations/deviations

There was one withdrawal from Cohort 2 as of the data cutoff date of 12/10/2022 for 1-month safety follow-up of all unsolicited AEs (Table 11). This was a participant 18-55 YOA (1/106 [0.9%]) who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg. The reason for the withdrawal was 'Physician decision'.

7.2.1.11. Baseline data

Study C4591044 Cohort 2 – Safety Analysis (1-month visit)

Baseline demographic characteristics for those included in the safety analysis subset, who received either a 30 µg or 60 µg dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5), at the time of the 1-month visit are shown in Table 13.

It was noted by the Sponsor that 12 participants overall received a **non-study vaccine** (including influenza, meningococcal or varicella vaccines) vs only 1 participant at the time of the 7-day visit. Of these 12, there were 5 participants 12-17 YOA who also received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg.

Table 13. Demographic Characteristics – Cohort 2 – Safety Population (1-month visit)

	Vaccine Group (as Administered)					
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					
	12-17 Years	18-55 Years		>55 Years		
	30 µg (N[a]=107) n[b] (%)	30 µg (N[a]=103) n[b] (%)	60 µg (N[a]=110) n[b] (%)	30 µg (N[a]=106) n[b] (%)	60 µg (N[a]=102) n[b] (%)	Total (N[a]=528) n[b] (%)
Sex						
Male	59 (55.1)	44 (42.7)	47 (42.7)	65 (61.3)	47 (46.1)	262 (49.6)
Female	48 (44.9)	59 (57.3)	63 (57.3)	41 (38.7)	55 (53.9)	266 (50.4)
Race						
White	91 (85.0)	82 (79.6)	90 (81.8)	84 (79.2)	92 (90.2)	439 (83.1)
Black or African American	9 (8.4)	9 (8.7)	11 (10.0)	16 (15.1)	8 (7.8)	53 (10.0)
American Indian or Alaska Native	0	0	0	1 (0.9)	0	1 (0.2)
Asian	3 (2.8)	10 (9.7)	9 (8.2)	3 (2.8)	2 (2.0)	27 (5.1)
Native Hawaiian or other Pacific Islander	0	0	0	1 (0.9)	0	1 (0.2)
Multiracial	3 (2.8)	2 (1.9)	0	1 (0.9)	0	6 (1.1)
Not reported	1 (0.9)	0	0	0	0	1 (0.2)
Ethnicity						
Hispanic/Latino	7 (6.5)	12 (11.7)	15 (13.6)	10 (9.4)	11 (10.8)	55 (10.4)
Non-Hispanic/non-Latino	98 (91.6)	90 (87.4)	94 (85.5)	96 (90.6)	88 (86.3)	466 (88.3)
Not reported	2 (1.9)	1 (1.0)	1 (0.9)	0	3 (2.9)	7 (1.3)
Age at vaccination (years)						
Mean (SD)	15.1 (1.38)	39.6 (8.83)	40.0 (9.90)	65.7 (6.14)	63.8 (6.25)	44.6 (19.94)
Median	15.0	40.0	41.0	65.0	63.0	47.0
Min, max	(12, 17)	(19, 55)	(18, 55)	(56, 79)	(56, 85)	(12, 85)
Baseline SARS-CoV-2 status						
Positive[c]	81 (75.7)	66 (64.1)	82 (74.5)	64 (60.4)	67 (65.7)	360 (68.2)
Negative[d]	26 (24.3)	37 (35.9)	28 (25.5)	42 (39.6)	35 (34.3)	168 (31.8)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months)[e]						
n	107	103	110	106	102	528
Mean (SD)	8.4 (1.23)	10.6 (1.71)	10.7 (1.39)	10.6 (1.25)	10.7 (1.27)	10.2 (1.66)
Median	8.4	11.0	11.0	11.0	11.0	10.5
Min, max	(5.6, 12.0)	(5.6, 14.3)	(6.6, 14.2)	(5.5, 13.0)	(6.6, 13.0)	(5.5, 14.3)
≥5 to <7 Months	11 (10.3)	5 (4.9)	3 (2.7)	1 (0.9)	1 (1.0)	21 (4.0)
≥7 to <9 Months	77 (72.0)	11 (10.7)	9 (8.2)	9 (8.5)	9 (8.8)	115 (21.8)
≥9 to ≤12 Months	19 (17.8)	75 (72.8)	90 (81.8)	89 (84.0)	82 (80.4)	355 (67.2)
>12 Months	0	12 (11.7)	8 (7.3)	7 (6.6)	10 (9.8)	37 (7.0)
Body mass index (BMI)						
Number of participants ≥16 years of age[f]	44	103	110	106	102	465
Underweight (<18.5 kg/m^2)	5 (11.4)	1 (1.0)	7 (6.4)	3 (2.8)	1 (1.0)	17 (3.7)
Normal weight (≥18.5-24.9 kg/m^2)	28 (63.6)	42 (40.8)	27 (24.5)	28 (26.4)	22 (21.6)	147 (31.6)
Overweight (≥25.0-29.9 kg/m^2)	8 (18.2)	34 (33.0)	32 (29.1)	34 (32.1)	42 (41.2)	150 (32.3)
Obese (≥30.0 kg/m^2)	3 (6.8)	26 (25.2)	44 (40.0)	41 (38.7)	37 (36.3)	151 (32.5)
Body mass index (BMI) 12-15 years of age/Obese[g]						
Number of participants 12-15 years of age[f]	63	N/A	N/A	N/A	N/A	63
Yes	6 (9.5)					6 (9.5)
No	57 (90.5)					57 (90.5)

Abbreviations: N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations except for BMI.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
e. For participant C4591044 1006 10061023 who received a different prior COVID-19 vaccine in error, time was calculated from the last reported dose of COVID-19 vaccine.
f. This value is the denominator for the percentage calculations for BMI.
g. For participants 12 through 15 years of age, obesity is defined as a BMI at or above the 95th percentile from the growth chart. Refer to the CDC growth charts at

Source: Table 11, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report, on 23/11/2022 (data cutoff 12/10/2022).

Evaluator's comments: Most participants were White (83.1%) with 10.0% Black or African American and 5.1% Asian. The median age was 47.0 years overall (15 years in the 12-17 YOA group; 40.0 and 41.0 years for 30 µg and 60 µg dosing in the 18-55 YOA group; and 65.0 and 63.0 years respectively in the > 55 YOA group). The gender split was within 1% of 50/50. Close to two thirds (i.e. 68.2%) had evidence of prior SARS-CoV-2 infection, in keeping with the phase of the pandemic. The median time since last vaccination was 11.0 months in both the 18-55 and > 55 YOA groups (30 µg and 60 µg dosing strata); however, was 8.4 months in those 12-17 YOA, reflecting the sequential rollout of third booster doses in prior studies. The majority (72.0%) of 12-17 YOA participants received their 3rd doses ≥ 7 to < 9 months prior, whereas the majorities (72.8 to 84.0%) of participants in the 18-55 and > 55 YOA groups received their 3rd doses ≥ 9 to < 12 months prior. Obesity was present in 5.6% of participants 12-17 YOA and between 25.2% and 40.7% of those in the 18-55 and > 55 YOA groups. The Sponsor stated that, 'The medical histories of participants at study baseline included conditions and procedures typically observed in the general population for each age group.' This was verified by the Evaluator upon inspection of the associated comorbidity tables.

Study C4591044 Cohort 2 – Descriptive immunogenicity analysis (data cutoff 12/10/2022)

Demographic characteristics for the participant subset used for the descriptive immunology analysis (with or without evidence of infection up to 1 month after study vaccination with a data cutoff of 12/10/2022) are shown in Table 14. Demographic characteristics for those without evidence of infection up to 1 month after study vaccination were shown on page 6 of the C4591044_C2_1MPD_Full_Safety_Sen_Immuno_Final_TLF_Bundle_2NOV22 file.

Table 14. Demographic Characteristics – 1-Month Immunogenicity Analysis – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity population

	Vaccine Group (as Randomized)		
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg
	18-55 Years (N[a]=38) n[b] (%)	>55 Years (N[a]=36) n[b] (%)	>55 Years (N[a]=40) n[b] (%)
Sex			
Male	18 (47.4)	22 (61.1)	17 (42.5)
Female	20 (52.6)	14 (38.9)	23 (57.5)
Race			
White	31 (81.6)	29 (80.6)	36 (90.0)
Black or African American	2 (5.3)	4 (11.1)	2 (5.0)
American Indian or Alaska Native	0	1 (2.8)	0
Asian	4 (10.5)	1 (2.8)	2 (5.0)
Multiracial	1 (2.6)	1 (2.8)	0
Ethnicity			
Hispanic/Latino	3 (7.9)	3 (8.3)	9 (22.5)
Non-Hispanic/non-Latino	35 (92.1)	33 (91.7)	31 (77.5)
Age at vaccination (years)			
Mean (SD)	39.9 (9.59)	66.5 (6.95)	65.4 (5.80)
Median	41.0	66.0	65.5
Min, max	(19, 54)	(57, 79)	(56, 79)
Baseline SARS-CoV-2 status			
Positive[c]	20 (52.6)	19 (52.8)	20 (50.0)
Negative[d]	18 (47.4)	17 (47.2)	20 (50.0)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months)			
n	38	36	40
Mean (SD)	10.4 (1.56)	10.9 (1.44)	6.9 (1.82)
Median	10.7	11.3	6.3
Min, max	(5.6, 12.8)	(5.5, 13.0)	(5.4, 13.1)
≥5 to <7 Months	1 (2.6)	1 (2.8)	30 (75.0)
≥7 to <9 Months	6 (15.8)	2 (5.6)	5 (12.5)
≥9 to ≤12 Months	28 (73.7)	29 (80.6)	4 (10.0)
>12 Months	3 (7.9)	4 (11.1)	1 (2.5)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	0	0	1 (2.5)
Normal weight (≥18.5-24.9 kg/m^2)	18 (47.4)	8 (22.2)	9 (22.5)
Overweight (≥25.0-29.9 kg/m^2)	13 (34.2)	11 (30.6)	12 (30.0)
Obese (≥30.0 kg/m^2)	7 (18.4)	17 (47.2)	18 (45.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 2, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Evaluator's comments: The groups were deliberately stratified to be balanced in relation to prior SARS-CoV-2 exposure, whereas in the Safety Population from Study C4591044 Cohort 2 about two thirds had prior exposure. This improves the ability to describe responses stratified by prior SARS-CoV-2 exposure but calls into question whether the subsets were otherwise randomly selected. The breakdown of race and age at vaccination were broadly similar to the safety population, as were the proportions of males and females in the two age groups. Time since last vaccination followed the same pattern as per the safety population (majority ≥ 9 to ≤ 12 months). Of note, in the comparator BNT162b2 bivalent (WT/OMI BA.1) 30 µg group, the majority (75%) of vaccinations were given more recently, between ≥ 5 to < 7 months. Hence the median time since vaccination was 4-5 months shorter in that group [> 55 YOA] than in the other two groups (6.3 months vs 10.7 months [18-55 YOA] and 11.3 months [> 55 YOA]).

The demographics for the subset of participants *without* evidence of infection up to 1-month post-vaccination were broadly similar to the group *with or without* evidence of infection.

Study C4591044 Cohort 2 – Descriptive immunogenicity analysis (data cutoff 2/12/2022)

Demographic characteristics for the participant subset used for the descriptive immunology analysis (with or without evidence of infection up to 1 month after study vaccination with a data cutoff of 2/12/2022) are shown in Table 15. Demographic characteristics for those without evidence of infection up to 1 month after study vaccination were broadly similar and were shown on page 6 of the 'C4591044_C2_1MPD_G2_G4_Immuno_TLF_Bundle_02Dec2022.pdf' file.

Although it was hoped that the control group from Study C4591031 Substudy E would have a similar proportion of baseline SARS-CoV-2 positive participants as the reference group from Study C4591044 Cohort 2, the Sponsor stated that, 'Because of substantially lower prior infection rate in C4591031 Substudy E, the subset selected still has a lower baseline infection rate than the groups in C4591044 Cohort 2.'

Table 15. Demographic Characteristics – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)			
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg	
	18-55 Years (N[a]=95) n[b] (%)	>55 Years (N[a]=102) n[b] (%)	18-55 Years (N[a]=100) n[b] (%)	>55 Years (N[a]=100) n[b] (%)
Sex				
Male	40 (42.1)	62 (60.8)	51 (51.0)	57 (57.0)
Female	55 (57.9)	40 (39.2)	49 (49.0)	43 (43.0)
Race				
White	75 (78.9)	80 (78.4)	77 (77.0)	89 (89.0)
Black or African American	9 (9.5)	16 (15.7)	7 (7.0)	7 (7.0)
American Indian or Alaska Native	0	1 (1.0)	0	0
Asian	9 (9.5)	3 (2.9)	14 (14.0)	4 (4.0)
Native Hawaiian or other Pacific Islander	0	1 (1.0)	2 (2.0)	0
Multiracial	2 (2.1)	1 (1.0)	0	0
Ethnicity				
Hispanic/Latino	12 (12.6)	10 (9.8)	11 (11.0)	18 (18.0)
Non-Hispanic/non-Latino	82 (86.3)	92 (90.2)	89 (89.0)	82 (82.0)
Not reported	1 (1.1)	0	0	0
Age at vaccination (years)				
Mean (SD)	39.4 (9.07)	65.6 (6.21)	41.2 (9.17)	67.0 (6.69)
Median	40.0	65.0	42.0	66.0
Min, max	(19, 55)	(56, 79)	(22, 55)	(56, 85)
Baseline SARS-CoV-2 status				
Positive[c]	62 (65.3)	62 (60.8)	33 (33.0)	36 (36.0)
Negative[d]	33 (34.7)	40 (39.2)	67 (67.0)	64 (64.0)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months)				
n	95	102	100	100
Mean (SD)	10.4 (1.61)	10.6 (1.26)	8.8 (1.60)	7.0 (1.79)
Median	10.9	11.0	8.6	6.3
Min, max	(5.6, 12.8)	(5.5, 13.0)	(5.7, 13.1)	(4.7, 11.5)
<5 Months	0	0	0	1 (1.0)
≥5 to <7 Months	5 (5.3)	1 (1.0)	10 (10.0)	72 (72.0)
≥7 to <9 Months	11 (11.6)	9 (8.8)	55 (55.0)	8 (8.0)
≥9 to ≤12 Months	72 (75.8)	86 (84.3)	30 (30.0)	19 (19.0)
>12 Months	7 (7.4)	6 (5.9)	5 (5.0)	0
Body mass index (BMI)				
Underweight (<18.5 kg/m^2)	1 (1.1)	3 (2.9)	1 (1.0)	0
Normal weight (≥18.5-24.9 kg/m^2)	38 (40.0)	27 (26.5)	20 (20.0)	22 (22.0)
Overweight (≥25.0-29.9 kg/m^2)	32 (33.7)	33 (32.4)	31 (31.0)	42 (42.0)
Obese (≥30.0 kg/m^2)	24 (25.3)	39 (38.2)	48 (48.0)	36 (36.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 2, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: There were some obvious differences between the two age-based study groups from Study C4591044 Cohort 2 and the two corresponding reference groups from Study C4591031 Substudy E; in relation to prior SARS-CoV-2 exposure and time since last vaccination.

Although the aim was for the groups to be balanced in relation to **prior SARS-CoV-2 exposure**, this wasn't feasible. All available participants from Study C4591044 Cohort 2 were included and their risk of prior exposure was 65.3% (18-55 YOA) and 60.8% (> 55 YOA). Recruitment of controls into the reference group from Study C4591031 Substudy E had dual aims: include ~ 100 participants in each age group *and* as far as possible, try and achieve balance or prior exposure risk with the study group. Even after including all baseline positive controls, supplemented with 'randomly selected' baseline negative controls, baseline positive rates were 33.0% (18-55 YOA) and 36.0% (> 55 YOA) in the reference group. The process of random selection into the reference group was not fully described but nonetheless, the study and reference groups were recently well matched across most demographic characteristics. The Evaluator's comments in section 7.2.1.9 contain an **EvQ** in relation to the process of random selection.

Time since last vaccination followed the same pattern as per the safety population (majority ≥ 9 to ≤ 12 months) for the study participants from Study C4591044 Cohort 2 who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg. The median time since 3rd dose was 10.9 and 11.0 months in those 18-55 YOA and > 55 YOA respectively, and the majority received their 3rd dose between ≥ 9 to ≤ 12 months prior (75.8% and 84.3% respectively). In the BNT162b2 bivalent (WT/OMI BA.1) 30 µg reference group, the median time since 3rd dose was 8.6 and 6.3 months in those 18-55 YOA and > 55 YOA respectively. The majority of those 18-55 YOA received their 3rd dose between ≥7 to < 9 months prior (55.0%), whereas the majority of those > 55 YOA received their 3rd dose between ≥ 5 to < 7 months prior (72.0%). The Evaluator would potentially expect higher pre-dose neutralising titres in the reference group and this could bias *against* the study group in most immunogenicity analyses, particularly in those without prior evidence of infection.

The potential biases inherent in these differences between study and reference groups are considered in the Evaluator's comments in each of the relevant sections.

7.2.1.12. Results for primary efficacy outcomes (data cutoff 2/12/2022)

Results for the primary immunogenicity objectives that are based on **statistical testing**, including formal superiority and non-inferiority testing (Table 49) are anticipated in 2023. Results for the primary immunogenicity objectives that are based on **descriptive analyses** (Table 49) are presented in the subsections that follow.

The results below derive from the '**Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022**' report, data cutoff 2/12/2022, dated 7/12/2022. This report provides '…the available immunogenicity results at 1 month after booster (dose 4) administration of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) to adults in Study C4591044. Results include data from a comparator subset of adults in Study C4591031 Substudy E who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg as a booster (dose 4) dose.'

The data only pertain to participants 18-55 YOA and > 55 YOA. The Sponsor has stated that, 'Immunogenicity data for **participants 12 to 17 years of age** will be provided in a separate report when available.'

Geometric mean titres and geometric fold rises

Omicron BA.4/5 neutralisation – participants without evidence of infection

Omicron BA.4/5 neutralising GMTs at 1 month after study vaccination are shown in Table 16 and Figure 4 for participants 18-55 YOA and > 55 YOA without evidence of infection. The corresponding GMFRs are shown in Table 17.

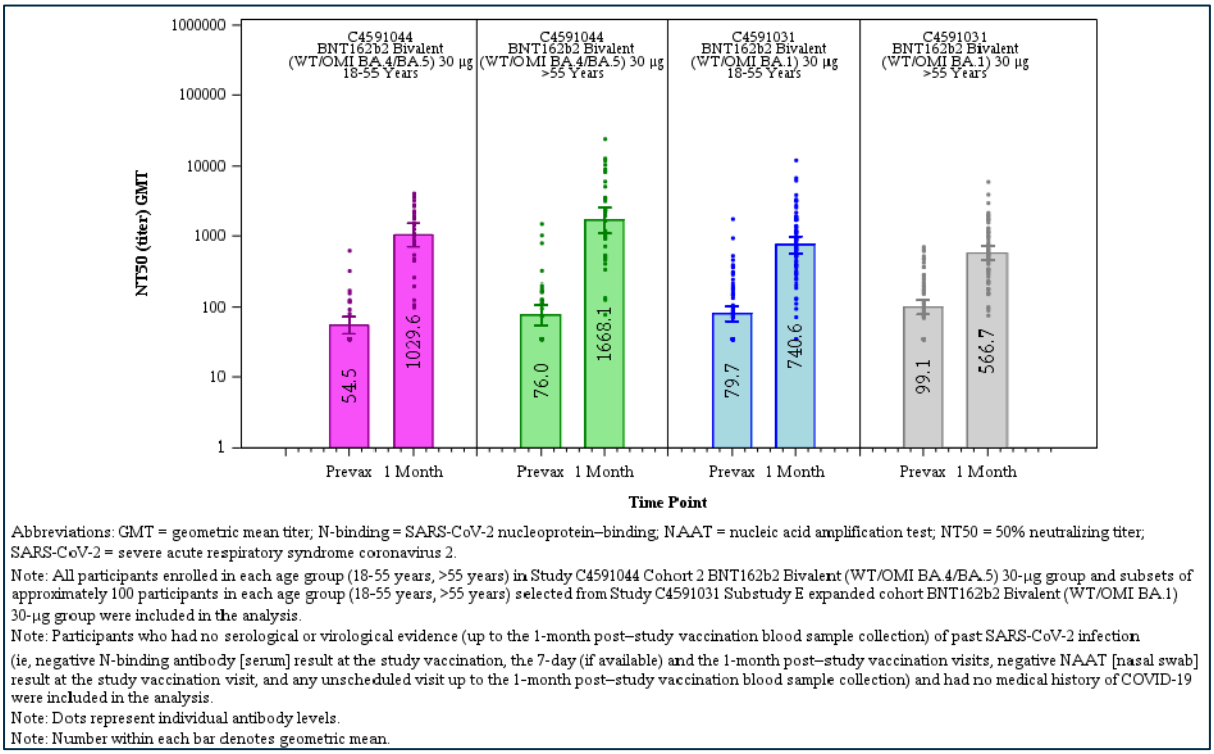
Table 16. Geometric Mean Titers – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
		18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	Prevax	32	54.5 (41.3, 71.9)	40	76.0 (54.7, 105.7)	67	79.7 (62.7, 101.1)	63	99.1 (78.1, 125.8)
	1 Month	32	1029.6 (702.6, 1508.9)	40	1668.1 (1089.6, 2553.7)	67	740.6 (557.2, 984.2)	64	566.7 (446.2, 719.9)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	Prevax	32	52.6 (34.0, 81.3)	40	84.7 (55.7, 128.6)	67	99.3 (75.4, 130.8)	64	114.5 (82.4, 159.3)
	1 Month	32	910.9 (634.8, 1307.1)	40	1481.5 (1020.3, 2151.2)	67	1338.6 (998.9, 1793.9)	64	944.7 (746.2, 1196.1)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	Prevax	32	455.3 (286.2, 724.2)	40	881.9 (601.6, 1292.7)	67	873.5 (682.8, 1117.3)	64	1028.9 (795.8, 1330.3)
	1 Month	32	6431.7 (4542.9, 9106.0)	40	8386.3 (6235.4, 11279.2)	67	5763.8 (4550.1, 7301.1)	64	5230.2 (4357.9, 6277.2)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Source: Table 3, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Figure 4. GMTs and 95% CIs: Omicron BA.4/BA.5 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Source: Figure 1, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Table 17. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
		18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month	32	18.9 (12.8, 27.8)	40	21.9 (14.2, 33.8)	67	9.3 (7.2, 12.1)	63	5.8 (4.5, 7.5)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1 Month	32	17.3 (11.1, 26.9)	40	17.5 (12.2, 25.1)	67	13.5 (10.3, 17.7)	64	8.2 (6.1, 11.2)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	32	14.1 (9.1, 22.0)	40	9.5 (6.4, 14.0)	67	6.6 (5.2, 8.3)	64	5.1 (3.9, 6.5)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point.

c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Source: Table 5, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: In participants without baseline evidence of infection, observed GMTs at 1 month post-study vaccination were higher for recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg, with GMFRs being more than double in both age groups. This is despite recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg having received their previous dose of BNT162b2 30 µg more recently than recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg (i.e. for participants 18-55 YOA, median time from last dose of BNT162b2 30 µg of 10.9 vs 8.6 months respectively; for participants > 55 YOA, 11.0 vs 6.3 months respectively), which was reflected in higher baseline titres in the BNT162b2 bivalent (WT/OMI BA.1) 30 µg group. For recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, GMTs and GMFRs were of similar magnitude in both the 18-55 and > 55 YOA groups.

The Evaluator concludes that in those without prior evidence of infection (i.e. baseline negative), BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appears to be neutralise Omicron BA.4/5 at least as well (if not better) than BNT162b2 bivalent (WT/OMI BA.1) 30 µg in both age groups. The Evaluator notes that 95% CIs were overlapping in the 18-55 YOA group but non-overlapping in the > 55 YOA group; however, only limited comparison is possible given the different selection criteria of cases and controls.

Omicron BA.4/5 neutralisation – participants with or without evidence of infection

Omicron BA.4/5 neutralising GMTs at 1 month after study vaccination are shown in Table 18 and Figure 5 for participants 18-55 YOA and > 55 YOA with or without evidence of infection. The corresponding GMFRs are shown in Table 19.

Table 18. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
			18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	95	338.3 (238.1, 480.7)	101	301.9 (215.6, 422.8)	100	151.5 (113.4, 202.3)	99	225.4 (164.1, 309.6)
		1 Month	95	2839.0 (2150.0, 3748.8)	102	3001.1 (2318.2, 3885.1)	100	1072.0 (816.1, 1408.1)	100	944.5 (733.8, 1215.6)
	Positive[d]	Prevax	62	900.3 (661.5, 1225.2)	61	745.8 (516.5, 1076.9)	33	558.4 (338.6, 920.9)	36	948.9 (576.4, 1562.1)
		1 Month	62	4678.4 (3438.9, 6364.6)	62	4383.6 (3261.9, 5891.1)	33	2271.4 (1346.7, 3831.2)	36	2341.6 (1526.5, 3592.1)
	Negative[e]	Prevax	33	53.8 (41.1, 70.5)	40	76.0 (54.7, 105.7)	67	79.7 (62.7, 101.1)	63	99.1 (78.1, 125.8)
		1 Month	33	1110.7 (743.9, 1658.4)	40	1668.1 (1089.6, 2553.7)	67	740.6 (557.2, 984.2)	64	566.7 (446.2, 719.9)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	All	Prevax	95	346.0 (240.0, 498.9)	102	365.1 (260.8, 511.1)	100	194.6 (142.4, 266.0)	100	316.3 (215.9, 463.4)
		1 Month	95	2407.2 (1884.9, 3074.2)	102	2656.1 (2089.6, 3376.3)	100	1819.0 (1401.6, 2360.6)	100	1617.7 (1274.7, 2053.0)
	Positive[d]	Prevax	62	934.3 (697.0, 1252.5)	62	937.3 (689.5, 1274.0)	33	762.3 (451.6, 1286.9)	36	1924.6 (1178.3, 3143.7)
		1 Month	62	3938.2 (3069.0, 5053.5)	62	3871.0 (2919.8, 5132.2)	33	3389.8 (2114.4, 5434.8)	36	4208.7 (2997.7, 5908.8)
	Negative[e]	Prevax	33	53.5 (35.0, 81.8)	40	84.7 (55.7, 128.6)	67	99.3 (75.4, 130.8)	64	114.5 (82.4, 159.3)
		1 Month	33	954.7 (664.4, 1371.8)	40	1481.5 (1020.3, 2151.2)	67	1338.6 (998.9, 1793.9)	64	944.7 (746.2, 1196.1)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	Prevax	95	2349.0 (1693.4, 3258.4)	101	2643.1 (1990.8, 3509.1)	100	1338.4 (1056.9, 1695.1)	100	1985.7 (1510.1, 2611.0)
		1 Month	95	11919.3 (9839.1, 14439.3)	102	12103.8 (9992.0, 14662.0)	99	6913.9 (5690.4, 8400.5)	100	7128.6 (5954.4, 8534.3)
	Positive[d]	Prevax	62	5615.4 (4406.4, 7156.1)	61	5428.8 (4112.6, 7166.3)	33	3183.8 (2185.4, 4638.2)	36	6390.0 (4353.9, 9378.3)
		1 Month	62	16214.4 (13340.3, 19707.6)	62	15336.7 (12079.9, 19471.6)	32	10119.7 (7341.3, 13949.6)	36	12362.0 (9000.5, 16978.9)
	Negative[e]	Prevax	33	456.8 (291.5, 716.0)	40	881.9 (601.6, 1292.7)	67	873.5 (682.8, 1117.3)	64	1028.9 (795.8, 1330.3)
		1 Month	33	6685.8 (4731.8, 9446.9)	40	8386.3 (6235.4, 11279.2)	67	5763.8 (4550.1, 7301.1)	64	5230.2 (4357.9, 6277.2)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

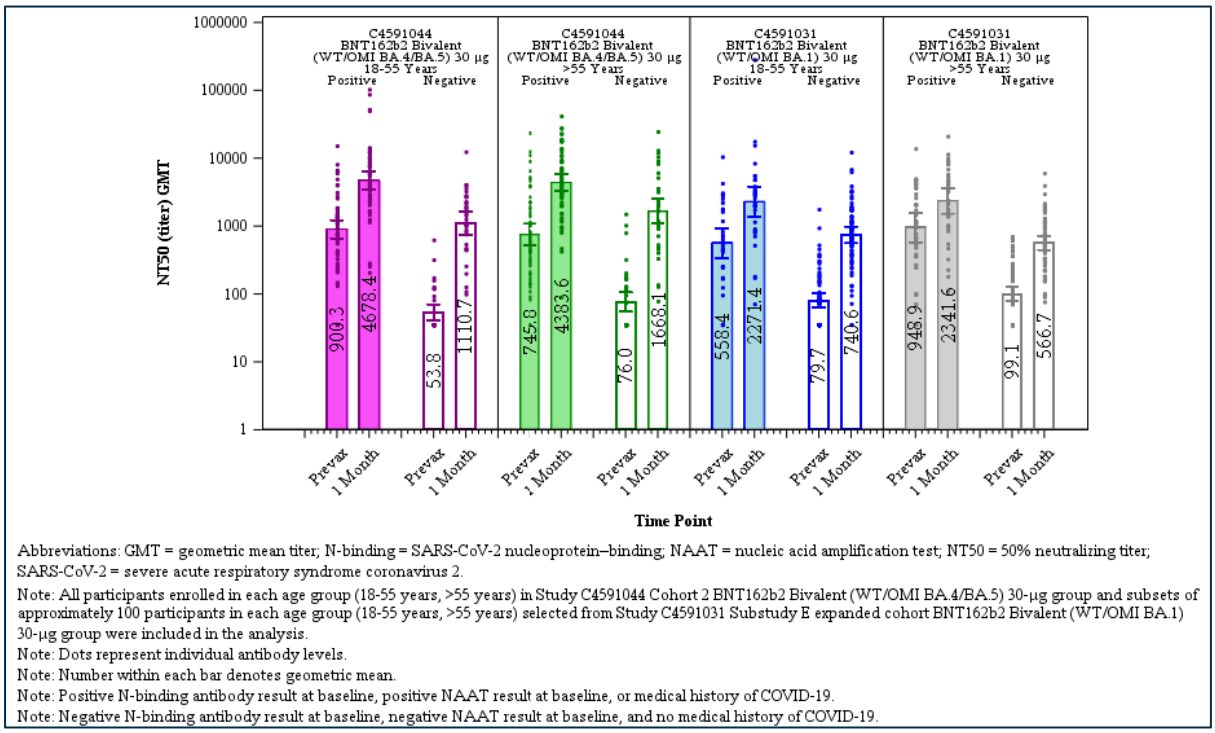
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 4, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Figure 5. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: Omicron BA.4/BA.5 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figure 2, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Table 19. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Baseline SARSCoV-2 Status – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
			18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	95	8.4 (6.3, 11.1)	101	9.9 (7.4, 13.2)	100	7.1 (5.7, 8.9)	99	4.2 (3.4, 5.2)
	Positive[d]	1 Month	62	5.2 (3.8, 7.1)	61	5.9 (4.2, 8.1)	33	4.1 (2.8, 5.9)	36	2.5 (1.8, 3.3)
	Negative[e]	1 Month	33	20.6 (13.6, 31.3)	40	21.9 (14.2, 33.8)	67	9.3 (7.2, 12.1)	63	5.8 (4.5, 7.5)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	All	1 Month	95	7.0 (5.3, 9.1)	102	7.3 (5.6, 9.5)	100	9.3 (7.3, 12.0)	100	5.1 (3.9, 6.6)
	Positive[d]	1 Month	62	4.2 (3.2, 5.6)	62	4.1 (3.1, 5.6)	33	4.4 (2.9, 6.7)	36	2.2 (1.5, 3.1)
	Negative[e]	1 Month	33	17.8 (11.6, 27.5)	40	17.5 (12.2, 25.1)	67	13.5 (10.3, 17.7)	64	8.2 (6.1, 11.2)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	95	5.1 (3.9, 6.6)	101	4.6 (3.7, 5.8)	99	5.2 (4.3, 6.3)	100	3.6 (2.9, 4.4)
	Positive[d]	1 Month	62	2.9 (2.3, 3.6)	61	2.9 (2.3, 3.6)	32	3.2 (2.4, 4.3)	36	1.9 (1.5, 2.6)
	Negative[e]	1 Month	33	14.6 (9.5, 22.6)	40	9.5 (6.4, 14.0)	67	6.6 (5.2, 8.3)	64	5.1 (3.9, 6.5)

Abbreviations: GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 6, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: In recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, observed GMTs at 1 month post-study vaccination were more than 4 times higher in participants 18-55 YOA who were baseline positive for SARS-CoV-2 vs baseline negative, and more than 2.5 times higher in participants > 55 YOA who were baseline positive vs negative. In those who were baseline positive, both GMTs and GMFRs were of a similar order of magnitude in those 18-55 YOA as those > 55 YOA.

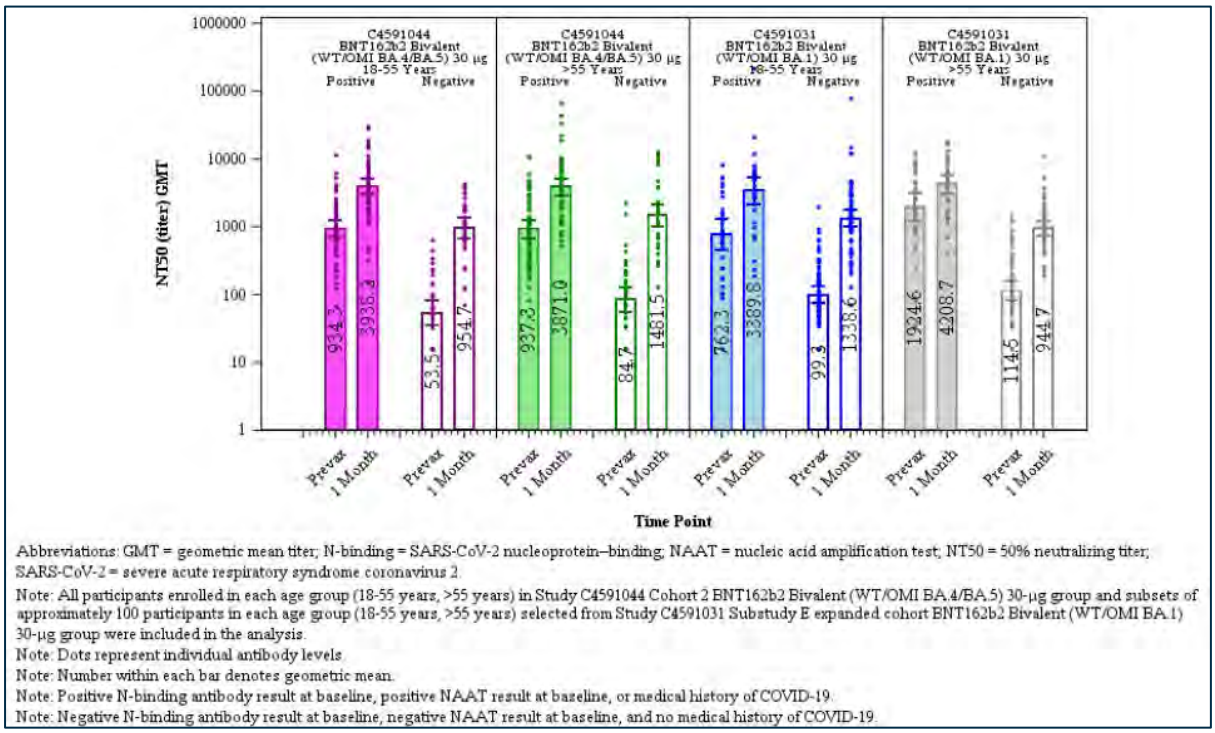
GMTs at 1 month in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg who were **baseline positive** were higher than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg in both age groups (i.e. for participants 18-55 YOA, GMTs of 4678.4 vs 2271.4 respectively; for participants > 55 YOA, GMTs of 4383.6 vs 2341.6 respectively [Figure 5]). Respective GMFRs at 1 month were also highest in BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients (vs BNT162b2 bivalent (WT/OMI BA.1) 30 µg recipients) across both age groups.

The Evaluator concludes that in those with prior evidence of infection (i.e. baseline positive), BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appears to be neutralise Omicron BA.4/5 at least as well (if not better) than BNT162b2 bivalent (WT/OMI BA.1) 30 µg in both age groups; however, there are overlapping 95% CIs in both instances.

Omicron BA.1 neutralisation – participants with or without evidence of infection

Omicron BA.1 neutralising GMTs at 1 month after study vaccination are shown in Table 18 and Figure 6 for participants 18-55 YOA and > 55 YOA with or without out evidence of infection. The corresponding GMFRs are shown in Table 19.

Figure 6. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: Omicron BA.1 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figure 4, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: In SARS-CoV-2 **baseline negative** participants, 1 month GMTs against Omicron BA.1 were lower in 18-55 YOA recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg, but higher in > 55 YOA recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg; however, in both instances, 95% CIs were overlapping. In part reflecting the effect of higher baseline GMTs in the BNT162b2 bivalent (WT/OMI BA.1) 30 µg group (likely due to more recent receipt of BNT162b2 30 µg), GMFRs were higher in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg in both age groups.

In SARS-CoV-2 **baseline positive** participants, 1 month GMTs against Omicron BA.1 were very similar for recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg, and across both age groups. GMFRs were similar in recipients of the two vaccines in the 18-55 YOA group but higher in the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group in those > 55 YOA.

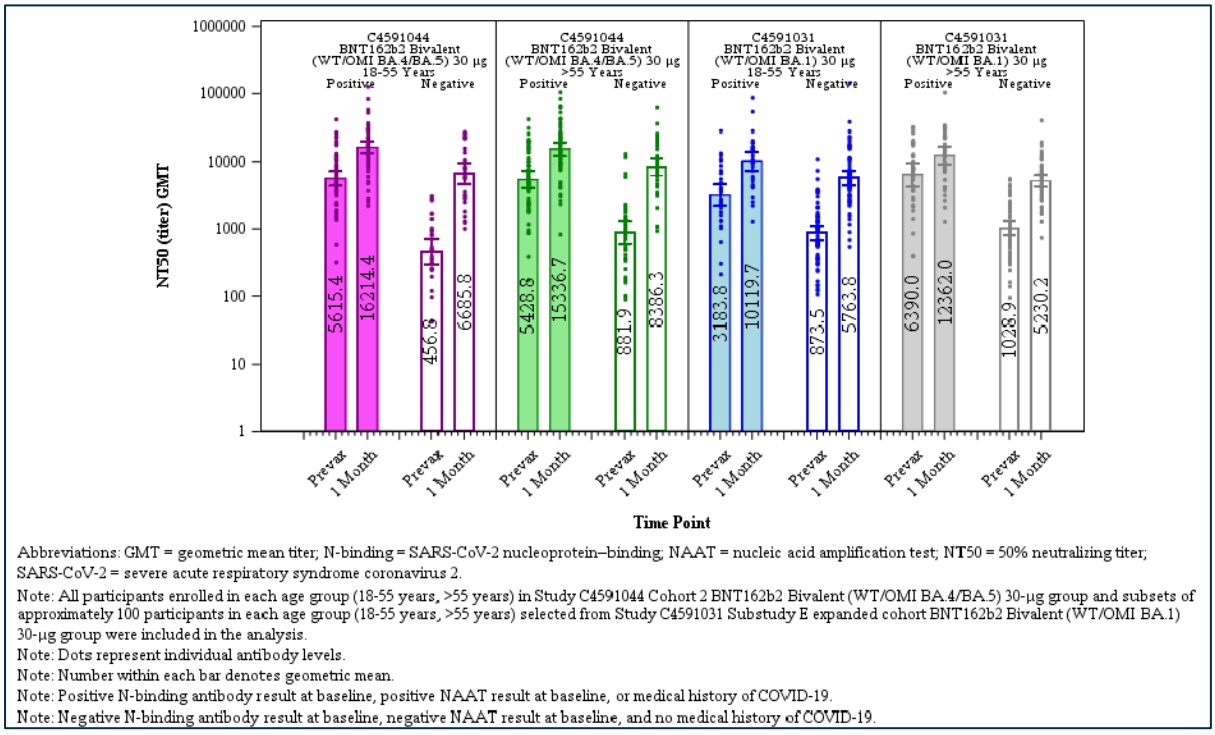
Noting the relatively small numbers, wide 95% CIs and differences in case/control selection criteria, the Evaluator concludes that neutralisation responses against Omicron BA.1 are

generally similar in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg.

Reference strain neutralisation – participants with or without evidence of infection

Reference strain neutralising GMTs at 1 month after study vaccination are shown in Table 18 and Figure 7 for participants 18-55 YOA and > 55 YOA with or without evidence of infection. The corresponding GMFRs are shown in Table 19.

Figure 7. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: Reference Strain – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figure 6, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: In SARS-CoV-2 **baseline negative** participants, 1 month GMTs against reference strain were higher in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg; the same pattern was seen in **baseline positive** participants. Noting that pre-vaccination neutralisation titres against reference strain were much higher in both baseline negative and baseline positive participants than neutralisation titres against Omicron BA.4/5 or Omicron BA.1, GMFRs were generally similar in both age groups for recipients of both vaccines in the SARS-CoV-2 **baseline positive** participants; however, GMFRs were higher for both age groups in BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients who were **baseline negative** (in the case of participants 18-55 YOA, the 95% CIs were non-overlapping).

Noting the relatively small numbers, wide 95% CIs and differences in case/control selection criteria, the Evaluator concludes that neutralisation responses against reference strain are generally similar in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 µg in **baseline positive** participants. Neutralisation

responses against reference strain appear to be higher in BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg participants in **baseline negative** participants, particularly in the 18-55 YOA group (noting the caveats above).

Seroresponse rates

Omicron BA.4/5 neutralisation – participants without evidence of infection

Omicron BA.4/5 seroresponse rates at 1 month after study vaccination are shown in Table 20 for participants 18-55 YOA and > 55 YOA without evidence of infection.

Table 20. Number (%) of Participants Achieving Seroresponse – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
		18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	1 Month	32	26 (81.3) (63.6, 92.8)	40	36 (90.0) (76.3, 97.2)	67	47 (70.1) (57.7, 80.7)	63	31 (49.2) (36.4, 62.1)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1 Month	32	23 (71.9) (53.3, 86.3)	40	37 (92.5) (79.6, 98.4)	67	59 (88.1) (77.8, 94.7)	64	44 (68.8) (55.9, 79.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	1 Month	32	26 (81.3) (63.6, 92.8)	40	30 (75.0) (58.8, 87.3)	67	48 (71.6) (59.3, 82.0)	64	35 (54.7) (41.7, 67.2)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
Note: Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.

Source: Table 7, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Omicron BA.4/5 neutralisation – participants with or without evidence of infection

Omicron BA.4/5 seroresponse rates at 1 month after study vaccination are shown in Table 21 for participants 18-55 YOA and > 55 YOA with or without evidence of infection.

Table 21. Number (%) of Participants Achieving Seroresponse, by Baseline SARS-CoV-2 Status – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2 and Subset of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 Bivalent (WT/OMI BA.1) 30 µg			
			18-55 Years		>55 Years		18-55 Years		>55 Years	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	95	61 (64.2) (53.7, 73.8)	101	72 (71.3) (61.4, 79.9)	100	62 (62.0) (51.7, 71.5)	99	38 (38.4) (28.8, 48.7)
	Positive[e]	1 Month	62	34 (54.8) (41.7, 67.5)	61	36 (59.0) (45.7, 71.4)	33	15 (45.5) (28.1, 63.6)	36	7 (19.4) (8.2, 36.0)
	Negative[f]	1 Month	33	27 (81.8) (64.5, 93.0)	40	36 (90.0) (76.3, 97.2)	67	47 (70.1) (57.7, 80.7)	63	31 (49.2) (36.4, 62.1)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	All	1 Month	95	52 (54.7) (44.2, 65.0)	102	65 (63.7) (53.6, 73.0)	100	75 (75.0) (65.3, 83.1)	100	52 (52.0) (41.8, 62.1)
	Positive[e]	1 Month	62	28 (45.2) (32.5, 58.3)	62	28 (45.2) (32.5, 58.3)	33	16 (48.5) (30.8, 66.5)	36	8 (22.2) (10.1, 39.2)
	Negative[f]	1 Month	33	24 (72.7) (54.5, 86.7)	40	37 (92.5) (79.6, 98.4)	67	59 (88.1) (77.8, 94.7)	64	44 (68.8) (55.9, 79.8)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	95	47 (49.5) (39.1, 59.9)	101	51 (50.5) (40.4, 60.6)	99	59 (59.6) (49.3, 69.3)	100	41 (41.0) (31.3, 51.3)
	Positive[e]	1 Month	62	20 (32.3) (20.9, 45.3)	61	21 (34.4) (22.7, 47.7)	32	11 (34.4) (18.6, 53.2)	36	6 (16.7) (6.4, 32.8)
	Negative[f]	1 Month	33	27 (81.8) (64.5, 93.0)	40	30 (75.0) (58.8, 87.3)	67	48 (71.6) (59.3, 82.0)	64	35 (54.7) (41.7, 67.2)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and subsets of approximately 100 participants in each age group (18-55 years, >55 years) selected from Study C4591031 Substudy E expanded cohort BNT162b2 Bivalent (WT/OMI BA.1) 30-µg group were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 8, 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022.

Evaluator's comments: See collated comments following the section below on reference strain.

Omicron BA.1 neutralisation – participants with or without evidence of infection

Omicron BA.1 seroresponse rates at 1 month after study vaccination are shown in Table 21 for participants 18-55 YOA and > 55 YOA with or without evidence of infection.

Evaluator's comments: See collated comments following the section below on reference strain.

Reference strain – participants with or without evidence of infection

Reference strain seroresponse rates at 1 month after study vaccination are shown in Table 21 for participants 18-55 YOA and > 55 YOA with or without evidence of infection.

Evaluator's comments: Seroresponse rates reflect ≥ 4-fold rises in post-dose vs pre-dose antibody titres so will be expected to be higher in baseline SARS-CoV-2 negative participants then SARS-CoV-2 positive participants due to relatively lower pre-dose titres (even if post-dose GMTs are higher in baseline positive participants). This pattern was observed for both vaccines and in both age groups for all neutralisation responses studied (i.e. Omicron BA.4/5, Omicron BA.1 and reference strain).

In **baseline negative** participants, seroresponse rates for **neutralisation of Omicron BA.4/5** were higher in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg in both age groups (i.e. participants 18-55 YOA, 81.8%; participants > 55 YOA, 90.0%) than in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 μg (i.e. 70.1% and 49.2% respectively). The 95% CIs were non-overlapping in the participants > 55 YOA. Seroresponse rates were, as expected, lower in **baseline positive** participants than in baseline negative participants; however, were again higher in both age groups of recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg than recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 μg.

Seroresponse rates for **neutralisation of Omicron BA.1** were slightly higher in participants 18-55 YOA in recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 μg than in recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg for both baseline negative and baseline positive participants. The opposite was seen in participants > 55 YOA but in all cases and in all age / SARS-CoV-2-exposure subgroups, 95% CIs were overlapping.

Seroresponse rates for **neutralisation of reference strain** in **baseline negative** participants who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg were 81.8% in participants 18-55 YOA and 75.0% in participants > 55 YOA; these were of a similar magnitude for seroresponse rates for neutralisation of Omicron BA.4/5 (quoted above, 81.8% and 90% respectively). In **baseline positive** recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg, seroresponse rates were lower; 32.3% in participants 18-55 YOA and 34.4% in participants > 55 YOA. In most subgroups, seroresponse rates were similar if not higher in BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg recipients than in BNT162b2 bivalent (WT/OMI BA.1) 30 μg recipients.

Noting the relatively small numbers, wide 95% CIs and differences in case/control selection criteria, the Evaluator concludes that seroresponse rates against **Omicron BA.4/5** appeared higher for recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg than for recipients of BNT162b2 bivalent (WT/OMI BA.1) 30 μg in both baseline negative and positive participants. For **reference strain**, seroresponse rates were more similar between vaccine groups but still slightly higher in baseline negative participants in the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg group. For **Omicron BA.1**, seroresponse rates were generally similar between vaccine groups in baseline positive and negative participants and in both age groups.

7.2.1.13. Results for secondary efficacy outcomes

One of the secondary immunogenicity **objectives** was for:

> 'Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg compared to BNT162b2 30 μg given as a second booster dose to BNT162b2-experience participants 18 through 55 and > 55 years of age.', noting that 'The participants from C4591031 Substudy E expanded cohort who received BNT162b2 30 μg as a second booster dose will be used as comparator group for this objective.'

The **endpoints** and **estimands** for this objective were Omicron BA.4/5 and reference strain neutralising GMTs, GMFRs and seroresponse rates from before the study vaccination to each time point following vaccination.

The present submission includes such immunogenicity data out to one month post-vaccination, as presented in the sections that follow, noting the earlier DCO of 12/10/2022 meant that a

smaller subset of participants was examined compared to those described for the primary immunogenicity objective in section 7.2.1.12 (DCO 2/12/2022).

The baseline characteristics for these participants in the secondary immunogenicity analyses were shown in Table 14.

Geometric mean titres (data cutoff 12/10/2022)

Omicron BA.4/5 neutralisation and reference strain neutralisation

Neutralising titres against Omicron BA.4/5 comparing 4th dose booster vaccination with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg vs BNT162b2 30 µg are shown in Table 22. These results are stratified by baseline positive vs baseline negative SARS-CoV-2 exposure and are also shown for those groups combined Table 22. Parallel data for neutralising titres against reference strain are also shown in Table 22.

Table 22. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – 1-Month Immunogenicity Analysis – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	38	63.7 (38.7, 104.9)	36	67.9 (39.7, 116.3)	40	82.1 (47.6, 141.8)
		1 Month	38	605.9 (413.3, 888.2)	36	896.4 (577.3, 1392.0)	40	236.3 (148.6, 375.7)
	Positive[d]	Prevax	20	197.0 (117.8, 329.4)	19	206.6 (115.9, 368.3)	20	226.3 (110.4, 463.8)
		1 Month	20	1173.8 (763.3, 1805.0)	19	1376.9 (820.1, 2311.6)	20	629.0 (371.2, 1066.0)
	Negative[e]	Prevax	18	18.2 (12.8, 25.9)	17	19.6 (12.4, 31.1)	20	29.8 (16.9, 52.5)
		1 Month	18	290.6 (180.6, 467.7)	17	554.9 (271.3, 1135.1)	20	88.8 (55.3, 142.6)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	All	Prevax	38	558.2 (347.4, 896.8)	36	598.3 (372.2, 961.8)	40	874.3 (479.7, 1593.3)
		1 Month	38	2830.2 (2155.0, 3716.9)	36	3483.6 (2430.9, 4992.3)	40	2604.7 (1863.6, 3640.7)
	Positive[d]	Prevax	20	1371.9 (887.2, 2121.3)	19	1376.9 (854.0, 2219.9)	20	2516.0 (1291.8, 4900.4)
		1 Month	20	4231.4 (3002.9, 5962.6)	19	4847.4 (3228.6, 7277.6)	20	5120.0 (3465.6, 7564.2)
	Negative[e]	Prevax	18	205.5 (110.6, 381.8)	17	235.7 (126.8, 438.2)	20	303.8 (137.9, 669.3)
		1 Month	18	1810.2 (1276.0, 2568.1)	17	2408.1 (1310.7, 4424.5)	20	1325.1 (924.2, 1900.1)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 3, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Evaluator's comments: See the following section on GMFRs for a combined discussion of GMTs and GMFRs.

Geometric fold rises (data cutoff 12/10/2022)

Omicron BA.4/5 neutralisation and reference strain neutralisation

GMFRs against Omicron BA.4/5 comparing 4th dose booster vaccination with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg vs BNT162b2 30 µg are shown in Table 23. These results are stratified by baseline positive vs baseline negative SARS-CoV-2 exposure and are also shown for those groups combined Table 23. Parallel data for GMFRs against reference strain are also shown in Table 23.

Table 23. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Baseline SARS-CoV-2 Status – 1-Month Immunogenicity Analysis – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	38	9.5 (6.7, 13.6)	36	13.2 (8.0, 21.6)	40	2.9 (2.1, 3.9)
	Positive[d]	1 Month	20	6.0 (3.5, 10.1)	19	6.7 (3.5, 12.7)	20	2.8 (1.9, 4.1)
	Negative[e]	1 Month	18	16.0 (10.8, 23.7)	17	28.3 (15.2, 52.8)	20	3.0 (1.8, 4.9)
SARS-CoV-2 FFRNT - reference strain - NT50 (titer)	All	1 Month	38	5.1 (3.5, 7.3)	36	5.8 (3.9, 8.6)	40	3.0 (2.1, 4.3)
	Positive[d]	1 Month	20	3.1 (2.0, 4.9)	19	3.5 (2.1, 6.0)	20	2.0 (1.4, 2.9)
	Negative[e]	1 Month	18	8.8 (5.4, 14.4)	17	10.2 (6.3, 16.6)	20	4.4 (2.3, 8.2)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from each age group (18-55 years, >55 years) in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point.

c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 4, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Evaluator's comments: The Evaluator notes the relatively small numbers of participants across the 3 study groups (~ 36-40 in each overall) and across the subgroups stratified by baseline positive or negative SARS-CoV-2 exposure (6 subgroups of ~ 17-20 in each). This introduces some expected imprecision into the results, as evident by wide 95% CIs in some instances. The reference BNT162b2 30 µg group only included participants > 55 YOA whereas the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group included age group 18-55 and > 55 YOA.

Also, given the differential recruitment of participants into Study C4591044 Cohort 2 and Study C4591031 Substudy E, it is quite possible (if not likely) that there were differences in the proportions of variants/sublineages of SARS-CoV-2 that resulted in prior exposure in the baseline SARS-CoV-2 positive groups. The Evaluator would expect these strain-related differences to potentially effect neutralisation responses measured against different variants/sublineages (e.g. Omicron BA.4/5, reference strain) in both the overall analyses and sub-analyses among baseline SARS-CoV-2 participants.

As shown in the baseline demographic characteristics (Table 14), the time between Dose 3 of BNT162b2 30 µg and Dose 4 of either BNT162b2 30 µg (Study C4591031 Substudy E) or BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg (Study C4591044 Cohort 2) was substantially shorter for the Substudy E participants (median of 6.3 months [Study C4591031 Substudy E] vs 10.7 [18-55 YOA] and 11.3 months [> 55 YOA] respectively). Hence, the higher baseline neutralising titres evident in the Study C4591031 Substudy E participants were to be expected (in the order of roughly 50%).

Because of this 'advantage', the Evaluator would have expected *relatively* higher post-dose titres in Study C4591031 Substudy E participants against Omicron BA.4/5 than might otherwise have been observed for that group, and *absolutely* higher post-dose titres (cf the Study C4591044 Cohort 2 participants) against reference strain.

The Evaluator notes the following:

- In baseline SARS-CoV-2 negative participants, GMFRs were higher in BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients (both 18-55 YOA *and* > 55 YOA) than in BNT162b2 30 µg recipients; both against Omicron BA.4/5 *and* reference strain in all 4 subgroup comparisons.
- 1 month post-dose GMTs were higher for BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients in *both* age groups compared to > 55 YOA recipients of BNT162b2 30 µg in all sub-group analyses apart from baseline SARS-CoV-2 positive participants responses against reference strain.
- 1 month post-dose GMTs were more than twice as high in participants with baseline SARS-CoV-2 exposure than in those without baseline SARS-CoV-2 exposure in all vaccine groups and in all age groups, both against Omicron BA.4/5 and reference strain.
- In recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, for all measures (including neutralising of Omicron BA.4/5 *or* reference strain), both 1 month post-dose GMTs and GMFRs were higher in the > 55 YOA group than in the 18-55 YOA group.

In conclusion, based on the available data and with reference to the caveats above, immune responses among BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients ≥ 18 YOA appeared to be more robust than in those > 55 YOA given BNT162b2 30 µg as a 4th dose, both for Omicron BA.4/5 and reference strain (for all but baseline SARS-CoV-2 participants against reference strain). This was despite the 3rd dose being given more recently in recipients of BNT162b2 30 µg. GMTs were more than twice as high in those with prior SARS-CoV-2 exposure (in all age groups and against both Omicron BA.4/5 and reference strain).

7.2.1.14. Results for exploratory efficacy outcomes – Additional new variant neutralisation data (data cutoff 12/10/2022)

'Descriptive immunogenicity analyses from Study C4591044 Cohort 2 were performed to characterize **Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB** neutralization responses following a booster (dose 4) dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to the BNT162b2 30 µg' vaccine. These analyses utilised a non-validated FFRNT.

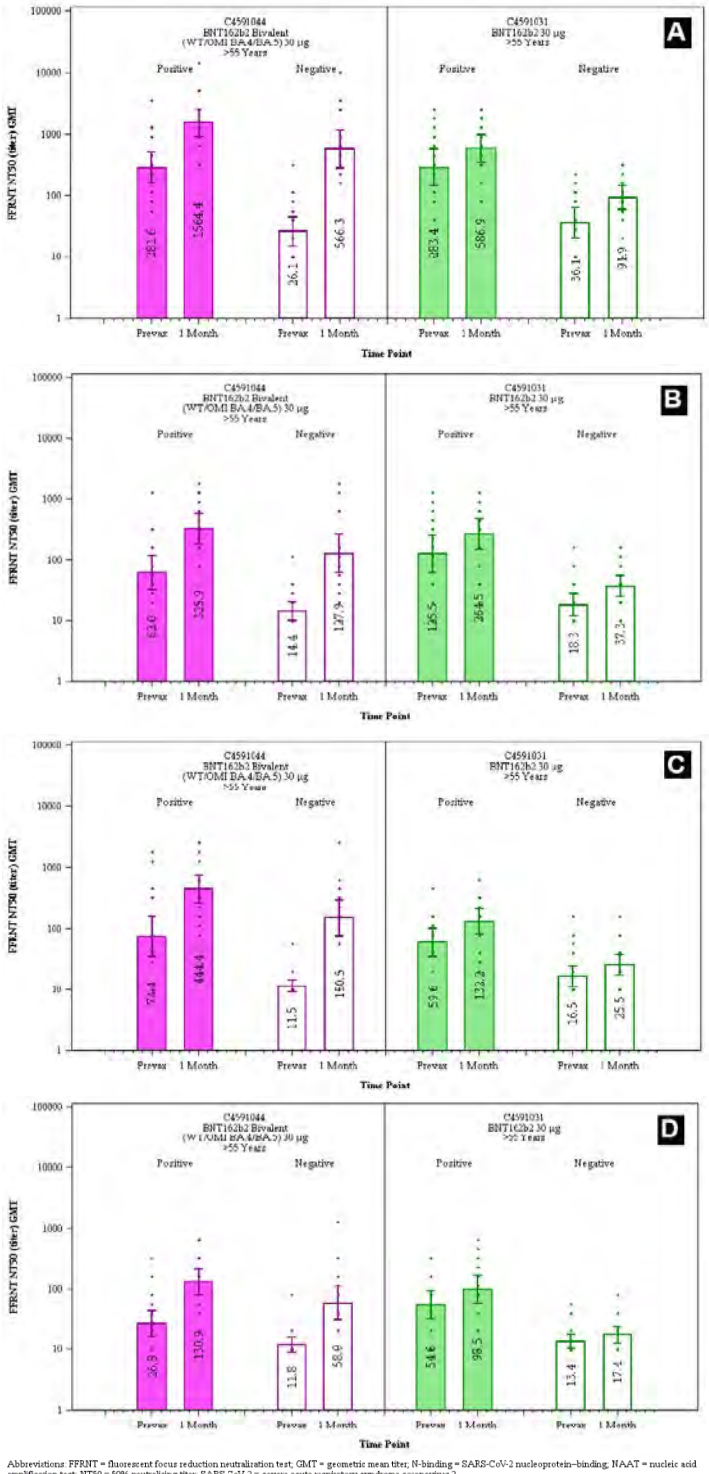
Those who had received a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg were a subset of approximately participants from Study C4591044 Cohort 2 and the control group were approximately 40 participants who had received a 4th dose of BNT162b2 30 µg in Study C4591031 Substudy E (Table 52). All participants were > 55 YOA and there was deliberate selection to enable roughly equal numbers of baseline SARS-CoV-2 positive vs negative participants.

The **baseline demographic characteristics** for these participant subsets were shown in Table 2 of the 'Study C4591044 Cohort 2-Additional Variant Neutralization Data' report. Median ages were 66.0 years for the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg subset and 65.5 years for the BNT162b2 30 µg subset. The median times from the 3rd dose of BNT162b2 30 µg to the study vaccination (4th dose) were 11.3 and 6.3 months respectively.

Geometric mean titres (data cutoff 12/10/2022)

GMTs at 1 month post 4th dose are shown for each of the four new variants (i.e. Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB) in Table 53, overall and stratified by exposure to SARS-CoV-2 (positive or negative). The same data are represented graphically in Figure 8.

Figure 8. Geometric Mean Titers and 95% CIs, by Baseline SARS-CoV-2 Status: FFRNT NT50 – (A) Omicron BA.4.6, (B) Omicron BA.2.75.2, (C) Omicron BQ.1.1, (D) Omicron XBB – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age - Evaluable Immunogenicity Population



Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figures 2, 4, 6 and 8, 1 Month Post Dose Immunogenicity Data – New Variants, Study C4591044 Cohort 2 (Sentinel Group) report.

Evaluator's comments: These have been amalgamated into those following the section on seroresponse rates (below).

Geometric fold rises (data cutoff 12/10/2022)

Geometric mean fold rises (GMFRs) of neutralising titres from before study vaccination to 1 month post-dose for Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB are shown in Table 24.

Table 24. Geometric Mean Fold Rises From Before Study Vaccination to Each Subsequent Time Point, by Baseline SARSCoV-2 Status – New Variants Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMFR[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.4.6 - NT50 (titer)	All	1 Month	36	10.6 (6.7, 16.8)	40	2.3 (1.9, 2.8)
	Positive[d]	1 Month	19	5.6 (3.1, 9.8)	20	2.1 (1.5, 2.8)
	Negative[e]	1 Month	17	21.7 (11.6, 40.5)	20	2.5 (1.9, 3.5)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	1 Month	36	6.7 (4.3, 10.5)	40	2.1 (1.7, 2.5)
	Positive[d]	1 Month	19	5.3 (2.8, 9.8)	20	2.1 (1.6, 2.7)
	Negative[e]	1 Month	17	8.9 (4.5, 17.5)	20	2.0 (1.6, 2.6)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	1 Month	36	8.6 (5.5, 13.5)	40	1.8 (1.6, 2.2)
	Positive[d]	1 Month	19	6.0 (3.2, 11.2)	20	2.2 (1.8, 2.7)
	Negative[e]	1 Month	17	13.0 (6.9, 24.8)	20	1.5 (1.2, 1.9)
SARS-CoV-2 FFRNT - Omicron XBB - NT50 (titer)	All	1 Month	36	4.9 (3.4, 7.2)	40	1.5 (1.3, 1.8)
	Positive[d]	1 Month	19	4.9 (2.8, 8.5)	20	1.8 (1.5, 2.2)
	Negative[e]	1 Month	17	5.0 (2.8, 8.9)	20	1.3 (1.1, 1.6)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point.
c. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 4, 1 Month Post Dose Immunogenicity Data – New Variants, Study C4591044 Cohort 2 (Sentinel Group) report.

Evaluator's comments: These have been amalgamated into those following the section on seroresponse rates (below).

Seroresponse rates (data cutoff 12/10/2022)

'Seroresponse was defined as achieving a ≥4-fold rise from baseline (or postvaccination assay result ≥4 × LLOQ if the baseline measurement was below LLOQ).' Seroresponses from before

study vaccination to 1 month post-dose for Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB are shown in Table 25.

Table 25. Number (%) of Participants Achieving Seroresponse, by Baseline SARS-CoV-2 Status – New Variants Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 FFRNT - Omicron BA.4.6 - NT50 (titer)	All	1 Month	36	27 (75.0) (57.8, 87.9)	40	8 (20.0) (9.1, 35.6)
	Positive[e]	1 Month	19	11 (57.9) (33.5, 79.7)	20	5 (25.0) (8.7, 49.1)
	Negative[f]	1 Month	17	16 (94.1) (71.3, 99.9)	20	3 (15.0) (3.2, 37.9)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	1 Month	36	24 (66.7) (49.0, 81.4)	40	6 (15.0) (5.7, 29.8)
	Positive[e]	1 Month	19	12 (63.2) (38.4, 83.7)	20	5 (25.0) (8.7, 49.1)
	Negative[f]	1 Month	17	12 (70.6) (44.0, 89.7)	20	1 (5.0) (0.1, 24.9)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	1 Month	36	25 (69.4) (51.9, 83.7)	40	4 (10.0) (2.8, 23.7)
	Positive[e]	1 Month	19	12 (63.2) (38.4, 83.7)	20	4 (20.0) (5.7, 43.7)
	Negative[f]	1 Month	17	13 (76.5) (50.1, 93.2)	20	0 (0.0) (0.0, 16.8)
SARS-CoV-2 FFRNT - Omicron XBB - NT50 (titer)	All	1 Month	36	14 (38.9) (23.1, 56.5)	40	2 (5.0) (0.6, 16.9)
	Positive[e]	1 Month	19	7 (36.8) (16.3, 61.6)	20	2 (10.0) (1.2, 31.7)
	Negative[f]	1 Month	17	7 (41.2) (18.4, 67.1)	20	0 (0.0) (0.0, 16.8)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 5, 1 Month Post Dose Immunogenicity Data – New Variants, Study C4591044 Cohort 2 (Sentinel Group) report.

Evaluator's comments: Despite having had their 3rd dose more remotely, baseline pre-dose titres were similar in the baseline SARS-CoV-2-negative participant subsets given BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg (~11.3 months) compared to BNT162b2 30 µg (~ 6.3 months) as a 4th dose. This meant that it was feasible to compare 1 month post-dose responses between groups in those without prior SARS-CoV-2 exposure, who were of most interest.

In those who were **baseline negative for SARS-CoV-2 exposure**, 1 month post-dose GMTs against the 4 new variants ranged from 3.39 to 6.16-fold higher in the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group compared to the BNT162b2 30 µg group. In recipients of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, neutralisation (based on GMFR) was most effective against Omicron BA.4.6, followed by BQ.1.1, then BA.2.75.2 and finally XBB.

In those who were **baseline positive for SARS-CoV-2 exposure**, pre-dose neutralisation titres were higher than in those who were baseline negative as expected. Again, neutralisation (based on GMFR) against all 4 new variants was more effective in those receiving BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg than BNT162b2 30 µg, with neutralisation against Omicron XBB being least effective. Compared to baseline negative SARS-CoV-2 participants, 1 month post-dose GMTs ranged from 2.22 to 2.95 higher in those who were baseline SARS-CoV-2 positive.

As the same participant subsets were used to examine Omicron BA.4/5 responses, the Sponsor was able to make a comparison with responses to the new variants and as stated:

- 'When compared to GMFRs against Omicron BA.4/BA.5 in prior 1 month post-dose analysis among participants > 55 years of age in same subset of evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection up to 1 month after the study vaccination, GMFRs against Omicron BA.4.6 were similar (21.7 vs 28.3), while GMFRs against Omicron BQ.1.1 (13.0), BA.2.75.2 (8.9), and XBB (5.0) were lower compared to BA.4/BA.5 (28.3).'

Using the traditional definition for **seroresponse** of a ≥ 4-fold rise in neutralising titre 1 month following a dose of vaccine; in the SARS-CoV-2 negative group, seroresponses were seen against Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB in 94.1%, 70.6%, 76.5%, and 41.2% of participants respectively in the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group but only 15.0%, 5.0%, 0.0%, and 0.0% respectively in the BNT162b2 30 µg group. In their prior analysis of seroresponse against BA.4/5, this was seen in 100% of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg participants in the baseline SARS-CoV-2 negative group.

Within the limits of the analyses, the data provide support for the **conclusions** that a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg induces superior immune responses than BNT162b2 30 µg to the 4 new variants studied in both baseline positive and negative SARS-CoV-2-exposure groups. Omicron XBB was least effectively neutralised whereas Omicron BA.4.6 responses were only slightly lower than those for BA.4/5 in parallel analyses. It is difficult to extrapolate these results to definite differences in correlates of protection against symptomatic or severe COVID-19 but reasonable to conclude that BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg is likely to be at least as good or better than BNT162b2 30 µg. Of note, the fold rises of responses against the new variants following BNT162b2 30 µg in the baseline SARS-CoV-2 negative group were frequently lower than those considered a seroresponse (e.g. 0.0% seroresponses against Omicron BQ.1.1 and XBB).

7.2.1.15. Evaluator commentary (primary and secondary efficacy outcomes – Study C4591044 Cohort 2)

Conclusions drawn by the Sponsor in relation to the analysis of primary immunogenicity data from Study C4591044 Cohort 2 and Study C4591031 Substudy E include:

- '…BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg demonstrated a robust vaccine-elicited immune response.'
- '…a booster (dose 4) dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg elicited higher Omicron BA.4/BA.5 specific neutralization titers at 1 month after study vaccination in both age groups of 18 to 55 and > 55 years compared with comparator groups of BNT162b2-experienced participants 18 to 55 years and > 55 years of age from C4591031 Substudy E who received a booster (dose 4) dose of BNT162b2 Bivalent (WT/OMI BA.1) 30 µg vaccine.'
- 'Overall, immune responses against Omicron BA.1 and reference strain at 1 month after vaccination with BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg were comparable to responses observed in participants who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg vaccine.'
- In relation to Omicron BA.1 and reference strain, variable patterns in immune responses across age groups and/or vaccine groups could be influenced by different numbers of

participants in each age group, heterogeneity in SARS-CoV-2 exposure history (including variants and sublineages) and additional unmeasured factors.
- In general, GMFRs were higher in participants without prior SARS-CoV-2 infection and GMTs were higher in participants with prior infection for both vaccines.
- 'In summary, these data indicate the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) vaccine is immunogenic against circulating Omicron sublineages in both younger and older adults and suggest that vaccines containing contemporary versions of SARS-CoV-2 may provide increased protection against COVID-19 due to Omicron, which is among > 99% of circulating strains.'

The Evaluator is primarily interested in the robustness of the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg immune response in the context of currently circulating Omicron sublineages such as Omicron BA.4/5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB. Ideally, the Evaluator would have preferred the analysis to have included a contemporaneous randomised control group receiving a 4th dose of BNT162b2 30 µg (i.e. COMIRNATY original) rather than a historical control group given another type of bivalent sub-variant vaccine. The use of controls from Study C4591031 Substudy E was subject to a selection procedure that may have inconsistently matched demographic characteristics, as well as likely differences in the type of sub-variants constituting prior exposure (somewhat mitigated by the stratified analysis of baseline negative participants) and proportionately large differences in time between receipt of 3rd and 4th doses. In addition, participant numbers were relatively small with wide 95% CIs that were non-overlapping in most pairwise subgroup comparisons and the analyses were descriptive rather than a statistical examination of superiority and/or non-inferiority. There was no correlation with clinical efficacy in Study C4591044 Cohort 2 and there is still no firmly established correlate of protection involving neutralisation responses.

The data suggest that a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg (given approximately 11 months post-3rd dose) boosts pre-dose Omicron BA.4/5 neutralising GMTs in participants who have no prior to SARS-CoV-2 by a GMFR of 18.9 (95% CI: 12.8, 27.8) in participants 18-55 YOA and 21.0 (95% CI: 14.2, 33.8) in participants > 55 YOA. Seroresponse rates in those age groups are 81.3% (95% CI: 63.6, 92.8) and 90.0% (95% CI: 76.3, 97.2) respectively. A 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg also boosts pre-existing responses in participants with prior SARS-CoV-2 exposure, with higher GMTs but lower GMFRs (reflecting the higher relative baseline titres).

Responses against Omicron BA.4/5 from a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appear as good or better than those generated by BNT162b2 bivalent (WT/OMI BA.1) 30 µg or BNT162b2 30 µg (albeit with smaller numbers and less certainty [reflecting an earlier data cutoff] in that latter comparison). Responses against other variants/sub-variants (i.e reference strain and Omicron BA.1) appear relatively preserved compared to booster vaccination using a 4th dose of BNT162b2 bivalent (WT/OMI BA.1) 30 µg.

In the current phase of the Australian pandemic, the Evaluator thinks it is likely that a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg would provide additional clinical protection relative to no booster at all and that it would be no worse than having a booster dose of the currently available BNT162b2 bivalent (WT/OMI BA.1) 30 µg or BNT162b2 30 µg. It may even prove superior, pending formal statistical hypothesis testing due in the new year, as specified in the study protocol (Table 49). Of note, these immunogenicity data only pertain to adults ≥ 18 YOA and do not include adolescents.

EvQset3: In the 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022, it is stated that, 'Immunogenicity data for participants 12 to 17 years of age will be provided in a separate report when available.' Please clarify when those data are intended to be submitted and also the timing for submission of the superiority and noninferiority testing specified in the primary immunogenicity objectives.

7.3. Other efficacy studies

7.3.1. Study C4591031

'Study C4591031 is a Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Substudies D and E have been designed to assess the safety, tolerability, and immunogenicity of monovalent and bivalent Omicron variant-modified vaccine in BNT162b2-experienced participants enrolled to receive booster dose(s) of either the BNT162b2 prototype vaccine or an Omicron BA.1 variant-modified vaccine. Study C4591031 (Substudy D and Substudy E) utilized the Omicron variant-modified vaccine BNT162b2 OMICRON (B.1.1.529) BA.1 (hereafter referred to as BNT162b2 OMI) as a monovalent vaccine or a bivalent vaccine in combination with BNT162b2. BNT162b2 OMI is a BNT162b2 RNA-LNP vaccine utilizing modified RNA and encoding the P2 S containing Omicron BA.1 variant-specific mutations.'

7.3.1.1. Study C4591031 Substudy D – Cohort 2

'C4591031 Substudy D is an ongoing, randomized Phase 3 observer-blinded substudy evaluating an additional booster (fourth) dose of BNT162b2 30-µg and the Omicron variant-modified BNT162b2 OMI 30-µg in approximately 640 BNT162b2-experienced participants in Cohort 2 who have received 3 doses of BNT162b2.'

7.3.1.2. Study C4591031 Substudy D – Cohort 3

'Study C4591031 Substudy D Cohort 3 is an ongoing, randomized, Phase 3 study in healthy adults ≥ 18 to ≤ 55 years of age designed to evaluate safety, tolerability and immunogenicity of monovalent BNT162b2 OMI 30-µg compared to BNT162b2 30-µg administered as a 2-dose primary series to BNT162b2 naïve participants.'

Data were presented in a report titled, 'Study C4591031 Substudy D-Cohort 3-Sentinel Group-Immunogenicity Data' with a DCO of 25/04/2022. This involved 30 participants who received a 2 dose primary series of monovalent BNT162b2 OMI 30µg given 3 weeks apart. The evaluable immunogenicity population was 29 participants. There were only 9/29 (31.0%) participants without prior evidence of SARS-CoV-2 infection.

Geometric mean titres, GMFRs and seroresponses (data cutoff 25/04/2022)

At 1 month following the primary series in participants without prior exposure to SARS-CoV-2, GMFRs (95% CI) and seroresponses (% [95% CI]) were:

- Omicron BA.1 – GMFR 54.9 (31.1, 96.7), seroresponse 100 (66.4, 100.0).
- Reference strain – GMFR 1.1 (0.9, 1.3), seroresponse 0.0 (0.0, 33.6).
- Delta – GMFR 2.1 (0.6, 7.3), seroresponse 11.1 (0.3, 48.2).

Comparative GMTs (95% CI)[5] at 1 month following the primary series in participants without prior exposure to SARS-CoV-2 were:

- Omicron BA.1 – GMT 718.4 (421.7, 1223.9).
- Omicron BA.2 – GMT 127.0 (57.7, 279.3).
- Omicron BA.2.12.1 – GMT 104.8 (38.7, 283.3).
- Omicron BA.4/5 – GMT 17.8 (6.8, 46.6).

Evaluator's comments: The Evaluator agrees with the Sponsor that, 'A monovalent Omicron BA.1 primary (2-Dose) series in BNT162b2 vaccine-naïve individuals elicited an effective but Omicron BA.1-focused response in participants 18 to 55 years of age in Study C4591031 Substudy D Cohort 3, with limited neutralization of other variants of concern (Delta) or the

[5] N.b. GMFRs were not presented for each of these Omicron sublineages.

SARS-CoV-2 reference strain (USA-WA1/2020).' Among the Omicron sublineages studied, neutralisation was worst against Omicron BA.4/5 (GMFRs and seroresponses were not presented in that group). As the current submission is for use of a BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg vaccine as a booster dose rather than a primary series, the Evaluator doesn't find these presented data to provide much support to the current application.

7.3.1.3. Study C4591031 Substudy E

'C4591031 Substudy E is a randomized, Phase 3 observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of the high-dose monovalent BNT162b2 OMI (60 μg), high-dose BNT162b2 (60 μg), and a high-dose bivalent vaccine [combination of BNT162b2 OMI and BNT162b2 (30 μg of each)], compared to monovalent BNT162b2 OMI 30 μg, BNT162b2 30 μg, and bivalent BNT162b2 OMI and BNT162b2 (15 μg of each), given as a fourth dose. Approximately 1840 participants > 55 years of age and who had received 3 prior doses of BNT162b2 (30-μg doses), with the most recent dose being 5 to 12 months prior to randomization were enrolled in this substudy. Participants were randomized at a ratio of 1:1:1:1:1:1.'

7.3.1. Study C4591001

'Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 safety, immunogenicity and efficacy registration study. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study enrolling up to approximately 46,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. This study served as the basis for licensure in individuals ≥ 12 years of age.'

7.3.1.1. Study C4591001 – Booster dose

'Immunogenicity and safety evaluations of a booster dose were conducted in a subset of Phase 3 participants who received a third dose of BNT162b2 30 μg at least 6 months after their second dose.'

7.3.1.2. Study C4591001 – Variants of concern

'Evaluations of SARS-CoV-2 variants of concern (VOC) responses (in participants who received a SARS-CoV-2 Beta variant (originally identified in South Africa) vaccine [BNT162b2$_{SA}$] as a primary 2-dose series in BNT162b2-naïve participants and as a third and fourth dose after 2 doses of BNT162b2 30 μg were conducted in a subset of Phase 3 participants 18 to 55 years of age. For primary series evaluation, participants received BNT162b2$_{SA}$ 30-μg as two doses administered 3 weeks apart. For booster dose evaluation, participants who had received two prior doses of BNT162b2 30-μg received 1 or 2 booster doses (given 1 month apart) of BNT162b2$_{SA}$ 30-μg, with the first booster given at least 6 months after the 2nd dose of BNT162b2 and the second booster dose given 1 month after the first booster dose.'

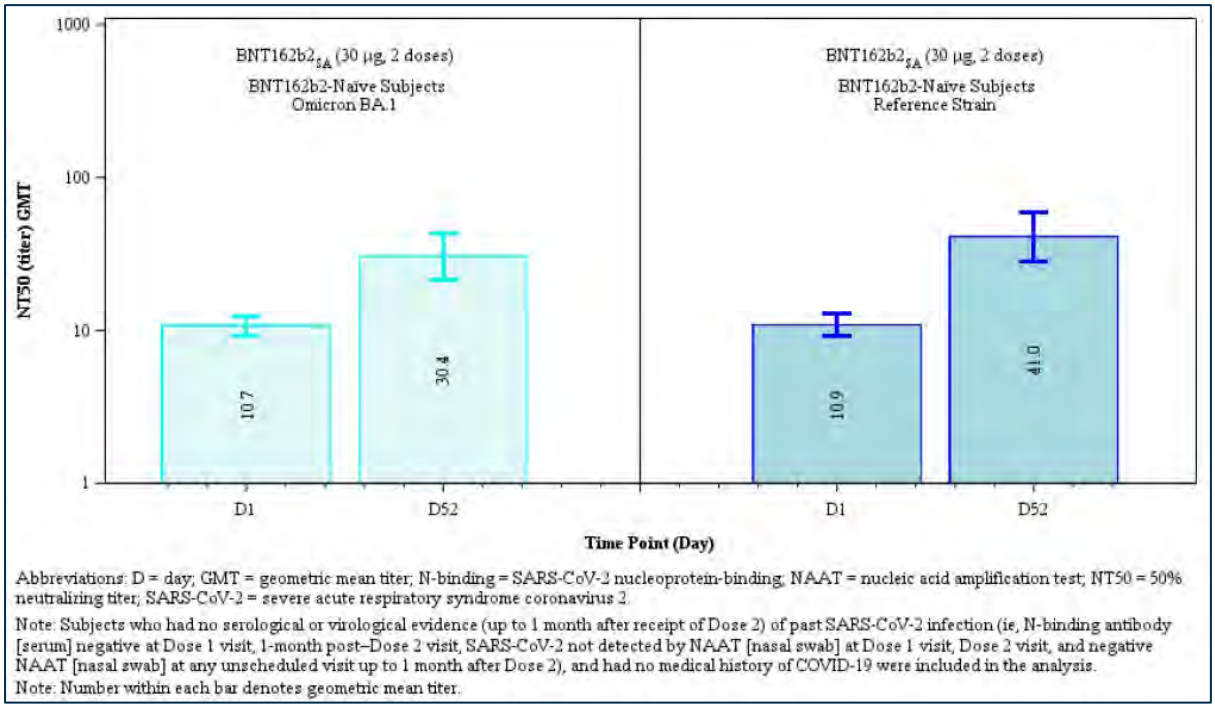
Omicron BA.1-specific neutralising titres were determined using an FFRNT. Data were presented in a report titled, 'C4591001 (Beta Modified Vaccine) COVID-19 Vaccine Omicron Neutralization Ad Hoc Report' (approved 27/07/2022).

Geometric mean titres (data cutoff 23/05/2022)

BNT162b2-Naïve Participants – Primary Series of BNT162b2$_{SA}$

Omicron BA.1-specific neutralising titres for participants 18-55 YOA without prior evidence of SARS-CoV-2 infection at 1 month following a primary series of BNT162b2$_{SA}$ 30μg are shown in Figure 9. The GMFR from before Dose 1 to 1 month post-Dose 2 was 2.8 (95% CI: 1.9, 4.2).

Figure 9. Geometric Mean Titers and 95% CIs: SARS-CoV-2 Neutralization Assay – NT50 – Phase 3 – Omicron Neutralization Set – BNT162b2-Naive Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population



Abbreviations: D = day; GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of Dose 2) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 visit, 1-month post–Dose 2 visit, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 visit, Dose 2 visit, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2), and had no medical history of COVID-19 were included in the analysis.

Note: Number within each bar denotes geometric mean titer.

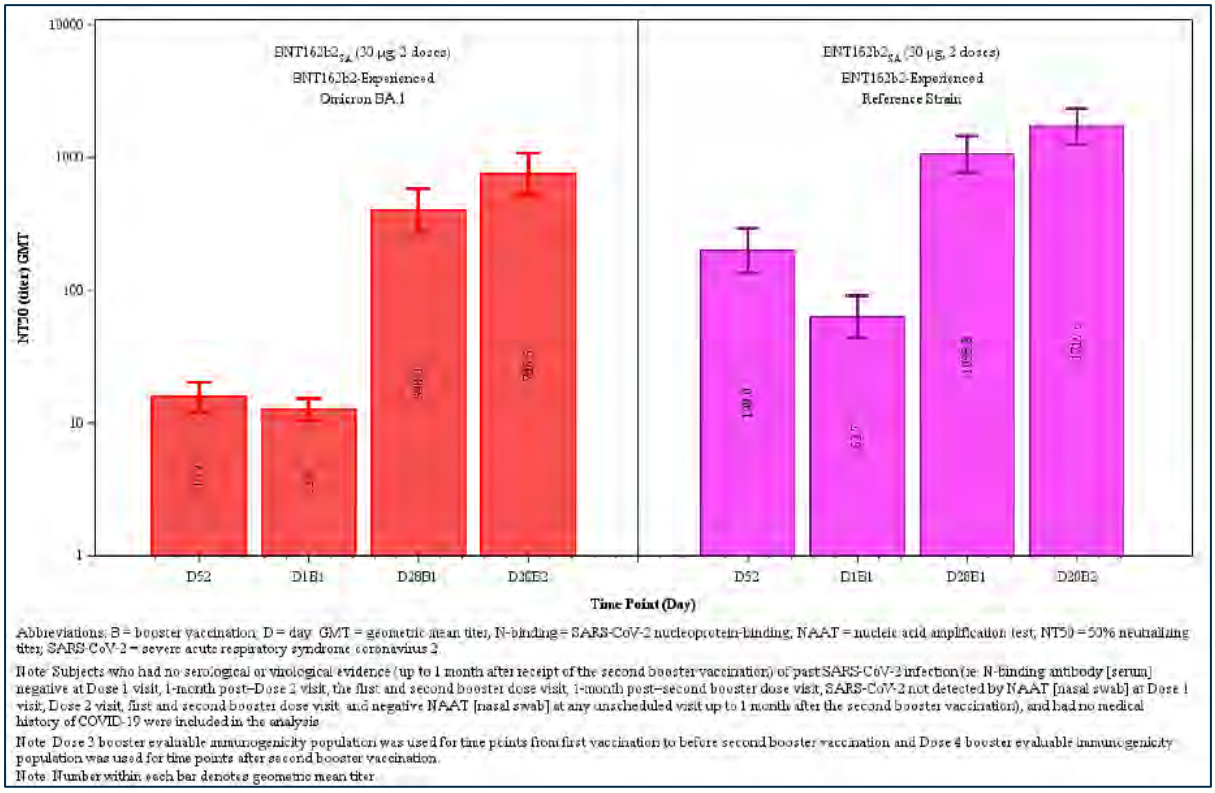
Source: Figure 1, C4591001 (Beta Modified Vaccine) COVID-19 Vaccine Omicron Neutralization Ad Hoc Report, DCO 23/05/2022.

BNT162b2-Experienced Participants – Booster Doses of BNT162b2$_{SA}$

Omicron BA.1-specific neutralising titres for participants 18-55 YOA without prior evidence of SARS-CoV-2 infection at 1 month following a first or second booster dose of BNT162b2$_{SA}$ 30µg (i.e. as Doses 3 and 4) are shown in Figure 10.

'For the Omicron BA.1 variant, the GMFR from before Dose 3 (first booster) to 1-month post-Dose 3 (first booster) for participants without evidence of prior SARS-CoV-2 infection in the Booster evaluable immunogenicity population was 31.6 (95% CI: 21.1, 47.4). The GMFR from before Dose 3 (first booster) to 1-month post-Dose 4 (second booster) was 59.3 (95% CI: 38.0, 92.4).'

Figure 10. GMTs and 95% CIs – NT50 – BNT162b2 – Experienced Subjects Without Evidence of Infection up to 1 Month After Second Booster Dose Who Were Assigned to Receive 2 Booster Doses of BNT162b2$_{SA}$ – Booster Evaluable Immunogenicity Population



Abbreviations: B = booster vaccination, D = day, GMT = geometric mean titer, N-binding = SARS-CoV-2 nucleoprotein-binding, NAAT = nucleic acid amplification test, NT50 = 50% neutralizing titer, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Subjects who had no serological or virological evidence (up to 1 month after receipt of the second booster vaccination) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Dose 1 visit, 1-month post–Dose 2 visit, the first and second booster dose visit, 1-month post–second booster dose visit, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 visit, Dose 2 visit, first and second booster dose visit, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after the second booster vaccination), and had no medical history of COVID-19 were included in the analysis.

Note: Dose 2 booster evaluable immunogenicity population was used for time points from first vaccination to before second booster vaccination and Dose 4 booster evaluable immunogenicity population was used for time points after second booster vaccination.

Note: Number within each bar denotes geometric mean titer.

Source: Figure 2, C4591001 (Beta Modified Vaccine) COVID-19 Vaccine Omicron Neutralization Ad Hoc Report, DCO 23/05/2022.

Evaluator's comments: The monovalent BNT162b2$_{SA}$ 30µg vaccine is based on the spike protein of the 'South African' (or Beta [B.1.351]) VOC of SARS-CoV-2 that was first detected in late 2020. That VOC is genetically distinct from the Omicron VOC. From the data presented, the BNT162b2$_{SA}$ 30µg vaccine appears to have limited potential as a primary series in the Omicron era, with a GMFR of 2.8-fold at 1 month post-Dose 2 being well below what would normally be considered as a seroresponse (i.e. ≥ 4-fold rise in titres). It would appear to have more potential as a booster dose, with a GMFR of 31.6 following Dose 3. Whether this would be any more effective than the original BNT162b2 30 µg in this setting was not studied comparatively here. Also, it is difficult to infer the vaccine's potential usefulness against newer sublineages of Omicron (such as BA.4/5) and other emerging Omicron sublineages (such as BA.4.6, BA.2.75.2, BQ.1.1, and XBB). Given the intention of provisionally registering COMIRNATY Original/Omicron BA.4-5 is to supersede both COMIRNATY Original and COMIRNATY Original/Omicron BA.1 as a booster dose in this current era of emerging Omicron sublineages, the Evaluator doesn't find the data from BNT162b2$_{SA}$ 30µg to provide much support to the current application.

7.3.2. Real-world effectiveness data (USA)

7.3.2.1. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022[6]

A study of RWE was performed by the US CDC following their country's decision to recommend vaccination with a bivalent COVID-19 mRNA vaccine (issued 1/09/2022) as a booster to anyone ≥ 12 YOA (Pfizer) or ≥ 18 YOA (Moderna) who had completed at least a primary series of any FDA authorized or approved monovalent vaccine (i.e. including non-mRNA vaccines) at least ≥ 2 months earlier. This was expanded to children 5-11 YOA on 12/10/2022.

The analysis was performed using a **test-negative design** where case patients were those recording a positive laboratory based NAAT for SARS-CoV-2 in the presence of one or more compatible symptoms and control patients were those who recorded a negative result. This allows comparison of the odds of receiving a bivalent booster dose (after 2, 3 or 4 monovalent doses) to being in a non-boosted control group. Vaccine effectiveness was calculated as (1 – OR) x 100.

'**Absolute vaccine effectiveness**' (aVE) was calculated using a vaccinated group who had received a bivalent COVID-19 mRNA booster dose compared to a control group who had been unvaccinated. '**Relative vaccine effectiveness**' (rVE) was calculated using a control group who had received ≥ 2 prior doses of a COVID-19 vaccine and the effect of waning immunity was examined by stratifying those whose last monovalent dose was 2-3, 4-5, 6-7 or ≥ 8 months prior.

The **study data** derived from the Increasing Community Access to Testing (ICATT) program, which was implemented to provide free access to COVID-19 diagnostic testing through pharmacies in areas with high social vulnerability.[7] The **period covered** was 14/09/2022 through 11/11/2022, during which Omicron BA.4/5 predominated initially (81% of tests were taken during that period) and transitioned to other sublineages (including Omicron BA.4.6, BA.5.2.6, BF.7, BQ.1, and BQ.1.1) toward the end of the study.

The **total number of tests** (n = 360626) (including those that were positive [34%] or negative [66%]), along with the number of participants having received prior monovalent vaccination ± bivalent boosters is shown in Table 54. Tests and vaccination status are further stratified by time frame of test (aligning with predominant SARS-CoV-2 variants circulating), age group, gender, race and ethnicity, and history of self-reported prior SARS-CoV-2 positivity are also shown. In those receiving a booster dose, the median time from dosing to testing was 1 month.

After ≥ 2 doses of a monovalent vaccine, **aVE of a bivalent booster** dose (compared to being unvaccinated) was 43% in participants 18-49 YOA, 28% in those 50-64 YOA and 22% in those ≥ 65 YOA (Table 26).

[6] Accessed from https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm on 4/01/2023.
[7] More details about the ICATT program can be found here: https://www.cdc.gov/icatt/index.html (accessed 8/12/2022).

Table 26. Absolute vaccine effectiveness against symptomatic SARS-CoV-2 infection for a single bivalent mRNA COVID-19 booster dose received after 2, 3, or 4 doses of monovalent vaccine compared with no doses, by age group and number of monovalent COVID-19 vaccine doses — Increasing Community Access to Testing program, United States, September–November 2022

	Absolute VE (95% CI), by no. of monovalent doses received before the bivalent vaccine dose			
Age group, yrs	2 doses	3 doses	4 doses*	≥2 doses
18–49	41 (31–49)	43 (39–46)	NA	43 (39–46)
50–64	50 (35–61)	25 (17–33)	28 (20–34)	28 (22–33)
≥65	32 (9–49)	19 (8–29)	23 (15–30)	22 (15–29)

Abbreviations: NA = not applicable; VE = vaccine effectiveness.
* Persons aged <50 years without moderate or severe immunocompromise were not eligible for a fourth monovalent (second booster) dose.

Source: https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7148e1-H.pdf (accessed 8/12/22).

The **rVE of a bivalent booster** dose (compared to controls having received ≥ 2 monovalent vaccine doses) increased along with the number of months since the last monovalent dose as shown in Table 27. 'At 2–3 months and ≥ 8 months after receipt of the most recent monovalent dose, rVE of a bivalent mRNA COVID-19 vaccine dose was 30% and 56% among persons aged 18–49 years, 31% and 48% among persons aged 50–64 years, and 28% and 43% among persons aged ≥ 65 years, respectively.'

Although the results were not shown, the authors reported that, 'Results limited to the **period of BA.4/BA.5 predominance** were not meaningfully different from the results shown, which include data from the period when BA.4/BA.5 sublineages (including BA.4.6, BA.5.2.6, BF.7, BQ.1, and BQ.1.1) predominated.'

Table 27. Relative vaccine effectiveness of a single bivalent mRNA COVID-19 booster dose against symptomatic SARS-CoV-2 infection* received after 2, 3, or 4 monovalent vaccine doses, by age group, number of monovalent COVID-19 vaccine doses received, and interval since last monovalent dose — Increasing Community Access to Testing program, United States, September–November 2022

Age group, yrs/mos since receipt of most recent monovalent dose	Relative VE (95% CI), by no. of monovalent doses received†			
	2 doses	3 doses	4 doses§	≥2 doses
18–49				
2–3	45 (31–56)	24 (14–33)	NA	30 (22–37)
4–5	47 (35–57)	41 (35–47)	NA	43 (38–48)
6–7	42 (30–52)	47 (42–52)	NA	46 (41–50)
≥8	53 (45–60)	58 (56–61)	NA	56 (53–58)
50–64				
2–3	—	15 (–4–31)	33 (24–41)	31 (24–38)
4–5	44 (18–62)	31 (18–42)	36 (29–43)	36 (30–41)
6–7	46 (22–62)	36 (25–45)	40 (32–47)	38 (32–43)
≥8	61 (49–70)	51 (45–55)	NA	48 (45–51)
≥65				
2–3	—	—	32 (23–40)	28 (19–35)
4–5	—	21 (1–36)	36 (29–42)	33 (27–39)
6–7	—	14 (–6–30)	40 (33–46)	36 (29–41)
≥8	45 (27–58)	42 (35–48)	NA	43 (39–46)

Abbreviations: NA = not applicable; VE = vaccine effectiveness.

* VE estimates with 95% CIs >50 percentage points are not shown because of imprecision.

† Total number of monovalent doses received for persons who did and did not receive a bivalent booster dose.

§ Persons aged <50 years without moderate or severe immunocompromise were not eligible for a fourth monovalent (second booster) dose. Because of timing of authorization, not enough persons ≥8 months from the fourth dose (second booster) were available to include in analyses.

Source: https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7148e1-H.pdf (accessed 8/12/22).

Evaluator's comments: A bivalent mRNA booster dose given after ≥ 2 prior monovalent doses had useful effectiveness against symptomatic COVID-19 that was more apparent as time went by, indicating restoration of waning protection of a prior monovalent prior series with or without monovalent booster(s). The magnitude of relative vaccine effectiveness (the most generalisable measure to a population like ours with a high prior rate of monovalent vaccination) was clinically useful in most subgroups, peaking at 61% in those 50-64 YOA who had received a 2 dose primary series with the last dose ≥ 8 months ago. As calculated rVEs were similar whether 2, 3 or 4 prior monovalent doses were received, the results suggest '…similar additional benefit of the bivalent vaccine regardless of the number or previous monovalent doses received, when controlling for time since receipt of last monovalent dose.' During this period of Omicron BA.4/5 and its sublineage predominance, that supports use of bivalent COVID-19 mRNA vaccine as the preferred booster in each of those pre-dose scenarios.

The Evaluator notes a number of limitations of the study in relation to generalising these measures of vaccine effectiveness to the Australian situation:

- The type of mRNA vaccine used was not recorded (Pfizer vs Moderna) and it's possible there could be big differences in the effectiveness of each vaccine that were 'averaged out' in the

final estimates; however, previous RWE has shown fairly similar VE for the reference strain-based vaccines and this scenario seems relatively unlikely.
- The study didn't compare use of a bivalent vaccine to another dose of a monovalent vaccine. It is possible that the level of additional protection afforded would be the same or better using a monovalent booster dose.
- The baseline exposure status of participants to prior SARS-CoV-2 infection was only estimated by self-reporting, not measured. Hence, the potential additional protection of natural infection (e.g. Omicron BA.4/5) couldn't be studied.
- Effectiveness against severe COVID-19 was not studied.
- As > 90% of US adults have received ≥ 1 COVID-19 vaccine dose, the aVE estimates may be unstable given that small proportion of unvaccinated individuals may exhibit different behaviours or risks for acquiring SARS-CoV-2 compared to vaccinated individuals (e.g. rates of baseline prior infection may have been very different to the rates from self-reporting). There may also be differences in test-seeking behaviour.
- '…vaccination status, previous infection history, and underlying medical conditions were self-reported and might be subject to recall bias.'
- As the uptake of bivalent mRNA booster doses has been low in the USA to date (approximately 10% of those eligible through 15/11/2022) there could be bias related to early vaccine seeking behaviours.
- SARS-CoV-2 exposure risk (e.g. protective measures like mask use) was not measured, potentially leading to residual confounding.
- Variants were not elucidated and could further vary going forward.
- The population studied was one of higher social vulnerability in the USA (all immunocompetent by study design).

Overall, the Evaluator feels that in the absence of vaccine efficacy data, the results of this RWE study lend some support to the conclusion that a BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg booster may provide some additional protection against Omicron BA.4/5 and its sublineages for someone who has had 2-4 prior doses of monovalent vaccine (relative to not having another booster dose at all, whether that be monovalent or bivalent). Given that monovalent vaccine-induced immunity wanes over time and may not be as effective against Omicron BA.4/5 and its sublineages, this is most relevant for those who are many months away from their last dose. It is not possible to say from the data whether the bivalent booster would be any better than a monovalent booster.

7.3.2.2. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults — VISION Network, Nine States, September–November 2022[8]

This study was conducted in the USA following the recommendation to vaccinate adults with a single bivalent booster dose that was made on 1/09/2022. Pertinent **characteristics** included:

- Conducted in 9 states between 13/09/2022 and 18/11/2022.
  - During this time, Omicron BA.5 was predominant and new Omicron BA.4/5 subvariants were emerging.
- Test-negative case-control design in those being tested for SARS-CoV-2.
  - Analysis 1: Emergency department (ED) / Urgent care (UC) encounter.
  - Analysis 2: Hospitalization for a COVID-19-like illness.
- Evaluated VE in adults ≥ 18 YOA who had received 2, 3 or 4 prior monovalent mRNA doses compared to: (1) no previous vaccination; and (2) previous receipt of 2, 3 or 4 monovalent mRNA doses.

[8] Accessed from https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e1.htm on 4/01/2023.

    - The odds of having a bivalent booster was compared among case patients (i.e. having received a positive SARS-CoV-2 test) and control patients (i.e. having received a negative SARS-CoV-2 test).
    - ORs and 95% CIs were calculated using multivariable logistic regression that adjusted for age, race and ethnicity, sex, calendar day (days since 1/01/2021), geographic region and local SARS-CoV-2 circulation (proportion of positive SARS-CoV-2 results in tested patients in regions surrounding the facility).
- Excluded immunocompromised adults.

The main **results** and authors' **conclusions** were as follows:

- 'VE of a bivalent booster dose (after 2, 3, or 4 monovalent doses) against COVID-19–associated ED/UC encounters was 56% compared with no vaccination, 31% compared with monovalent vaccination only with last dose 2–4 months earlier, and 50% compared with monovalent vaccination only with last dose ≥ 11 months earlier.'
- 'VE of a bivalent booster dose (after 2, 3, or 4 monovalent doses) against COVID-19–associated hospitalizations was 57% compared with no vaccination, 38% compared with monovalent vaccination only with last dose 5–7 months earlier, and 45% compared with monovalent vaccination only with last dose ≥ 11 months earlier.'
- 'Bivalent vaccines administered after 2, 3, or 4 monovalent doses were effective in preventing medically attended COVID-19 compared with no vaccination and provided additional protection compared with past monovalent vaccination only, with relative protection increasing with time since receipt of the last monovalent dose.'

Limitations of the study included:

- Although > 50% received a Pfizer vaccine as their most recent mRNA dose, the VE of Pfizer vs Moderna mRNA vaccines was not studied separately.
- There was no estimate of prior natural SARS-CoV-2 infection, which could have potentially effected baseline immunity.
- Residual confounding (e.g. behavioural differences in antiviral seeking behaviour) could be present.
- The study wasn't powered to separate the effects of 2 vs 3 vs 4 prior doses of mRNA vaccine; they were lumped together.
- The study was only from 9 of the 50 US states and may not represent the entire population.
- Those choosing to receive booster doses were likely a skewed population. They were older in the case of the ED/UC analysis (but similar for the hospitalisation analysis) and more than half had previously received 4 monovalent doses in both analyses (higher than in the non-booster, previously vaccinated groups – 17% for the ED/UC analysis and 24% for the hospitalisation analysis had received 4 monovalent doses in those control groups).
- The effect of a booster dose of bivalent mRNA vaccine was not compared to another booster dose of a monovalent mRNA vaccine.

Evaluator's comments: These data derive from adults ≥ 18 YOA who likely had more severe illness than those in the study evaluated in section 7.3.2.1, given they were seeking care in either an emergency department or urgent care setting *or* hospitalised. The results are broadly consistent with that other study in suggesting additional protection from a bivalent mRNA booster beyond no booster at all in previously vaccinated participants, and also compared to an unvaccinated group. Both studies suggest that protection is relatively greater as immunity from prior vaccination wanes. Unfortunately, no comparison can be made with another dose of monovalent booster. There are many caveats and limitations as listed above.

7.3.2.3. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years — IVY Network, 18 States, September 8–November 30, 2022[9]

This study was conducted in the USA following the recommendation to vaccinate adults with a single bivalent booster dose that was made on 1/09/2022. Pertinent **characteristics** included:

- Conducted in 22 hospitals in 18 states between 8/09/2022 and 30/11/2022.
    - During this time, Omicron BA.5 was predominant and new Omicron BA.4/5 subvariants were emerging.
- Test-negative case-control design in patients hospitalised for a COVID-19-like illness and who were tested for SARS-CoV-2.
- Evaluated VE in adults ≥ 65 YOA who had received ≥ 2 prior monovalent mRNA doses compared to: (1) no previous vaccination; and (2) previous receipt of ≥ 2 monovalent mRNA doses.
    - The odds of having a bivalent booster was compared among case patients (i.e. having received a positive SARS-CoV-2 test) and control patients (i.e. having received a negative SARS-CoV-2 test).
    - ORs and 95% CIs were calculated using multivariable logistic regression that adjusted for 'U.S. Department of Health and Human Services region, admission date in 2-week intervals, continuous age, sex, race, and Hispanic or Latino (Hispanic) ethnicity.'
- Excluded immunocompromised adults and also control patients testing positive on PCR for influenza 'because of potential correlation between COVID-19 and influenza vaccination behaviors'.

The main **results** and authors' **conclusions** were as follows:

- There were 798 patients included (381 case patients and 417 control patients) and 74% had multiple underlying conditions.
- 'When compared with unvaccinated persons, VE of a bivalent booster dose received ≥7 days before illness onset (median = 29 days) against COVID-19–associated hospitalization was 84%.'
- 'Compared with persons who received ≥ 2 monovalent-only mRNA vaccine doses, relative VE of a bivalent booster dose was 73%.'
- 'These early findings show that a bivalent booster dose provided strong protection against COVID-19–associated hospitalization in older adults and additional protection among persons with previous monovalent-only mRNA vaccination.'
- 'When compared with patients whose last monovalent dose was 6–11 months and ≥ 12 months before illness onset, relative VE of a bivalent booster dose was 78% and 83%, respectively.'

Limitations of the study included:

- The proportion of participants who received a Pfizer vaccine as their most recent mRNA dose was not specified.
- There was no estimate of prior natural SARS-CoV-2 infection, which could have potentially effected baseline immunity.
- Residual confounding (e.g. behavioural differences in antiviral seeking behaviour) could be present.
- The study wasn't powered to separate the effects of 2 vs 3 vs 4 prior doses of mRNA vaccine; they were lumped together.

[9] Accessed from https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e2.htm on 4/01/2023.

- The study was only from 18 of the 50 US states and may not represent the entire population.
- It is possible that those choosing to receive booster doses were a skewed population. The proportions of participants who had previously received a 4th dose of monovalent vaccine may have differed between cases and controls but wasn't provided.
- The effect of a booster dose of bivalent mRNA vaccine was not compared to another booster dose of a monovalent mRNA vaccine.

Evaluator's comments: This is a higher risk cohort aged ≥ 65 YOA in whom there were frequently comorbidities and the VE estimates against more severe disease (i.e. hospitalisation) were higher than in either of the previous two studies in this section (7.3.2). The same themes were observed here: additional protection from a bivalent mRNA booster beyond that of ≥ 2 prior monovalent doses *or* being unvaccinated. Protection was modestly relatively greater as time since previous vaccination waned (i.e. 6-11 vs ≥ 12 months); however, the < 6 months group could not be studied due to small numbers. As with the previous two studies, there were many limitations.

7.3.3. Evaluator commentary: other efficacy studies

The other efficacy studies provide weak supportive evidence suggesting that COMIRNATY Original/Omicron BA.1 would be less effective as a booster than COMIRNATY Original/Omicron BA.4-5 in the present phase of the Australian pandemic (dominated by Omicron BA.4/5 and other sublineages). The real world evidence of vaccine effectiveness from the USA suggests that a combination wild type/Omicron BA.4/5 mRNA booster provides additional protection against symptomatic *and* moderate to severe COVID-19 relative to no booster but with many caveats (as noted in the preceding comments, above). The magnitude of that protection is likely relatively greater as the time since prior vaccination lengthens. VE estimates from the RWE were greatest in the highest risk group ≥ 65 YOA and against the highest severity of illness studied (i.e. hospitalisation).

7.4. Analyses performed across trials: pooled and meta analyses

Not applicable.

7.5. Evaluator's conclusions on clinical efficacy

These conclusions should be read in the context of the previous conclusions regarding immunogenicity in adult participants that were presented in section 14.5.1.

7.5.1. Adults (Round 1 CER)

The Evaluator concludes that:

- A 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg (given approximately 11 months post-3rd dose) boosts pre-dose Omicron BA.4/5 neutralising GMTs in participants who have no prior to SARS-CoV-2 by a GMFR of 18.9 (95% CI: 12.8, 27.8) in participants 18-55 YOA and 21.0 (95% CI: 14.2, 33.8) in participants > 55 YOA. Seroresponse rates in those age groups are 81.3% (95% CI: 63.6, 92.8) and 90.0% (95% CI: 76.3, 97.2) respectively. A 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg also boosts pre-existing responses in participants with prior SARS-CoV-2 exposure, with higher GMTs but lower GMFRs (reflecting the higher relative baseline titres).
- Responses against Omicron BA.4/5 from a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appear as good or better than those generated by BNT162b2 bivalent

(WT/OMI BA.1) 30 µg or BNT162b2 30 µg (albeit with smaller numbers and less certainty [reflecting an earlier data cutoff] in that latter comparison).
- Responses against other variants/sub-variants (i.e reference strain and Omicron BA.1) appear relatively preserved compared to booster vaccination using a 4th dose of BNT162b2 bivalent (WT/OMI BA.1) 30 µg. There are also some data showing boosting of responses to the emerging sublineages of Omicron (i.e. BA.4.6, BA.2.75.2, BQ.1.1, and XBB).
- It is likely that a 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg would provide additional clinical protection relative to no booster at all and that it would be no worse than having a booster dose of the currently available BNT162b2 bivalent (WT/OMI BA.1) 30 µg or BNT162b2 30 µg. It may even prove superior.
- The real world evidence of vaccine effectiveness from the USA suggests that a combination wild type/Omicron BA.4/5 mRNA booster provides additional protection against symptomatic *and* moderate-severe COVID-19 relative to no booster but with many caveats (as noted in the preceding comments, above).
- COMIRNATY Original/Omicron BA.1 would likely be less effective as a booster than COMIRNATY Original/Omicron BA.4-5 in the present phase of the Australian pandemic (dominated by Omicron BA.4/5 and other sublineages).
- Of note, these immunogenicity data only pertain to adults ≥ 18 YOA and do not include adolescents.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.1.2. Pivotal and/or main efficacy studies

8.1.2.1. Study C4591044: An Interventional, Randomized, Active-Controlled, Phase 2/3 Study To Investigate The Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals

The study design and other characteristics are described in section 7.2.1, with study procedures for collection of safety data described in section 7.2.1.8.

Pertinent points in relation to safety included the following:

- 'Reactogenicity and antipyretic/pain medication use was recorded for 7 days after study vaccination using prompts from an electronic diary (e-diary). Grading scales were based on FDA guidance.'
    - 'Descriptive statistics were provided for each reactogenicity endpoint for each vaccine group, including counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% confidence intervals (CIs).'
- 'AEs were collected from the study vaccination up to 1 month after the study vaccination, and serious AEs (SAEs) were collected from study vaccination up to 6 months post-Dose.'
    - 'AEs and SAEs were categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of AEs and SAEs were provided for each vaccine group.'

- 'Myocarditis and pericarditis are designated in the C4591044 protocol as AEs of special interest (AESIs)… For other AEs of specific clinical interest, Pfizer evaluates a dynamic list of MedDRA AE terms during clinical safety data review and signal detection.'
- 'Narratives for safety events were prepared for participants in cases of death, vaccine-related SAE, safety-related withdrawal, and/or AE of clinical interest.'

8.1.3. Other studies

8.1.3.1. Other efficacy studies

Safety data are included for Study C4591031 Substudy D and Study C4591031 Substudy E and also for Study C4591001 (the relevant study subsets are described briefly in section 8.4.1.1).

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

Study BNT162-17

This is an ongoing Phase 2 study to evaluate monovalent and bivalent BNT162b2-based vaccines given as third (booster) doses in healthy participants (start date 25/08/2021). There are 3 parts and 6 cohorts; those relevant in providing supporting data for the present submission are as follows:

- **Part A**: cohorts of ~ 20 participants 18-55 YOA. Cohorts 1 and 4 were BNT162b2-experienced, having received 2 doses of BNT162b2 30 µg at least 6 months earlier.
  - **Cohort 1**: Received one dose of bivalent BNT162b2 (B.1.1.7 + B.1.617.2) 30 µg on Day 1, consisting of 15 µg of each of those 2 monovalent vaccines.
  - **Cohort 4**: Received one dose of monovalent BNT162b2 (B.1.617.2) 30 µg on Day 1.
- **Part B**: initiated after review of reactogenicity and available immunogenicity data from Part A. **Cohorts 1 and 4** were as previously described but consisted of ~ 300 participants (18-85 YOA) each. The BNT162b2-experienced participants were from study BNT1622-02 / C4591001 and had received 2 doses BNT162b2 30 µg (as above) at least 6 months prior.

Reactogenicity data were collected using an e-diary in the 7 days following vaccination and Grading scales based on FDA guidance. **AEs** were collected from the booster (Dose 3) to 1 month after the last dose administered and **SAEs** were collected up to 6 months.

Baseline characteristics

There were 370 participants in Cohort 1 (21 in Part A and 349 in Part B) with 9 discontinuations and 372 participants in Cohort 4 (20 in Part A and 352 in Part B) with 2 discontinuations. None of the discontinuations were because of AEs.

The baseline characteristics were presented in Table 14.1.3.1_1 of the BNT162-17 study tables document for Cohort 1 and Table 14.1.3.1_4 for Cohort 4. In **Cohort 1**, the median age was 49.0 years, 87.8% were < 65 YOA, 51.4% were male and the median duration between Doses 2 and 3 was 309 days. In **Cohort 4**, the median age was 51.0 years, 80.4% were < 65 YOA, 53.2% were male and the median duration between Doses 2 and 3 was 265 days.

8.1.3.3. Studies evaluable for safety only

Not applicable.

8.2. Studies that assessed safety as the sole primary outcome

Not applicable.

8.3. Patient exposure

This is described in each of the relevant sections for safety.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

Solicited adverse events (reactogenicity)

An overview of the reactogenicity profile for 30 µg doses is presented in Table 28 and Table 29 for BNT162b2-experienced participants from:

- Study C4591001 who received a booster dose (Dose 3) of the original BNT162b2 30 µg (n = 289) or of Beta variant-modified vaccine (BNT162b2$_{SA}$) 30 µg (n = 298),
- Study C4591031 Substudy D who received a booster dose (Dose 4) of either the original BNT162b2 30 µg (n = 294) or monovalent Omicron variant-modified BNT162b2 (BNT162b2 OMI BA.1) 30 µg (n = 306), and
- Study C4591031 Substudy E who received a booster dose (Dose 4) of either the original BNT162b2 30 µg (n = 298), monovalent BNT162b2 OMI BA.1 30 µg (n = 301) or bivalent BNT162b2 + BNT162b2 OMI BA.1 30 µg (n=301).
- Study C4591044 Cohort 2 who received a booster dose (Dose 4) of either 30 µg (n = 298) or 60 µg (n = 205) BNT162b2 bivalent (WT/OMI BA.4/BA.5).

Table 28. Participants Reporting Local Reactions and Systemic Events Within 7 Days Post Dose 3 or Dose 4 of BNT162b2, Monovalent BNT162b2 OMI, Bivalent BNT162b2 + BNT162b2 OMI or BNT162b2$_{SA}$ at 30 µg Dose Level in Studies C4591001, Studies C4591031 Substudy D and C4591031 Substudy E

Events	C4591031 Substudy D[a]		C4591031 Substudy E[b]			C4591001[c]	
	BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI 30 µg	BNT162b2 + BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2$_{SA}$ 30 µg
	Dose 4 (N=294)	Dose 4 (N=306)	Dose 4 (N=298)	Dose 4 (N=301)	Dose 4 (N=301)	Dose 3 (N=289)	Dose 3 (N=298)
Local reaction at injection site							
Pain	77.9%	78.4%	60.1%	66.1%	58.1%	83.0%	82.9%
Swelling	8.5%	8.8%	6.0%	8.3%	6.6%	8.0%	6.7%
Redness	7.1%	4.2%	6.4%	6.3%	7.0%	5.9%	5.0%
Systemic events							
Fatigue	64.3%	60.5%	45.3%	52.5%	49.2%	63.7%	69.8%
Headache	47.6%	45.1%	26.5%	36.5%	33.6%	48.4%	53.0%
Muscle pain	33.7%	28.4%	19.8%	23.9%	22.3%	39.1%	38.6%
Chills	31.6%	26.1%	16.4%	25.6%	13.0%	29.1%	36.6%
Joint pain	23.5%	15.0%	9.1%	16.6%	11.3%	25.3%	22.5%
Fever (≥38.0°C)	8.5%	7.2%	3.7%	8.3%	5.0%	8.7%	9.4%
Vomiting	2.7%	1.6%	1.3%	3.0%	1.7%	1.7%	0.7%
Diarrhea	8.5%	11.8%	4.4%	8.0%	9.0%	8.7%	9.7%

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).
b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).
c. BNT162b2-experienced participants (18 to 55 years of age) who were randomized to receive a booster (Dose 3) dose of BNT162b2 30 µg or BNT162b2$_{SA}$ 30 µg approximately 6 months after their second dose of BNT162b2 30 µg (Dose 2).

Source: Table 1, Clinical Overview – Safety VOC Vaccines.

Table 29. Participants Reporting Local Reactions and Systemic Events Within 7 Days Post Dose 4 of BNT162b2, Monovalent BNT162b2 OMI BA.1, Bivalent BNT162b2 + BNT162b2 OMI BA.1 or Bivalent BNT162b2 + BNT162b2 OMI BA.4/BA.5 at 30 µg or 60 µg Dose Level in Studies C4591031 Substudy D (Cohort 2), C4591031 Substudy E, and C4591044 Cohort 2

C4591031 Substudy D[a]		C4591031 Substudy E[b]			C4591044 Cohort 2[c]				
BNT162b2 OMI BA.1 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI BA.1 30 µg	BNT162b2 + BNT162b2 OMI BA.1 30 µg	BNT162b2 Bivalent 30 µg (WT/OMI BA.4/BA.5)			BNT162b2 Bivalent 60 µg (WT/OMI BA.4/BA.5)	
(18 to 55 Years)			(>55 Years)		12-17 Y	18-55 Y	>55 Y	18-55 Y	>55 Y
(N=294)	(N=306)	(N=298)	(N=301)	(N=301)	(N=97)	(N=99)	(N=100)	(N=106)	(N=99)
Local reaction at injection site									
Pain									
77.9%	78.4%	60.1%	66.1%	58.1%	70.1%	80.8%	56.0%	93.4%	69.7%
Swelling									
8.5%	8.8%	6.0%	8.3%	6.6%	8.2%	7.1%	2.0%	15.1%	9.2%
Redness									
7.1%	4.2%	6.4%	6.3%	7.0%	6.2%	6.1%	2.0%	11.3%	7.1%
Systemic events									
Fatigue									
64.3%	60.5%	45.3%	52.5%	49.2%	67.0%	63.6%	38.0%	68.9%	52.0%
Headache									
47.6%	45.1%	26.5%	36.5%	33.6%	49.5%	44.4%	29.0%	46.2%	34.7%
Muscle pain									
33.7%	28.4%	19.8%	23.9%	22.3%	27.8%	32.3%	21.0%	40.6%	23.5%
Chills									
31.6%	26.1%	16.4%	25.6%	13.0%	22.7%	15.2%	13.0%	26.4%	22.4%
Joint pain									
23.5%	15.0%	9.1%	16.6%	11.3%	11.3%	17.2%	12.0%	23.6%	14.3%
Fever (≥38.0°C)									
8.5%	7.2%	3.7%	8.3%	5.0%	9.3%	5.1%	8.0%	11.3%	14.3%
Vomiting									
2.7%	1.6%	1.3%	3.0%	1.7%	3.1%	2.0%	1.0%	1.9%	3.1%
Diarrhea									
8.5%	11.8%	4.4%	8.0%	9.0%	6.2%	13.1%	8.0%	13.2%	7.1%
Use of Antipyretic or pain medication									
38.8%	39.5%	26.8%	34.9%	29.2%	35.1%	30.3%	30.0%	50.9%	38.8%

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).
b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).
c. BNT162b2-experienced participants (≥12 years of age) who received BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30- or 60-µg as a booster dose (Dose 4) approximately 150 to 365 days after their last dose (Dose 3).

Source: Table 8, 7 Day Post Dose Safety Data: Study C4591044 Cohort 2 report, also same as Table 15, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report.

Evaluator's comments: Reactogenicity profiles for vaccines containing a 30 µg dose were generally similar regardless of the makeup (i.e. original and/or variant-modified, whether Omicron BA.1 or BA.4/5) with no meaningful clinical differences between vaccines. The size of each 30 µg group – approximately 300 participants – is in keeping with the number recommended in the ACCESS consortium statement for variant-modified vaccines[10] as being sufficient to adequately characterise the reactogenicity profile.

Unsolicited adverse events

'An overview of adverse events (AEs) reported for BNT162b2-experienced participants who received a booster dose of either the BNT162b2, Beta variant-modified or Omicron variant-modified (monovalent or bivalent) vaccine is provided in Table 30.'

[10] See https://www.tga.gov.au/resources/publication/publications/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic (accessed 21/11/2022).

Table 30. Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 or Dose 4 to 1 Month After Dose 3 or Dose 4 of BNT162b2, Monovalent BNT162b2 OMI, Bivalent BNT162b2 + BNT162b2 OMI or BNT162b2$_{SA}$ at 30 µg Dose Level in Studies C4591001, Studies C4591031 Substudy D and C4591031 Substudy E

Adverse Events	C4591031 Substudy D[a]		C4591031 Substudy E[b]			C4591001[c]	
	BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2 30 µg	BNT162b2 OMI 30 µg	BNT162b2 + BNT162b2 OMI 30 µg	BNT162b2 30 µg	BNT162b2$_{SA}$ 30 µg
	Dose 4 (N=315)	Dose 4 (N=325)	Dose 4 (N=305)	Dose 4 (N=307)	Dose 4 (N=305)	Dose 3 (N=306)	Dose 3 (N=315)
Any AE	18 (5.7%)	12 (3.7%)	18 (5.9%)	26 (8.5%)	19 (6.2%)	46 (15.0%)	34 (10.8%)
Related	10 (3.2%)	5 (1.5%)	4 (1.3%)	10 (3.3%)	7 (2.3%)	25 (8.2%)	23 (7.3%)
Severe	4 (1.3%)	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Life-threatening	0	0	0	0	0	0	0
Any SAE	1 (0.3%)	1 (0.3%)	0	3 (1.0%)	1 (0.3%)	0	1 (0.3%)
Related	0	0	0	1 (0.3%)	0	0	0
Severe	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Life-threatening	0	0	0	0	0	0	0
Any nonserious AE	17 (5.4%)	12 (3.7%)	18 (5.9%)	24 (7.8%)	18 (5.9%)	46 (15.0%)	33 (10.5%)
Related	10 (3.2%)	5 (1.5%)	4 (1.3%)	10 (3.3%)	7 (2.3%)	25 (8.2%)	23 (7.3%)
Severe	4 (1/3%)	1 (0.3%)	0	0	0	1 (0.3%)	0
Life-threatening	0	0	0	0	0	0	0
Any AE leading to withdrawal	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0

a. BNT162b2-experienced participants (18 to 55 years of age) who received either BNT162b2 30 µg or BNT162b2 OMI 30 µg as a booster (Dose 4) approximately 3 to 6 months (90 to 180 days) after their last dose (Dose 3).

b. BNT162b2-experienced participants (>55 years of age) who received BNT162b2 30 µg or BNT162b2 OMI 30 µg or BNT162b2 + BNT162b2 OMI 30 µg as a booster dose (Dose 4) approximately 5 to 12 months after their last dose (Dose 3).

c. BNT162b2-experienced participants (18 to 55 years of age) who were randomized to receive a booster (Dose 3) dose of BNT162b2 30 µg or BNT162b2$_{SA}$ 30 µg approximately 6 months after their second dose of BNT162b2 30 µg (Dose 2).

Source: Table 2, Clinical Overview – Safety VOC Vaccines.

Evaluator's comments: The Sponsor stated in the Clinical Overview referenced above that, 'Although the data are limited, there were no AEs or SAEs or trends that raised new safety concerns.' Further, that, 'Review of the postmarketing data from individuals who received BNT162b2 30 µg as primary series or as a booster in the past 12 months have not identified any new safety concerns.' The Evaluator is interested in further reviewing each of the SAEs listed in Table 30. **EvQset3**: Please provide participant narratives (including discussion of relatedness) for each of the 7 SAEs listed in Table 2 of the 'COVID-19 Vaccine 2.5 Clinical Overview – Safety VOC Vaccines', dated 15/08/2022.

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.1.3. Pivotal and/or main efficacy studies – Study C4591044 Cohort 2

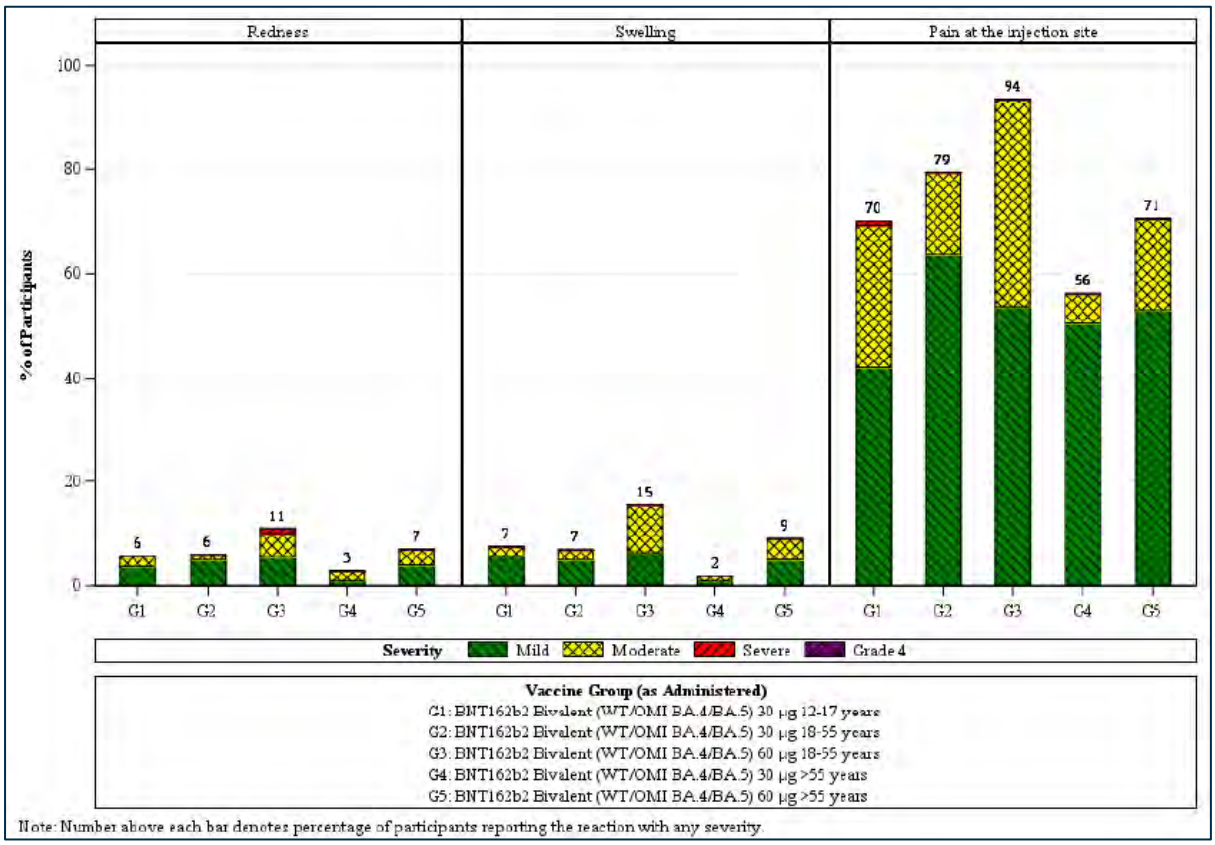
Solicited adverse events (reactogenicity) – Study C4591044

These data were presented in a report labelled '1 Month Post Dose Safety and Immunogenicity (Sentinel) Data: Study C4591044 Cohort 2', dated November 2022, with a data cutoff of 12/10/2022.

Local reactogenicity – Study C4591044 Cohort 2 (7-day visit)

The frequency of local reactions by maximum severity within 7 days of study vaccination is shown in Table 55 and Figure 11. Day of onset and duration of reactions are shown in Table 56 and Table 57 respectively.

Figure 11. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population



Source: Figure 5, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data: Study C4591044 Cohort 2, DCO 12/10/2022.

Evaluator's comments: Pain at the injection site was the commonest **local reaction**, followed by swelling and then redness. In the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients, the frequency of any local reaction was 70.1% (95% CI: 60.5, 78.6) in those 12-17 YOA, 83.3% (95% CI: 74.7, 90.0) in those 18-55 YOA and 57.1% (95% CI: 47.1, 66.8) in those > 55 YOA. In the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg recipients, the frequency of any local reaction was higher, being 93.6% (95% CI: 87.3, 97.4) in those 18-55 YOA and 71.6% (95% CI: 61.8, 80.1) in those > 55 YOA.

The frequencies and severities of **local reactions** for the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg dose were in keeping with the pattern of prior booster studies for BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg. Frequencies and severities were notably lower in those > 55 YOA than in the younger age groups, in keeping with earlier studies also. There was only 1 (0.9%) severe reaction of pain at the injection site in a 12-17 YOA participant (Grade 3) given BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg but there were otherwise no Grade 3 or Grade 4 reactions in any of the 30 µg groups.

The frequency and severity of **local reactions** was higher in the respective 60 µg age groups; however, severity was driven by a higher proportion of moderate reactions relative to mild reactions in those given 60 µg dosing and there was only 1 (0.9%) severe reaction of redness in a participant 18-55 YOA. There were no Grade 4 reactions in those given 60 µg.

'The median onset for all local reactions was 1 to 3 days, and all events resolved within a median duration of 1 to 3 days after onset.' These **times to onset** and **durations** are in keeping

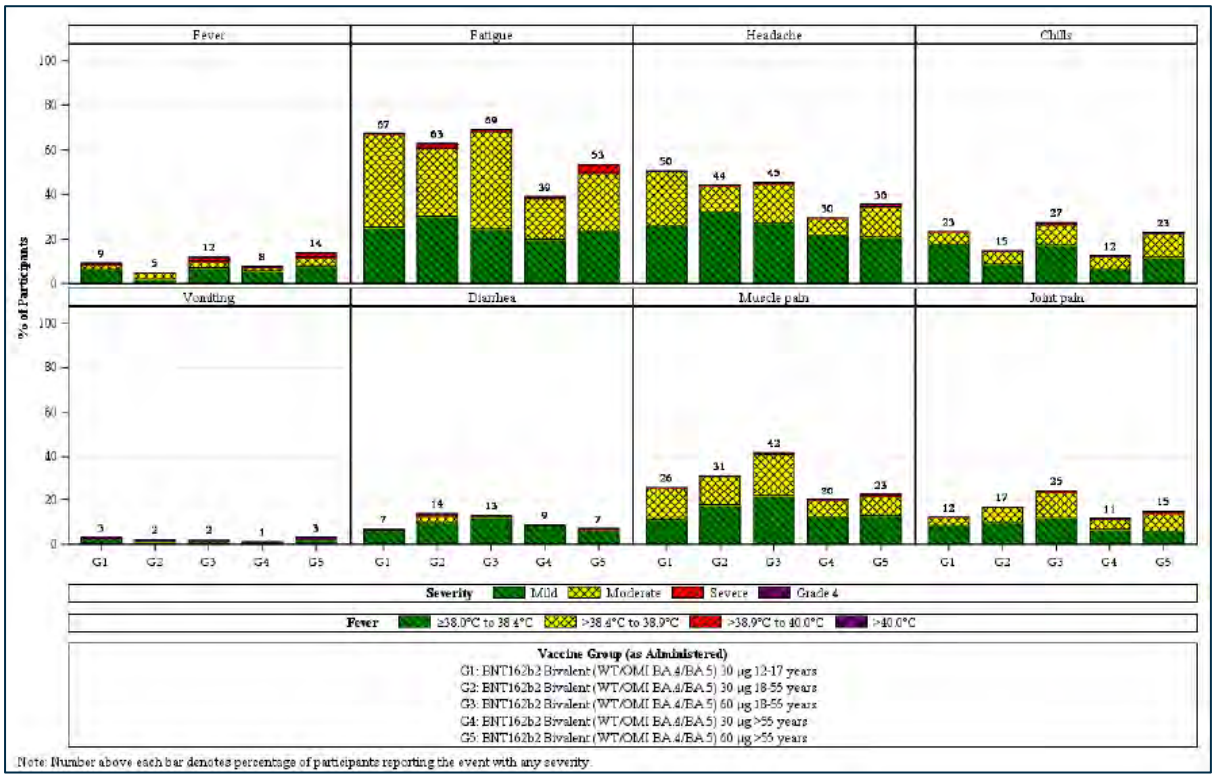
with previously reported reactogenicity for BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg.

Overall, local reactogenicity to BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg has been characterised in close to 300 (n = 314) participants with broadly even recruitment into age groups 12-17, 18-55 and > 55 YOA. The Evaluator agrees with the conclusion of the Sponsor that, 'The pattern of local reactions reported within 7 days after the BNT162b2 bivalent (WT + OMI BA.4/BA.5) vaccine was generally similar to those previously observed in association with an Omicron BA.1-modified BNT162b2 bivalent vaccine and to the original BNT162b2 vaccine within the respective age groups.' The size of the group – just over 300 participants – is in keeping with the number recommended in the ACCESS consortium statement for variant-modified vaccines as being sufficient to adequately characterise the reactogenicity profile.[11]

Systemic reactogenicity – Study C4591044 Cohort 2 (7-day visit)

The frequency of systemic reactions by maximum severity within 7 days of study vaccination is shown in Table 58 (Part 1), Table 59 (Part 2) and Figure 12. Day of onset and duration of reaction are shown in Table 60 and Table 61 respectively.

Figure 12. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population



Source: Figure 6, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data: Study C4591044 Cohort 2, DCO 12/10/2022.

Evaluator's comments: Fatigue was the commonest **systemic reaction**, followed by headache, then muscle pain, then chills. In the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients, the frequency of any systemic reaction was 80.4% (95% CI: 71.6, 87.4) in those 12-17 YOA,

[11] See https://www.tga.gov.au/resources/publication/publications/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic (accessed 21/11/2022).

75.5% (95% CI: 66.0, 83.5) in those 18-55 YOA and 56.2% (95% CI: 46.2, 65.9) in those > 55 YOA. Use of antipyretic or pain medication was reported in close to a third of participants in each group.

The frequencies and severities of **systemic reactions** for the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg dose were in keeping with the pattern of prior booster studies for BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg. Frequencies and severities were notably lower in those > 55 YOA for most systemic reactions and overall than in the younger age groups, in keeping with earlier studies also. For each type of systemic reaction, severe reactions were experienced by no more than 2% of participants in any of the 30 µg dosing groups and there were no Grade 4 reactions reported in either the 30 µg or 60 µg dosing groups.

The frequency and severity of **systemic reactions** was higher for most types of reactions in the respective 60 µg dosing age subgroups and was largely driven by a higher proportion of moderate reactions relative to mild reactions. For each type of systemic reaction, severe reactions were experienced by no more than 2% of participants in any of the 60 µg dosing groups, other than severe fatigue, which affected 4.0% of those > 55 YOA. There were no Grade 4 reactions reported in those given 60 µg dosing.

'The median onset for all systemic events was 2 to 4 days, and all events resolved within a median duration of 1 to 2 days after onset.' These **times to onset** and **durations** are in keeping with previously reported reactogenicity for BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg.

Overall, systemic reactogenicity to BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg has been characterised in approximately 300 (n = 314) participants with broadly even recruitment into age groups 12-17, 18-55 and > 55 YOA. The Evaluator agrees with the conclusion of the Sponsor that, 'The pattern of systemic events reported within 7 days after the BNT162b2 bivalent (WT/OMI BA.4/BA.5) vaccine was generally similar to those previously observed in association with an Omicron BA.1-modified BNT162b2 bivalent vaccine and to the original BNT162b2 vaccine within the respective age groups.' The size of the group – just over 300 participants – is in keeping with the number recommended in the ACCESS consortium statement for variant-modified vaccines as being sufficient to adequately characterise the reactogenicity profile.[12]

Overview of adverse events

Recalling that 521/528 (98.7%) of the Safety Population completed 1 month follow-up (Table 11), an overview of all AEs from Study C4591044 Cohort 2 is shown in Table 31.

[12] See https://www.tga.gov.au/resources/publication/publications/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic (accessed 21/11/2022).

Table 31. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month after the Study Vaccination – Cohort 2 – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
Adverse Event	30 µg (N[a]=107) n[b] (%)	30 µg (N[a]=103) n[b] (%)	60 µg (N[a]=110) n[b] (%)	30 µg (N[a]=106) n[b] (%)	60 µg (N[a]=102) n[b] (%)
Any adverse event	8 (7.5)	3 (2.9)	9 (8.2)	4 (3.8)	7 (6.9)
Related[c]	6 (5.6)	1 (1.0)	3 (2.7)	1 (0.9)	1 (1.0)
Severe	0	0	0	1 (0.9)	0
Life-threatening	0	0	0	0	0
Any serious adverse event	0	0	0	1 (0.9)	0
Related[c]	0	0	0	0	0
Severe	0	0	0	1 (0.9)	0
Life-threatening	0	0	0	0	0
Any nonserious adverse event	8 (7.5)	3 (2.9)	9 (8.2)	4 (3.8)	7 (6.9)
Related[c]	6 (5.6)	1 (1.0)	3 (2.7)	1 (0.9)	1 (1.0)
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Any adverse event leading to withdrawal	0	0	0	0	0
Related[c]	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Death	0	0	0	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to the study intervention.

Source: Table 12, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Evaluator's comments: Among the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg dosing age groups, the frequency of **any AE** was highest in those 12-17 YOA (7.5%) than in those 18-55 YOA (2.9%) or > 55 YOA (3.8%). The same pattern was seen for **any *related* AE** (5.6%, 1.0% and 0.9% respectively).

Frequencies of **any AE** were higher for the 60 µg dose than the 30 µg dose for both the 18-55 YOA group (8.2% vs 2.9% respectively) and > 55 YOA group (6.9% vs 3.8%); however, differences in **any *related* AE** were only really apparent in the 18-55 YOA group (2.7% vs 1.0%) rather than in the > 55 YOA group (1.0% vs 0.9%).

There were no **deaths** and no **AEs leading to study withdrawal**. There was one severe (but non-life-threatening) AE that was also recorded as a severe serious **SAE** (an event of dyspnoea); this occurred in the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg group in a participant > 55 YOA and was deemed unrelated to IP.

The Sponsor reported, 'No additional participants reported AEs from 1 month after study vaccination to the cutoff date.' (cutoff date 12/10/2022) (recalling that **median duration of follow-up was 1.6 months** [section 7.2.1.9]). The Sponsor also stated that, 'No clinically

meaningful differences in the overview of AEs were observed by sex or baseline SARS-CoV-2 status subgroups.' The Evaluator has reviewed the tables stratified by sex and baseline SARS-CoV-2 status in the C4591044_C2_1MPD_Full_Safety_Sen_Immuno_Final_TLF_Bundle_2NOV22 file (p109 and p113 respectively) and agrees with this statement.

Although there was no placebo-control group, the frequencies of AEs (and particularly severe AEs and SAEs) was low and in keeping with previous COMIRNATY booster studies. There was a dose-related pattern in AEs that was most pronounced in the 18-55 YOA group and an age-related pattern that was most pronounced in the 12-17 YOA group compared to those ≥ 18 YOA.

Analysis of all adverse events (data cutoff 12/10/2022)

The Sponsor presented a summary of all AEs (regardless of relatedness to IP) in Table 13 of the '1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report'. There were 2 AEs of lymphadenopathy, both in participants 18-55 YOA and one each in the 30 µg and 60 µg dosing groups.

There was one Grade 2 AE of 'Troponin increased' in a s4 year old s47F in the 30 µg dosing group (participant study ID C4591001 s 47F). This occurred on Day s47F (vaccination was on Day 1). The same participant experienced a Grade 3 SAE of 'Dyspnoea/Shortness of Breath' on Day s47F and Grade 1 AEs of 'Supraventricular extrasystoles/Premature Atrial Complexes' and 'Rales/Right Basilar Crackles' on Day s47F. All 4 AEs were deemed unrelated to IP. The available details for these events are presented in Table 32. Further details about the SAE are shown in section 8.4.3.3.

There was one AE of 'Menstruation irregular' in a participant 18-55 YOA in the 60 µg dosing group (a s47F female participant s4 YOA who missed her menstrual period); this was deemed related to IP.

Table 32. Listing of Adverse Events - Cohort 2 - Participant C4591001 s 47F

Vaccine Group (as Administered)	Age Group (Years)	Age(Years)/ Race/Sex/ Participant	System Organ Class	Preferred Term/ AE Investigator Text	Onset Date	Rel Day[a]/ Dur (Days)[b]	Toxicity Grade	Vax Rel[c]	Cause of AE	Action: Investigational Vaccine Dose/Participant	Outcome (End Date)	SAE/Imm AE (Yes/No)
		s47F M/ C4591001 s47F	RESP	Dyspnoea/ Shortness of Breath	s47F	15/C	3	No	O	NA/TC	RG	Y/N
			INV	Troponin increased/ Elevated Troponin	s47F	22/C	2	No	O	NA	N	N/N
			CARD	Supraventricular extrasystoles/ Premature Atrial Complexes	s47F	31/C	1	No	O	NA	N	N/N
			RESP	Rales/ Right Basilar Crackles	s47F	31/C	1	No	O	NA	N	N/N

Abbreviations: C = continuing; Dur = duration; Imm = immediate; NA = not applicable. Refer to the AE legend page (Listing 16.2.7.1) for additional definitions.
Note: MedDRA (v25.0) coding dictionary applied.
Note: * = Prevaccination AE.
a. Relative day (Rel Day) = date of AE - date of study vaccination + 1. For an AE that occurred before the date of the study vaccination, + 1 was not added to compute relative day.
b. Duration (days) was calculated as the difference from the start of the first reported event to resolution of the last reported event, inclusive.
c. Vaccine related (Vax Rel): relationship to study intervention as assessed by the investigator.

Source: Extracted from 16.2.7.4, page 272-273 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file. Legend: System Organ Class: RESP = Respiratory, thoracic and mediastinal disorders; INV = Investigations; CARD = Cardiac disorders; Cause of AE: O = Other; Action: NA = Not applicable, TC = Concomitant drug treatment given; Outcome: RG = Recovering/resolving, N = Not recovered/not resolved.

Evaluator's comments: Most of the recorded AEs were consistent with reactogenicity events that were reported as AEs (e.g. the SOCs with the most AEs were 'General disorders and administration site conditions' and 'Musculoskeletal and connective tissue disorders' [inclusive of PTs myalgia and arthralgia]). There were no AEs (outside of reactogenicity-related events) that were reported in > 2 participants. The frequencies of expected related AEs like lymphadenopathy and menstrual irregularities was low and in keeping with the existing PI for COMIRNATY. The Evaluator would like more details about the participant with the raised troponin, given myocarditis was not reported. **EvQset2**: Participant C4591001[s 47F] reported 4 AEs (including one SAE) following vaccination with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and all were deemed unrelated to the investigational product (IP). Please ensure detailed narratives for these 4 AEs are included in the formal submission, including justification for why they were deemed unrelated to IP.

The Sponsor has stated that, 'No clinically meaningful differences in AEs by SOC/PT were observed by sex or baseline SARS-CoV-2 status subgroups.' The Evaluator has reviewed the tables stratified by sex and baseline SARS-CoV-2 status in the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22NOV22 file and agrees with this statement.

8.4.1.4. Other studies

Other efficacy studies

Supportive safety data was provided from the following studies:

- Study C4591001 who received a booster dose (Dose 3) of the original BNT162b2 30 µg or of Beta variant-modified vaccine (BNT162b2$_{SA}$) 30 µg.
- Study C4591031 Substudy D who received a booster dose (Dose 4) of either the original BNT162b2 30 µg or monovalent Omicron variant-modified BNT162b2 (BNT162b2 OMI BA.1) 30 µg.
- Study C4591031 Substudy E who received a booster dose (Dose 4) of either the original BNT162b2 30 µg, monovalent BNT162b2 OMI BA.1 30 µg or bivalent BNT162b2 + BNT162b2 OMI BA.1 30 µg.

See the **integrated safety analyses** for a summary of reactogenicity from these studies, section 8.4.1.1. The **safety data** for these studies was evaluated in relation to the submission for provisional registration of COMIRNATY Original/Omicron BA.1 (PM-2022-03551-1-2) and the CER is available at TRIM: D22-5946058. The Evaluator's overall conclusions on clinical safety in that CER are shown below.

Evaluator's overall conclusions on clinical safety from 'D22-5946058 COMIRNATY OMICRON BA.1 (tozinameran riltozinameran) Sponsor copy FINAL 4 October 2022':

Safety data are provided by the pivotal study, Study C4591031 Substudy E, and two additional studies, Study C4591031 Substudy D and Study C4591001: BNT162b2$_{SA}$ VOC Booster Subset. Each of these studies is ongoing. Only the pivotal study, Study C4591031 Substudy E, pertains to the proposed bivalent vaccine, COMIRNATY Original/Omicron BA.1.

The safety profile of BNT162b2 30 µg is known. COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] is provisionally approved in Australia for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older and COMIRNATY (tozinameran) COVID-19 VACCINE is provisionally approved in Australia for Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.

The safety data provided by the pivotal study, Study C4591031 Substudy E, in relation to the proposed BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) vaccine are limited. In the pivotal study, 305 participants received BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) and were followed-up for a median duration of 1.7 months. This number of participants exposed to BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) appears to be consistent with the guidance in "Points to consider for strain changes in authorised COVID-19 vaccines in an ongoing SARS-COV-2 pandemic" (9) in relation to a change in the sequence related to a new variant. However, COMIRNATY Original/Omicron BA.1 is a new combination vaccine which includes a new variant.

No new safety concerns were identified with the administration of BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) in this study. The safety results for BNT162b2 (15 µg) + BNT162b2 OMI (15 µg) were consistent with the safety profile for COMIRNATY described in the currently approved PI. The proportion of participants reported with specific local reaction and systemic reaction preferred terms were similar for participants who were SARS-CoV-2 positive and SARS-CoV-2 negative at Baseline, respectively.

No new concerns that could impact on the safety of COMIRNATY Original/Omicron BA.1 were evident from the safety data provided by Study C4591031 Substudy D and Study C4591001 $BNT162b2_{SA}$ VOC Booster Subset.

Studies with evaluable safety data: dose finding and pharmacology

Study BNT162-17 – solicited adverse events (reactogenicity)

Local reactogenicity is shown for Cohort 1 (i.e. bivalent BNT162b2 [B.1.1.7 + B.1.617.2] 30 µg) in Figure 19 and for Cohort 4 (i.e. monovalent BNT162b2 [B.1.617.2] 30 µg) in Figure 20. There were no Grade 4 reactions in either cohort.

Systemic reactogenicity is shown for Cohort 1 in Figure 21 and Figure 22, and for Cohort 4 in Figure 23 and Figure 24. There were no Grade 4 reactions in either cohort.

Evaluator's comments: Most local and systemic reactogenicity was mild to moderate in severity and there were no Grade 4 reactions. Overall, the pattern of reactogenicity was similar to other booster studies (e.g. see Table 28 and Table 29) and raised no new concerns. These data provide minor support for the conclusion that a variety of monovalent and bivalent versions of BNT162b2 30 µg are reasonably well tolerated.

Study BNT162-17 – unsolicited adverse events

In **Cohort 1** (i.e. bivalent BNT162b2 [B.1.1.7 + B.1.617.2] 30 µg), AEs were reported in 14.1% of participants and related AEs in 2.7%. There were no participants with Grade ≥ 3 AEs, no SAEs, no AEs leading to withdrawal and no deaths. The pattern of AEs showed a predominance of reactogenicity-related events and lymphadenopathy. There was one event of drug hypersensitivity (non-anaphylaxis).

In **Cohort 4** (i.e. monovalent BNT162b2 [B.1.617.2] 30 µg), AEs were reported in 12.1% of participants and related AEs in 4.6%. There were 2/372 (0.5%) participants with Grade ≥3 AEs, and one participant with a related Grade 3 AE (an event of myocarditis); this occurred in Part B in a participant aged 56-85 years and was also coded as an AESI. There were no SAEs, no AEs leading to withdrawal and no deaths. The pattern of AEs showed a predominance of reactogenicity-related events and lymphadenopathy.

The event of **myocarditis** in a **Cohort 4** participant occurred in a s47F YOA and was coded by the Investigator as 'probable myocarditis'. Approximately s47F hours post-dose, the participant experienced chest pain lasting 3 hours and tachycardia lasting 13 hours. Upon review 3 days later the symptoms had resolved but a Troponin I level was elevated and there

were non-specific ECG abnormalities. An echocardiogram was normal. The participant was not hospitalised. It was assessed by the Investigator and Sponsor as being related to vaccination.

Evaluator's comments: The AE profile observed in recipients of BNT162b2 (B.1.1.7 + B.1.617.2) 30 µg and BNT162b2 (B.1.617.2) 30 µg was generally consistent with the known safety profile of BNT162b2 30 µg. The related case of myocarditis was mild. There were no new safety concerns identified. These data provide minor support for the conclusion that these bivalent and monovalent variant-based vaccines have a similar safety profile to BNT162b2 30 µg; however, the number of participants was relatively small and the follow-up brief. Of note, these boosters were given to recipients of 2 prior doses of BNT162b2 30 µg and not 3 prior doses, like in study Study C4591044 Cohort 2.

Studies evaluable for safety only

Not applicable.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

Not applicable.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.2.3. Pivotal and/or main efficacy studies – Study C4591044 Cohort 2 (data cutoff 12/10/2022)

Treatment-related AEs were reported by 12 (2.3%) participants overall and are shown by SOC and PT in Table 33.

Table 33. Number (%) of Participants Reporting at Least 1 Related Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term – Cohort 2 – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years				>55 Years			
	30 µg (N[a]=107)		30 µg (N[a]=103)		60 µg (N[a]=110)		30 µg (N[a]=106)		60 µg (N[a]=102)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	6 (5.6)	(2.1, 11.8)	1 (1.0)	(0.0, 5.3)	3 (2.7)	(0.6, 7.8)	1 (0.9)	(0.0, 5.1)	1 (1.0)	(0.0, 5.3)
Blood and lymphatic system disorders	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.3)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	0	(0.0, 3.6)
Lymphadenopathy	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.3)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	0	(0.0, 3.6)
General disorders and administration site conditions	4 (3.7)	(1.0, 9.3)	0	(0.0, 3.5)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.3)
Fatigue	3 (2.8)	(0.6, 8.0)	0	(0.0, 3.5)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	0	(0.0, 3.6)
Injection site pain	2 (1.9)	(0.2, 6.6)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.3)
Chills	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Injection site erythema	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Musculoskeletal and connective tissue disorders	2 (1.9)	(0.2, 6.6)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Myalgia	2 (1.9)	(0.2, 6.6)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Nervous system disorders	2 (1.9)	(0.2, 6.6)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Headache	2 (1.9)	(0.2, 6.6)	0	(0.0, 3.5)	0	(0.0, 3.3)	0	(0.0, 3.4)	0	(0.0, 3.6)
Reproductive system and breast disorders	0	(0.0, 3.4)	0	(0.0, 3.5)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	0	(0.0, 3.6)
Menstruation irregular	0	(0.0, 3.4)	0	(0.0, 3.5)	1 (0.9)	(0.0, 5.0)	0	(0.0, 3.4)	0	(0.0, 3.6)
Skin and subcutaneous tissue disorders	0	(0.0, 3.4)	0	(0.0, 3.5)	0	(0.0, 3.3)	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.6)
Erythema	0	(0.0, 3.4)	0	(0.0, 3.5)	0	(0.0, 3.3)	1 (0.9)	(0.0, 5.1)	0	(0.0, 3.6)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

Source: Table 14, 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report (data cutoff 12/10/2022).

Evaluator's comments: As expected, most of the related events were reactogenicity events, lymphadenopathy or menstrual irregularity. There was one case of skin erythema (another known treatment related event from existing PI). The Evaluator notes the case of 'Troponin increased' mentioned as an AE in section 8.4.1.3 that appears to have been deemed unrelated to IP and would like to seek further details about the narrative for that case (see Clinical Questions, set 2 in section 12.1.1.2).

8.4.2.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

Not applicable.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.3.3. Pivotal and/or main efficacy studies – Study C4591044 Cohort 2 (data cutoff 12/10/2022)

There were no deaths, no life-threatening AEs and no AEs leading to study withdrawal through 1 month post-vaccination.

Serious adverse events

There was only one SAE, a severe SAE of dyspnoea in participant C4591001 s47F > 55 YOA who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg. This was deemed unrelated to IP.

The Sponsor's description of this event was as follows:

> 'One (1) SAE of dyspnoea (shortness of breath) was reported in a participant in the > 55 years of age group who received a booster dose of BNT162b2 bivalent 30-µg. This SAE was reported in an s47F , s47F participant s47F years of age, considered by the investigator to be severe and not related to study intervention. AE onset was s47F days after vaccination and was ongoing as of the data cutoff date (12 October 2022). No further details were specified.'

This participant experienced other AEs as presented in section 8.4.1.3 and Table 32.

8.4.3.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

Not applicable.

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.4.3. Pivotal and/or main efficacy studies

There were no discontinuations due to AEs in Study C4591044.

8.4.4.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

Not applicable.

8.5.2. Renal function and renal toxicity

Not applicable.

8.5.3. Other clinical chemistry

Not applicable.

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

Not applicable.

8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.4.3. Pivotal and/or main efficacy studies – Study C4591044 Cohort 2 (data cutoff 12/10/2022)

There were 2 AEs of treatment-related lymphadenopathy shown in Table 33. These were described by the Sponsor as follows:

> 'Once [sic] case was in a s47F participant s47F years of age with onset s47F days post vaccination, of left axillary lymphadenopathy considered by the investigator as related to study intervention, and it was reported as resolved within 6 days after onset.
>
> The other case was in a s47F or s47F participant s47F years of age with onset s47F days post vaccination, presenting with left axillary lymph node swelling. It was considered by the investigator as related to study intervention, and it was reported as resolved within 8 days after onset.'

Evaluator's comments: One of those participants was given 30 µg and the other 60 µg of BNT162b2 bivalent (WT/OMI BA.4/BA.5) but the Evaluator is unclear which is which. That said, they are both similar in their presentations and evolution and consistent with the known safety profile of COMIRNATY that has been documented in the PI for the original wildtype BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg vaccines.

8.5.4.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.5.5. Other laboratory tests

Not applicable.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

Not applicable.

8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.6.3. Pivotal and/or main efficacy studies

See discussion of 'unrelated' SAE and other AEs in response to the Clinical Questions (set 2, question 2) in section 12.1.1.2.

8.5.6.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.5.7. Vital signs and clinical examination findings

Not applicable.

8.5.8. Immunogenicity and immunological events

8.5.8.1. Integrated safety analyses

Not applicable.

8.5.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.8.3. Pivotal and/or main efficacy studies – Study C4591044 Cohort 2 (data cutoff 12/10/2022)

Immediate adverse events

There was 1 (1.0%) participant in the 12-17 YOA group who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and reported a non-severe immediate AE of injection site erythema within 30 minutes of study vaccination.

Evaluator's comments: Consistent with known safety profile.

AESIs

There were no AEs of anaphylaxis, hypersensitivity, appendicitis, Bell's palsy, myocarditis or pericarditis reported up to 1 month post-vaccination (or up to the data cutoff date of 12/10/2022, with a median of 1.6 months follow-up).

8.5.8.4. Other studies

Other efficacy studies

See section 8.4.1.4.

Studies with evaluable safety data: dose finding and pharmacology

See section 8.4.1.4.

Studies evaluable for safety only

Not applicable.

8.5.9. Serious skin reactions

Not applicable.

8.5.10. Other safety parameters

Not applicable.

8.6. Other safety issues

Not applicable.

8.7. Post marketing experience

8.7.1. Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged ≥12 Years — United States, August 31–October 23, 2022

The FDA approved bivalent Omicron BA.4/5 mRNA vaccines from Pfizer and Moderna on 31/08/2022 and ACIP recommended all persons ≥ 12 YOA receive an age-appropriate booster dose ≥ 2 months following prior vaccination on 1/09/2022. The CDC has reported safety monitoring data from the first 7 weeks of the rollout (31/08/2022 to 23/10/2022) from v-safe (voluntary smart phone monitoring via daily health survey in first week) and the VAERS program (passive surveillance of AEs mapped to MedDRA PTs).[13]

During that 7 week period, approximately 14.4 million persons aged ≥ 12 YOA received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and 8.2 million adults ≥ 18 YOA received the bivalent Moderna vaccine; 22.6 million people in total.

There were 211,959 v-safe participants in the 7 week period who reported receiving a bivalent booster dose (Table 62). Co-administration of another vaccine occurred in nearly 40% of those (nearly always this was influenza vaccine [98.3%]). Reactogenicity profiles are shown in (Table 63). Receipt of medical care was reported by 0.8% of registrants.

VAERS received 5542 reports of AEs during the surveillance period, of which 95.5% were non-serious (94.3% for BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and 96.8% for the bivalent Moderna vaccine) (Table 64). Among the 251 AEs classified as serious, there were 5 reports of myocarditis and 4 reports of pericarditis.

Conclusions reached by the CDC's authors included:

- 'Reporting frequencies of reactions and health impacts among the 211,959 v-safe registrants aged ≥ 12 years who received an age-appropriate bivalent booster vaccination are similar to those described after receipt of first and second booster vaccine doses among adults aged ≥ 50 years.'
- 'Among adults aged ≥ 18 years, reporting frequencies of local and systemic reactions after bivalent booster vaccination decreased with increasing age. This reporting pattern was also observed for primary series COVID-19 vaccination.'

[13] See https://www.cdc.gov/mmwr/volumes/71/wr/mm7144a3.htm (accessed on 5/12/2022).

- Caveats that v-safe is voluntary therefore may not be representative, VAERS is subject to reporting biases (especially under-reporting of non-serious events) and the surveillance period was relatively short (7 weeks).

Evaluator's comments: The available safety monitoring data from the US CDC following the first 7 weeks of the bivalent Omicron BA.4/5 mRNA vaccines rollout do not raise any new safety concerns. There is the possibility that reactogenicity and/or AEs were biased due to coadministration of the influenza vaccine (> 1/3 of v-safe registrants received co-administered influenza vaccine).

8.8. Evaluator's overall conclusions on clinical safety

Table 28 and Table 29 cross-reference **reactogenicity** data for Dose 3 vs Dose 4 boosters for the original BNT162b2 30 µg vaccine; along with Dose 4 data for BNT162b2 monovalent (OMI BA.1) 30 µg, BNT162b2 bivalent (WT/OMI BA.1) 30 µg, BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, and BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg. The reactogenicity profiles for the 30 µg dosing regimens are broadly similar, regardless of vaccine type and dose number (Dose 3 or Dose 4), but more reactogenicity was evident for the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg vaccine then for the 30 µg vaccines. Nearly all reactogenicity events reported for BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg in Study C4591044 Cohort 2 were mild or moderate in severity and there were no Grade 4 events. Thus, the proposed vaccine (BNT162b2 bivalent [WT/OMI BA.4/BA.5] 30 µg) can be said to be similarly well-tolerated as the Sponsor's previous booster vaccines across age groups from ≥ 12 YOA.

The **AE profile** of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg in Study C4591044 Cohort 2 within one-month post-vaccination mainly involved reactogenicity events, lymphadenopathy and an event of menstrual irregularity. There was one event of immediate redness at the injection site (after 30 minutes) but none of anaphylaxis or hypersensitivity. The only severe AE was also a severe SAE, an unrelated case of dyspnoea that occurred 15 days post-vaccination (n.b. the Evaluator is seeking more information about this case). There were no life-threatening AEs, none leading to study withdrawal or discontinuation and no deaths. Nor were any AESIs (inclusive of myocarditis and pericarditis) reported, although the Evaluator would like to further review the event of 'Troponin increased' that was deemed unrelated to IP.

The **supportive safety data** from the 'other efficacy studies' concerning other sub-variant BNT162b2-based vaccines (see section 8.4.1.4) do not raise any new safety concerns and nor do the available **real-world safety** monitoring data from the US CDC following the first 7 weeks of the bivalent Omicron BA.4/5 mRNA vaccines rollout.

Overall, based on the data available, BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appears well tolerated and has an acceptable safety profile in line with BNT162b2 30 µg and BNT162b2 bivalent (WT/OMI BA.1) 30 µg. There were no new safety signals identified. Of note, nearly all participants in Study C4591044 Cohort 2 had ≥ 1 month follow-up but the overall median follow-up was only 1.6 months. Ongoing monitoring for safety is needed.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Following 3 prior doses of BNT162b2 30 µg, COMIRNATY Original/Omicron BA.4-5 given as a 4th dose boosts neutralising responses against Omicron BA.4/5. Neutralising responses against Omicron BA.1 and the wild-type reference strain are relatively preserved relative to booster vaccination with COMIRNATY Original/Omicron BA.1 or COMIRNATY Original.	Neutralising responses against Omicron BA.4/5, Omicron BA.1 and reference strain were boosted in participants with *and* without prior exposure to SARS-CoV-2 infection. Neutralising responses against the currently prevalent Omicron BA.4/5 subvariant appear as good or better than those generated by the two provisionally registered booster vaccines, COMIRNATY Original/Omicron BA.1 and COMIRNATY Original. Boosting has been demonstrated, to varying degrees, among the newly emerging sublineages of the Omicron variant (i.e. BA.4.6, BA.2.75.2, BQ.1.1, and XBB). The immunogenicity data presented are only short-term, from 1 month following vaccination. Data for other immune responses have not been presented. Comparison of neutralising responses between COMIRNATY Original/Omicron BA.4-5, COMIRNATY Original/Omicron BA.1 and COMIRNATY Original is hampered by the use of non-contemporaneous data. This introduces a number of biases, most notably the types of SARS-CoV-2 variants/sublineages constituting prior exposure and time between 3rd dose and 4th booster dose. All of the immunogenicity data were generated from participants ≥ 18 YOA and there are no data available yet from individuals 12-17 YOA, who are included in the proposed therapeutic indication. Participants in Study C4591044 Cohort 2 had received 3 prior doses of BNT162b2 30 µg, hence the results may not be generalisable to those who've received fewer doses or alternate vaccines. Formal statistical hypothesis testing for superiority/non-inferiority of immune responses to BNT162b2 bivalent (WT/OMI

Indication	
Benefits	**Strengths and Uncertainties**
	BA.4/BA.5) 30 µg vs BNT162b2 30 µg is still pending (expected in 2023).

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
The clinical efficacy of COMIRNATY Original/Omicron BA.4-5 is unknown.	There were no clinical efficacy endpoints studied and neutralising responses have not been firmly established as a reliable correlate of protection. Real world evidence of vaccine effectiveness from the USA suggests that a combination wild type/Omicron BA.4/5 mRNA boosters provides additional protection against symptomatic COVID-19 (relative to no booster) but with many caveats (e.g. the relative proportions of each mRNA vaccine studied were not specified).
The short-term safety of COMIRNATY Original/Omicron BA.4-5 has not been fully characterised. The long-term safety of COMIRNATY Original/Omicron BA.4-5 is unknown.	Reactogenicity has been characterised in a sufficiently sized sample of participants ≥ 12 YOA and appears very similar to that of the two previously provisionally registered vaccines COMIRNATY Original and COMIRNATY Original/Omicron BA.1. Overall, the safety profile appears very similar to the Sponsor's currently provisionally registered vaccines (listed above) and no new safety concerns have been identified. Adverse events were reported for all age groups (12-17, 18-55 and > 55 YOA). Supportive safety data from the Sponsor's other studies of SARS-CoV-2 variant vaccines have not identified any new safety concerns; neither have the available real-world safety monitoring data from the US CDC following the first 7 weeks of the bivalent Omicron BA.4/5 mRNA vaccines rollout.

Risks	Strengths and Uncertainties
	The safety data provided from Study C4591044 Cohort 2 are limited to approximately 300 participants who received BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, which is not enough to adequately characterise the safety profile. Although nearly all participants from Study C4591044 Cohort 2 had ≥ 1 month safety follow-up, the overall median follow-up was only 1.6 months. Because of the limited size of the safety database and limited duration of follow-up, ongoing monitoring for safety is needed.

9.3. First round assessment of benefit-risk balance

The Evaluator notes that COMIRNATY Original/Omicron BA.4-5 was proposed as a booster (rather than a primary series) for individuals ≥ 12 YOA, at a time when Omicron BA.4/5 and its sublineages are the predominant circulating subvariants in Australia. Also, that COMIRNATY Original/Omicron BA.4-5 has been used in the US and EU since September 2022. Some real-world data on vaccine effectiveness and safety from the US have been published independent of the Sponsor and were available for review (involving millions of doses).

The **safety profile** of BNT162b2 30 µg (i.e. COMIRNATY Original) has been well characterised previously. The reactogenicity profile of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg appears very similar and is also in line with other variant vaccines studied by the Sponsor. The safety data from Study C4591044 Cohort 2 have not identified any new safety concerns but are limited to a relatively small safety database of ~ 300 participants receiving the 30 µg dose who were only followed for a median of 1.6 months. Of note, these reactogenicity and safety data derive from participants ≥ 12 YOA. Real-world safety data from the first 7 weeks of the US rollout have not identified any new safety concerns.

The **clinical efficacy** of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg has not been studied relative to placebo and although supportive, there were a number of caveats regarding the generalisability of the US real-world evidence on vaccine effectiveness (e.g. only available for adults ≥ 18 YOA and the effectiveness of the Pfizer and Moderna vaccines were not studied separately).

BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg is **immunogenic** in adults ≥ 18 YOA primed with 3 doses of BNT162b2 30 µg, with neutralising responses against Omicron BA.4/5 being higher than for the Sponsor's currently provisionally registered vaccines; however, subject to a number of caveats including relatively small numbers, overlapping CIs and the use of non-contemporaneous control data. In time, COMIRNATY Original/Omicron BA.4-5 may be shown to be superior to the current alternatives but data for those primary immunogenicity objectives will not be available until later in 2023. The proposed vaccine appears to retain useful neutralising activity against Omicron BA.1 and wild-type reference strain, as well as being immunogenic (to varying degrees) against the newly circulating Omicron sublineages BA.4.6, BA.2.75.2, BQ.1.1, and XBB.

There are missing data currently for immunogenicity in **adolescents 12-17 YOA** but the Sponsor has flagged that those data will become available at a later date. Of note, the proposed vaccine contains the same overall dose of mRNA (30 µg) that is used in BNT162b2 30 µg, which was provisionally approved for use as a booster for adolescents 12-15 YOA on 7/04/2022 (TRIM: D22-5365768). This approval was in part based on extrapolation of efficacy data from older adolescents and adults rather than direct immunogenicity or efficacy data in the target age group (TRIM: D22-5258116).

On balance, the Evaluator considers the **safety profile** of COMIRNATY Original/Omicron BA.4-5 is likely to be similar to the Sponsor's currently provisionally registered mRNA COVID-19 vaccines and that the **immunogenicity** is likely to be as good or better in relation to the currently circulating Omicron BA.4/5 SARS-CoV-2 subvariants. It is reassuring that the safety data included individuals down to 12-17 YOA and it seems reasonable to extrapolate likely immunogenicity and effectiveness to this age group at the proposed total dose of 30 µg mRNA.

It is noted that further data to address the primary immunogenicity objectives in terms of formal statistical hypothesis testing and participants 12-17 YOA is anticipated later in 2023.

Currently, the Evaluator finds the benefit-risk assessment to be **favourable**.

10. First round recommendation regarding authorisation

Based on the evaluation of the clinical data, the Evaluator recommends approval of COMIRNATY Original/Omicron BA.4-5 *as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older* subject to the following:

- Modification of the PI and CMI as described in section 11.1 and section 11.2 respectively, including providing an updated annotated PI that includes missing data as specified in section 11.1 and Table 65.
- Satisfactorily addressing the Clinical Questions posed by the Evaluator in section 12.1.1, including outlining a timeline for the receipt of further data in relation to the primary immunogenicity objectives (Table 49).

11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

The clinical aspects of the draft PI for COMIRNATY Original/Omicron BA.4-5 (Version: proposed-pi-ba45) in Sequence 0000 are not entirely satisfactory and should be revised, having regard to the comments below and to the comments in Table 65.

The draft PI for COMIRNATY Original/Omicron BA.4-5 COVID-19 VACCINE is based on the approved PI for COMIRNATY Original/Omicron BA.1 COVID-19 VACCINE (Version: pfpcodii11122, dated 14/11/2022), which was in turn based on the approved PI for COMIRNATY COVID-19 VACCINE [Tris/Sucrose Presentation] (Version: pfpcobii10522).

There is information that is common to the draft PI for COMIRNATY Original/Omicron BA.4-5 COVID-19 VACCINE and the approved PIs for COMIRNATY Original/Omicron BA.1 COVID-19 VACCINE and COMIRNATY COVID-19 VACCINE [Tris/Sucrose Presentation]. The sponsor has presented the proposed PI as an annotated version of the approved PI for COMIRNATY Original/Omicron BA.1 COVID-19 vaccine (Version: pfpcodii11122, dated 14/11/2022).

11.2. First round comments on draft CMI (clinical aspects)

The draft CMI was presented as an annotated version of the current CMI for COMIRNATY Original/Omicron BA.1 in which a number of changes were made in relation to:

- Replacing 'COMIRNATY Original/Omicron BA.1' with 'COMIRNATY Original/Omicron BA.4-5'.
- Replacing 'riltozinameran' with 'famtozinameran'.
- Replacing '18 years of age and older' with '12 years of age and older' or 'under 18 years' with 'under 12 years' where appropriate.
- Adding the clarifier 'as a booster dose' in 3 instances referring to administration of COMIRNATY Original/Omicron BA.4-5.

The Evaluator supports all of those changes to the CMI and is satisfied with the remainder of the CMI.

Sections 4 and 5 of the CMI contain information analogous to that presented in section '4.2 Dose and method of administration' of the PI in relation to the lower age limit for booster vaccination, which the Evaluator finds confusing and potentially contradictory for the reasons stated in section 1.5 of this CER. The Evaluator is seeking clarification in the form of a rolling Clinical Question (see section 12.1.1.3).

11.3. First round comments on draft RMP (Summary of Safety Concerns)

11.3.1. European Union Risk Management Plan: Version 9.0

The Evaluator reviewed 'Module SVII. Identified and Potential Risks' and 'Module SVIII. Summary of the Safety Concerns' within 'PART II. SAFETY SPECIFICATION' in the EU EMP: Version 9.0 (date of final sign off 4/11/2022). The 'Summary of Safety Concerns' is represented in Table 34.

Table 34. Summary of Safety Concerns (EU RMP)

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Source: Table 70, 'Module SVIII. Summary of the Safety Concerns', EU RMP: Version 9.0, date of final sign off 4/11/2022.

In relation to the 'Important Identified Risks' of 'Myocarditis and Pericarditis' in the 'Summary of Safety Concerns'; this is reflected by a subsection in the PI under section 4.4 of the PI 'Special warnings and precautions for use / General recommendations / Myocarditis and pericarditis' as follows:

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. Cases have occurred following first and second vaccinations and following booster doses. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not exclusively, in younger males. There have been reports in females. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis, including atypical presentations. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

For further details, please refer to the relevant clinical guidelines developed by the Australian Technical Advisory Group on Immunisation.

Source: Annotated PI section 4.4 'Special warnings and precautions for use / General recommendations'.

11.3.2. Australian Specific Annex: Version 0.7

The Sponsor has presented an Australia-Specific Annex: Version 0.7 that is based on the EU RMP: Version 9.0 (see section 11.3.1). In relation to the ASA, the Sponsor has stated that, 'There are no safety concerns for Australia that are additional to those proposed in the EU RMP.' No additional risk minimisation activities are proposed for Australia.

Evaluator's comments: The summary of safety concerns in the draft Risk Management Plan is satisfactory.

12. Clinical questions

12.1. Clinical questions

12.1.1. Rolling questions – Round 1 CER

12.1.1.1. Clinical set 1 (emailed to Sponsor 24/11/2022, D22-6198192)

Question 1

The data cutoff date in the '1 Month Post Dose Safety and Immunogenicity (Sentinel) Data: Study C4591044 Cohort 2' report (November 2022) is 12 October 2022. Please advise whether this data cutoff date will remain the same in the formal submission (due in December 2022) or whether a later data cutoff date will be utilised for reactogenicity, safety (adverse events) and/or immunogenicity.

Sponsor's reply (received 25/11/2022, D22-6198199)

'The new data to become available in December 2022 is of data cut-off date planned as 9 December 2022.

- C4591044 Cohort 2 Group 2 (18 to <55) & Group 4 (55+) – 1 month post-dose immunogenicity analysis (30 mcg dose only, total n=200).

We hope to be able to include this in the formal submission.'

Evaluator's comments

Noted.

Question resolved.

Question 2

Will the supportive study data from Study C4591031 (modules D and E) and Study C4591001 that are submitted with the formal submission in December 2022 have the same data cutoff dates as those reports had in submission PM-2022-03551-1-2 (COMIRNATY bivalent WT/OMI BA.1) or will those reports be updated with later data cutoff dates?

Sponsor's reply (received 25/11/2022, D22-6198199)

'The data cut-off dates remain the same for below listed supportive studies.

- Study C4591031 Substudy D
- Study C4591031 Substudy E (> 55 years)
- Study C4591001

New supportive study report for C4591031 Substudy E (1 month post dose Original/Omicron BA.1, 18-55 years) will be submitted with the formal submission.'

Evaluator's comments

Noted.

Question resolved.

12.1.1.2. Clinical set 2 (emailed to Sponsor 8/12/2022, TRIM: D22-6209605)

Question 1

Participant C4591001 s47F [redacted] reported 4 AEs (including one SAE) following vaccination with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and all were deemed unrelated to the investigational product (IP). Please ensure detailed narratives for these 4 AEs are included in the formal submission, including justification for why they were deemed unrelated to IP.

Sponsor's reply (received 23/12/2022, TRIM: D22-6258703)

The Sponsor provided additional details about the 4 AEs and the Evaluator assumes the SAE of 'Dyspnoea' was mislabelled as 'Leukemia' (i.e. a typo) given the description provided and the prior listing of 'Dyspnoea' as an SAE in the 'C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22' file (page 272). Leukaemia was listed in that participant's past medical history. Of note, a transthoracic echocardiogram performed during the investigations of these events was normal.

Evaluator's comments

The Evaluator feels the timing of these events and their description does not favour a diagnosis of myocarditis or cardiac ischaemia and agrees that all 4 events are unlikely to be related to vaccination.

Question resolved.

12.1.1.3. Clinical set 3 (emailed to Sponsor 22/12/2022, TRIM: D22-6256209)

Question 1

In the proposed PI section '**4.2 Dose and method of administration / Dosage / Booster dose in individuals**', the first paragraph facilitates administration of COMIRNATY Original/Omicron BA.4-5 as a booster to individuals ≥ 12 YOA who have previously received '…a COVID-19 vaccine primary series…' and is agnostic to the type of vaccine previously received, whether BNT162b2 30 µg or another vaccine. However, the second paragraph appears to restrict COMIRNATY Original/Omicron BA.4-5 to individuals ≥ 18 YOA where that primary series was '…another COVID-19 vaccine.', which would potentially include primary series of BNT162b2 30 µg as well as other Sponsors' vaccines. There is no advice regarding use of COMIRNATY Original/Omicron BA.4-5 after a previous booster dose. The CMI is worded similarly. In contrast, the advice provided from the US EUA amendment (Module 1.11.1) states clearly that 'Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in individuals 12 years of age and older as a single booster dose administered at least 2 months after either: completion of primary vaccination with any authorized or approved monovalent[14] COVID-19 vaccine, or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.' Please rewrite this section of the PI (and corresponding sections of the CMI) so it is clear what the intentions are in relation to: (1) lower age limit(s) and whether they differ in different circumstances; (2) the use of COMIRNATY Original/Omicron BA.4-5 after booster vaccination; (3) the type of vaccine previously administered for the primary series and/or booster; (4) the time between the most recent dose of primary series or booster and the booster dose of COMIRNATY Original/Omicron BA.4-5.

Sponsor's reply (received 6/01/2023, TRIM: D23-5014376)

The Sponsor responded as follows:

> 'The PI has been revised to include "COMIRNATY Original/Omicron BA.4-5 may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of COVID 19 vaccine" and is attached. Similar wording will be added to the corresponding sections of the CMI.'

This section of the revised annotated PI now appears as follows:

[14] Monovalent refers to any authorized or approved COVID-19 vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2.

4.2 Dose and method of administration

Dosage

Booster dose in individuals 12 years of age and older

A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older.

COMIRNATY Original/Omicron BA.4-5 may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of COVID 19 vaccine.~~COMIRNATY Original/Omicron BA.4-5 may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another COVID-19 vaccine.~~

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

Evaluator's comments

The response makes it clear that COMIRNATY Original/Omicron BA.4-5 can be given as the first booster dose following a primary series *or* as an additional booster dose following a prior booster dose; in both cases to individuals ≥ 12 YOA. It is implied (but not stated) that these prior doses could be with any type of COVID-19 vaccine (i.e. not just a previous version of COMIRNATY monovalent or bivalent). As questions related to homologous or heterologous boosting may remain in the minds of prescribers reading the PI, the Evaluator would prefer more definitive advice.

The time to booster dosing with COMIRNATY Original/Omicron BA.4-5 differs following a primary series (5 months) or previous booster (4 months). The current PI for COMIRNATY (i.e. the monovalent BNT162b2 30 µg) states that a first booster can be given ≥ 6 months after the primary series but is silent on the timing of a second or subsequent booster. The current PI for COMIRNATY Original/Omicron BA.1 states ≥ 5 months after the primary series but is silent on use of the vaccine as a second or subsequent booster.

The Evaluator notes the US recommendation that facilitates boosting in either setting (i.e. post-primary series or post-prior booster) from as early as 2 months following the prior dose. As the question of optimal timing hasn't been resolved through studies, the Evaluator would prefer to raise that question for the Delegate ± ACV.

Pending further consideration related to timing, the Evaluator recommends that the first 2 paragraphs of this section of the PI are revised to read (~~deleted text in strikethrough~~, new text in red):

> A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the completion of ~~a~~ any provisionally registered COVID-19 vaccine primary series in individuals 12 years of age and older.
>
> COMIRNATY Original/Omicron BA.4-5 may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of any provisionally registered ~~COVID 19~~ COVID-19 vaccine.

Question 2

The document titled, '2.5 Clinical Overview_VOC Safety Summary (Alpha and Delta Variant) - Omicron BA.4-BA.5 Modified Vaccine (C4591031 SSE)_MAA_August 2022', dated 24/08/2022, was provided in non-eCTD format along with the first tranche of data that were emailed to the TGA on 17/11/2022; however, the Evaluator could not locate it in the eCTD submission. Please clarify whether that document is intended to be part of the formal submission.

Sponsor's reply (received 22/12/2022, TRIM: D22-6256516)

The Sponsor responded as follows:

> 'It is noted that the document was missed in the initial submission eCTD sequence (0000). Assurance is provided that it will be included in the next available eCTD sequence for the application. Apologies for any inconveniences caused.'

Evaluator's comments

Noted.

Question resolved.

Question 3

In the 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, data cutoff 2/12/2022, dated 7/12/2022, it is stated that, 'Immunogenicity data for participants 12 to 17 years of age will be provided in a separate report when available.' Please clarify when those data are intended to be submitted. Also, please clarify the timing for submission of the superiority and noninferiority testing (all age groups) specified in the primary immunogenicity objectives.

Sponsor's reply (received 13/01/2023, TRIM: D23-5033120)

These data are planned to be reported in a single clinical study report which is expected to be available in February 2023.

Evaluator's comments

Noted.

Question resolved.

Question 4

Please provide participant narratives (including discussion of relatedness) for each of the 7 SAEs listed in Table 2 of the 'COVID-19 Vaccine 2.5 Clinical Overview – Safety VOC Vaccines', dated 15/08/2022.

Sponsor's reply (received 3/01/2023, TRIM: D22-5005390)

The Sponsor provided the requested detailed narratives for each of the 7 SAEs summarised in Table 30, all of which occurred in participants who had received vaccines other than BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg. All SAEs resulted in hospitalisation. Six were assessed as unrelated by Investigator and Sponsor, for which the diagnoses were: Recurrent bilateral deep venous thrombosis and pulmonary embolism; Migraines; Fluid retention; Prostate cancer; Gastroesophageal reflux disease; and Renal calculi.

AER number s47F described an SAE of 'Dehydration' in a s47F year old s47F recipient of BNT162b2 in Study C4591031 Substudy E. This participant had a number of prior comorbidities. s47F experienced a number of symptoms consistent with systemic reactogenicity and diarrhoea that began s47F following vaccination. This likely led to reduced drinking and dehydration that was initially manifest by tachycardia and mild dyspnoea. This resulted in a 1-2

day hospitalisation and recovery was complete by 11 days following vaccination. The SAE was assessed as related by Investigator and Sponsor.

Evaluator's comments

The Evaluator has reviewed the 7 narratives and agrees those SAEs are not likely to be related to vaccination. In the opinion of the Evaluator, this doesn't raise any new safety concerns.

Question resolved.

12.1.1.4. Clinical set 4 (emailed to Sponsor 10/01/2023, TRIM: D23-5020879)

Question 1

Please outline in detail the process that was used to randomly select baseline negative controls from Study C4591031 Substudy E into the reference group for the immunogenicity population described in section 3.2 of the 'Study C4591044 Cohort 2- 1 Month Post Dose_Immunogenicity Data-Groups 2 and 4-December 2022' report, dated 7/12/2022.

Sponsor's reply (received 19/01/2023, TRIM: D23-5047806)

The Sponsor responded as follows:

> 'The process used to select baseline negative controls from Study C4591031 Substudy E into the reference group for the immunogenicity population described in Section 3.2 is a simple 'random sampling' method using SAS software. The subset was selected from all evaluable participants without evidence of SARS-CoV-2 infection in the corresponding age and vaccine group of Study C4591031 Substudy E Expanded Cohort.'

Evaluator's comments

This is a satisfactorily random process for selection.

Question resolved.

12.1.2. Rolling questions – Round 2 CER

12.1.2.1. Clinical set 5 (emailed to Sponsor 02/02/2023, TRIM: D23-5086131)

Question 1

In the previously submitted document titled 'Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years)_1MPD_Immunogenicity Data' (see section 2.5 of eCTD submission e006875 [0003]) it is stated in the APPENDIX that additional data are provided in:

- Study C4591044 Cohort 2 – 1 Month Post Dose – Safety and Immunogenicity – Tables and Figures
- Study C4591044 Cohort 2 – 1 Month Post Dose – Safety and Immunogenicity – Listings

Please provide those Tables, Figures and Listings.

Sponsor's reply (received 7/02/23, TRIM: D23-5096715 [email] and D23-5096689 [files])

The Sponsor provided the 2 requested files in a non-eCTD submission.

Evaluator's comments

The additional data were considered in the evaluation. Notably there were no additional SAEs or deaths identified.

Question resolved.

Question 2

In the previously submitted document titled 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data' (see section 2.5 of eCTD submission e006875 [0003]) it is stated in the APPENDIX that additional data are provided in:

- Study C4591044 Cohort 2 and Cohort 3 – 1 Month Post Dose – Safety and Immunogenicity – Listings
- Study C4591044 Cohort 2 and Cohort 3 – 1 Month Post Dose – Safety and Immunogenicity Tables and Figures

Please provide those Tables, Figures and Listings.

Sponsor's reply (received 7/02/23, TRIM: D23-5096715 [email] and D23-5096689 [files])

The Sponsor provided the 2 requested files in a non-eCTD submission.

Evaluator's comments

The additional data were considered in the evaluation. Notably there was one additional SAE identified from Study C4591044 Cohort 3 in a s47F year old s47F with s47F The Evaluator would like to review a detailed participant narrative regarding this SAE and will request this as a rolling question in clinical set 6 (section 12.1.2.2).

Question resolved.

Question 3

The Evaluator notes 2 additional SAEs following enrolment of Cohort 3, as briefly described in section 3.2.3.4 of the document titled 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data' (section 2.5 of eCTD submission e006875 [0003]). One was a s47F year old s47F with s47F The other was a s47F year old s47F with s47F. Please provide detailed participant narratives for those 2 additional SAEs.

Sponsor's reply (received 7/02/2023, TRIM: D23-5096715)

The Sponsor provided 2 narratives as follows:

- A s47F, s47F female participant s47F years of age, with a pre-existing history of s47F, reported a severe SAE of worsening of s47F requiring hospitalization, on Day s47F after vaccination reported as resolved within 14 days. The event was assessed by the investigator as not related to study intervention.
- A s47F participant s47F years of age, with a pre-existing history of s47F, s47F & s47F, reported a severe SAE of s47F with onset on Day s47F after vaccination, resolving within 1 day. The participant reported several episodes of vomiting the day prior to onset of s47F, and had taken s47F usual s47F medications that morning. The event was assessed by the investigator as not related to study intervention.

Evaluator's comments

The response provided slightly more detail than was provided in the study report but less than provided in response to previous questions about SAEs (see clinical set 2, question 1 [section 12.1.1.2] and clinical set 3, question 4 [section 12.1.1.3]). If more detail is available, then the Evaluator would like to review it and will request this as a rolling question in clinical set 6 (section 12.1.2.2).

Question resolved.

Question 4

Please provide an interpretation of the potential safety signal for an increased risk of ischaemic stroke following boosting with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg that was identified by the US Centers for Disease Control in their presentation to the FDA's VRBPAC meeting on 26/01/2023. Please outline any plans the Sponsor has for ongoing surveillance of this potential safety signal.

Sponsor's reply (received 13/02/2023, TRIM: D23-5117573)

The Sponsor responded as follows:

> In January 2023, CDC contacted Pfizer regarding limited reports of ischemic stroke observed in the CDC Vaccine Safety DataLink (VSD) database in people 65 and older following vaccination with the Omicron BA.4/BA.5-adapted bivalent COVID-19 Vaccine by Pfizer and BioNTech. The reports constituted a statistical signal for further evaluation. Specifically, CDC observed report numbers for ischemic stroke that were higher 1-21 days after vaccination than in a comparison risk window of 22-42 days after vaccination. This statistical signal was first observed in late November 2022. A statistical signal should not be interpreted as a true effect (i.e., risk). Signal detection is performed by manufacturers and health authorities using different databases and methodologies and is designed to be sensitive and broad; it should be considered an indication that further investigation should be performed.
>
> Pfizer/BioNTech, the U.S. Food and Drug Administration (FDA), and other health authorities (EMA, WHO, Israel MOH) have not detected a similar statistical signal. Pfizer has evaluated the statistical signal identified by CDC and to date has not identified ischemic stroke in patients over 65 as a risk. Pfizer continues to monitor this issue.
>
> At the 26 Jan 2023 VRBPAC meeting to discuss future vaccination regimens for COVID-19, CDC discussed the statistical signal it had observed, indicating it has been decreasing over time and was not statistically significant in its most recent analysis. Because CDC's preliminary sub-analysis noted some of the patients with ischemic strokes had received the Pfizer-BioNTech bivalent vaccine with the high-dose influenza vaccine, the FDA is initiating an epidemiologic study to further investigate. The CDC continues to recommend vaccination with the Pfizer-BioNTech Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine for all authorized ages and indications.

Evaluator's comments

The Sponsor has provided an outline of their plans for further investigation and monitoring of the potential risk of ischaemic stroke that satisfies the Evaluator's concerns raised in section 14.6.

Question resolved.

12.1.2.2. Clinical set 6 (emailed to Sponsor 9/02/2023, TRIM: D23-5117571)

Question 1

Please refer to the rolling questions, clinical set no. 5, question no. 3 regarding the request for the detailed participant narratives for the additional 2 SAEs that were briefly described in section 3.2.3.4 of the document titled 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data' (non-eCTD version dated 18/01/2023). One was for a s47F year old s47F with s47F (participant C4591044 s47F). The other was for a s47F year old s47F with s47F (participant C4591044 s47F).

A similar question was asked about a previous SAE from Cohort 2 (participant C4591001 s47F s47F) in the rolling questions, clinical set no. 2, question no. 1. On that occasion, the Sponsor provided the attached 'Response to TGA query received on 08 December 2022' in their response of 23/12/2023. Other detailed narratives were provided by the Sponsor on 3/01/2023 in the attached 'Participant-Narratives' in response to the rolling questions, clinical set no. 3, question no. 4.

Those PDF documents included the level of detail that the Evaluator requires to evaluate these new SAEs. Please provide similarly detailed participant narratives for the 2 additional SAEs from Cohort 3 that are mentioned above.

Sponsor's reply (received 15/02/2023, TRIM: D23-5123112)

The Sponsor provided the narratives as follows:

- **Participant C4591044** [redacted] is a [redacted]-year-old [redacted] who received vaccination with BNT162b2 Bivalent (WT/OMI BA.4/5) in study C4591044 on [redacted] 2022. The participant's relevant past medical history included [redacted] and [redacted]

  The following information was reported: hospitalization for [redacted], with start date [redacted] 2022, described as "Worsening of [redacted] The participants was hospitalized for [redacted] from [redacted] 2022 and discharged on [redacted] 2022. The participant notified study site staff during the in-person study visit 3 that [redacted] was hospitalized for back pain onset on [redacted] 2022 until [redacted] 2022, and was transported to a [redacted] from [redacted] 2022 until [redacted] 2022. Hospital discharge paperwork was reviewed by study site staff, and it was noted that the participant was hospitalized for worsening of [redacted]. No information on investigations performed or treatment given was provided. Per source documents the participants condition returned to baseline on [redacted] 2022 and the outcome of the event was recovered on [redacted] 2022. The investigator considered there was not a reasonable possibility that the event "worsening of [redacted]" was related to study vaccine or clinical trial procedures. No further information is available regarding this event.

- **Participant C4591044** [redacted] is a [redacted]-year-old [redacted] participant who received vaccination with BNT162b2 Bivalent (WT/OMI BA.4/5) in study C4591044 on [redacted] 2022. The participant's relevant past medical history included [redacted] and [redacted] Concomitant medications included [redacted] and [redacted]

  Clinical course: the participant attended study site for Study Visit 2 on [redacted] 2022 and complained of dizziness and nausea. Blood pressure on arrival was [redacted] mmHg, pulse [redacted] bpm. [redacted] was laid down in exam room with legs raised and examined by the Investigator. Repeat blood pressure was [redacted] mmHg, pulse [redacted] bp. [redacted] reported dizziness improved on lying down but nausea was still present. [redacted] reported not eating much the previous day and 2 episodes of vomiting overnight and in the morning. [redacted] reported she had taken [redacted] anti-hypertensive medications (listed above) that morning while possibly being dehydrated after vomiting episodes. The participant had some food and drink while at the study site. Emergency Medical Services (EMS) were called who performed electrocardiogram with normal sinus rhythm. Repeat blood pressure measurements: [redacted] mmHg (supine), [redacted] mmHg (seated) and [redacted] mmHg (standing). The participant reported resolution of dizziness symptoms and did not attend the hospital. [redacted] was advised to follow up with [redacted] Primary Care Physician. The investigator considered there was not a reasonable possibility that the event hypotension was related to study vaccination or procedures. No further information is available regarding this event.

Evaluator's comments

Worsening of [redacted] in the case of participant C4591044 [redacted] occurred [redacted] days following vaccination with BNT162b2 Bivalent (WT/OMI BA.4/5) and the Evaluator does not consider this SAE to be temporally associated or related to IP.

Participant C4591044 [redacted] experienced hypotension [redacted] days following vaccination with BNT162b2 Bivalent (WT/OMI BA.4/5) in the context of ongoing anti-hypertensive use, vomiting and decreased oral intake (onset [redacted] days following vaccination). The hypotensive episode did not appear to be associated with anaphylaxis and was transient, resolving with oral food and fluid intake. The Evaluator agrees this is unlikely to be temporally associated or related to vaccination with IP.

Question resolved.

Question 2

In the document 'Study C4591044 Cohort 2 and Cohort 3 – 1 Month Post Dose – Safety and Immunogenicity – Listings' (filename: C4591044_1MPD_C2C3_Safety_Imm_Listings_Bundle.pdf) that was provided by the Sponsor on 7/02/2023 in response to the rolling questions, clinical set no.5, question no. 2, there was an additional SAE identified that occurred in a [redacted] year old [redacted] recipient of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg from Cohort 3 with [redacted] (participant C4591001 [redacted]).

This SAE had onset [redacted] days prior to the data cutoff and was not mentioned in the document titled 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data' (non-eCTD version dated 18/01/2023). Please provide a detailed participant narrative for this SAE, with the same level of detail specified in clinical set no. 6, question no. 1.

Sponsor's reply (received 15/02/2023, TRIM: D23-5123112)

The Sponsor provided the narrative as follows:

- **Participant C4591001** [redacted] is a [redacted]-year-old [redacted] participant who received vaccination with BNT162b2 Bivalent (WT/Omi BA.4/5) on [redacted] 2022. There was no relevant previous medical history or concomitant medications.

  The participant reported emergency room visit for lower abdominal pain and was admitted to hospital for intravenous antibiotics on [redacted] 2022 and discharged on [redacted] 2022. The participant was discharged home with oral antibiotics. The following investigations were reported: blood glucose [redacted] 2022): [redacted] mg/dl (normal range [redacted]); lipase ([redacted] 2022): [redacted] (normal range 0 – 59); computerised tomogram (CT) abdomen & pelvis ([redacted] 2022): [redacted]. The outcome of the event was recovered on [redacted] 2022. The investigator considered there was not a reasonable possibility that the event [redacted] was related to study vaccine or procedures. No further information is available regarding this event.

Evaluator's comments

Participant C4591001 [redacted] had an acute episode of [redacted] with onset [redacted] days following vaccination with BNT162b2 Bivalent (WT/Omi BA.4/5). The Evaluator agrees this is unlikely to be temporally associated or related to vaccination with IP.

12.1.3. Pharmacokinetics

Not applicable.

12.1.4. Pharmacodynamics

See rolling questions in section 12.1.

12.1.5. Efficacy

See rolling questions in section 12.1.

12.1.6. Safety

See rolling questions in section 12.1.

12.1.7. PI and CMI

See section 11.

12.2. Additional expert input

The submission was further considered at ACV meeting number 40, which was held on 18/01/2023.

13. First round evaluation errata

13.1. Minor editorial changes

None identified by the Evaluator. Not commented on by the Sponsor, for the reasons stated in section 14.

13.2. Minor errors of fact

None identified by the Evaluator. Not commented on by the Sponsor, for the reasons stated in section 14.

13.3. Significant errors of fact

None identified by the Evaluator. Not commented on by the Sponsor, for the reasons stated in section 14.

14. Second round evaluation

This was a rolling submission with most documents submitted by the Sponsor having been evaluated for the Round 1 CER following receipt by email in non-eCTD format. These documents were subsequently submitted in eCTD format (e006875 [0000-0003, 0005]), which were all available to the Evaluator by the time this Round 2 CER was prepared.

Given this was a rolling submission, the following points are pertinent to understanding the Round 2 CER:

- An ACV meeting was held on 18/01/2023 to provide advice to the Delegate in their consideration of provisional registration. The finalised Round 1 CER was available to the Delegate and ACV members prior to the meeting; however, was inadvertently not provided to the Sponsor at that time. Hence, there were no Sponsor comments on the Round 1 CER received prior to preparation of the Round 2 CER.
- The suggestions for changes to the PI and CMI described in section 11 were considered by the Delegate prior to their negotiations with the Sponsor regarding changes to the proposed PI following the ACV. The final, approved PI was uploaded in eCTD format to e006875 (0005).
- Two additional clinical study reports were submitted for evaluation just following the ACV and were considered by the Delegate prior to their decisions on 20/01/2023 'to provisionally register medicine(s), to approve product information, and to impose conditions under the Therapeutic Goods Act 1989' (TRIM ref: D23-5055082). These study reports contained:
    - Initial immunogenicity data for the 12-17 YOA group from Study C4591044 Cohort 2, evaluated in section 14.1.

    - Expanded immunogenicity data for the 18-55 and > 55 YOA groups from Study C4591044 Cohort 2 and Cohort 3 combined, evaluated in section 14.2.
    - Expanded safety data for the 18-55 and > 55 YOA groups from Study C4591044 Cohort 2 and Cohort 3 combined, evaluated in section 14.3.
- Clinical conditions imposed by the Delegate in their recommendation to provisionally register the medicine included:
    - An update of the Australian PI via a future submission is required for inclusion of adolescent immunogenicity data in 12-17 years old age group based on the Study C4591044. This may be undertaken after Clinical Evaluation Report (Round 2) by the TGA for the current submission PM-2022-05306-1-2 has been issued to the Sponsor.
    - Final Clinical Study Report for the Study C4591044 is to be provided to the TGA when it becomes available to the Sponsor.
- Safety data were also considered by the US FDA at their VRBPAC meeting on 26/01/2023, evaluated in section 14.4.
- The rolling questions arising from the Round 1 CER (clinical sets 1-4) were resolved prior to preparation of the Round 2 CER as discussed in section 12.1.1. Additional rolling questions arising from preparation of the Round 2 CER (clinical sets 5 and 6) are listed in section 12.1.2 and were resolved prior to completion of the Round 2 CER.

14.1. Immunogenicity results for 12-17 year of age participants from Study C4591044 Cohort 2 (data cutoff 12/10/2022)

These results were initially provided by email from the Sponsor in non-eCTD format on 19/01/2023 (TRIM: D22-5052381), following the Round 1 CER, in a study report named, 'Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_lmmunogenicity Data' (15/01/2023). They were later provided in eCTD format.

The analyses for this age group at this time (completed 1 month study visit by the data cutoff 12/10/2022) were purely descriptive and followed similar methodologies to calculate GMTs, GMFRs and seroresponse as previously described in the CER.

14.1.1. Immunogenicity population

'A total of 108 participants 12 through 17 years of age were randomized in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 μg group. The evaluable immunogenicity population for participants with or without evidence of infection up to 1 month after study vaccination included a total of 105 participants 12 through 17 years of age. The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 25 participants 12 through 17 years of age. There were 3 exclusions from the evaluable immunogenicity population, with the majority being due to not having at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination.'

14.1.2. Demographics

The demographics for this population are shown alongside the older age groups from Study C4591044 Cohort 2 and controls from Study C4591031 Substudy E in Table 66. Notable features were:

- White participants made up 84.8% and Black or African American 8.6%.
- Median age was 15.0 years.
- Females were 44.8% of participants.
- 'Overall, 75.2% of participants 12 through 17 years of age were baseline positive' for exposure to SARS-CoV-2 infection.
    - For participants 18-55 YOA receiving BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 μg this was 65.3%.

  - For participants > 55 YOA receiving BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg this was 60.8%.
- Median time from the last dose of BNT162b2 30 µg prior to the study to the study vaccination was 234 days, with the majority (73.3%) having received it ≥ 7 to < 9 months prior.
  - For participants 18-55 YOA receiving BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, this was 305 days and 74.7% having received it ≥ 9 to < 12 months respectively.
  - For participants > 55 YOA receiving BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg, this was 306 days and 85.3% having received it ≥ 9 to < 12 months respectively.

Evaluator's comments: There were systematic differences between the 12-17 YOA participants and those aged ≥ 18 YOA that make direct comparison between descriptive immunology results problematic. The median time between prior vaccine and study vaccine was close to 8 months in adolescents but around 10 months in adults, hence the Evaluator would expect baseline titres to be higher in adolescents due to lesser time for decay (this was indeed observed, see below sections of this CER). Also, coming off a higher baseline, post-vaccination titres would be expected to be higher, although GMFRs might be relatively reduced (e.g. this phenomenon is commonly seen with baseline 'positive' participants with prior exposure to SARS-CoV-2 in whom post-vaccination GMTs are higher but GMFRs are lower than 'negative' participants). Hence, higher post-vaccination titres might be expected in this group of adolescents relative to the adults just because they had less decay in their prior booster response. GMFR may correct for this to some extent, although the multiples in GMFRs can be relatively reduced coming off a higher baseline. The group without prior infection will be the easiest to assess differences in baseline titres, post-vaccination titres and GMFRs as they won't be affected by prior exposure – which is the other factor that makes direct comparison problematic. As the age based subgroups had their 3rd and/or 4th doses of booster at different stages of the pandemic, 'prior exposure' will have varied between the adolescents and adults, both in terms of the number of times they might have experienced SARS-CoV-2 infection and the type(s) of variants involve. So there will be quantitative as well as qualitative differences in existing immunity that will likely have differential effects on neutralising responses to different variants. The most problematic groups to compare will be those 'with or without evidence of infection' in whom the effects of time to 4th dose and prior exposure will have influence; at least in those 'without evidence of infection', the effect of prior exposure will be mainly removed and some comparison can be made with caution (albeit with wider confidence intervals).

14.1.3. Geometric mean titres

14.1.3.1. Omicron BA.4/5 neutralisation

GMTs for neutralisation of Omicron BA.4/5 at baseline and 1 month post-vaccination are shown in Table 35, along with neutralisation of Omicron BA.1 and reference strain. The source table included data for subgroups (i.e. exposure to SARS-CoV-2 and sex) and also results for the 2 adult age groups. The same data are represented graphically in Figure 13.

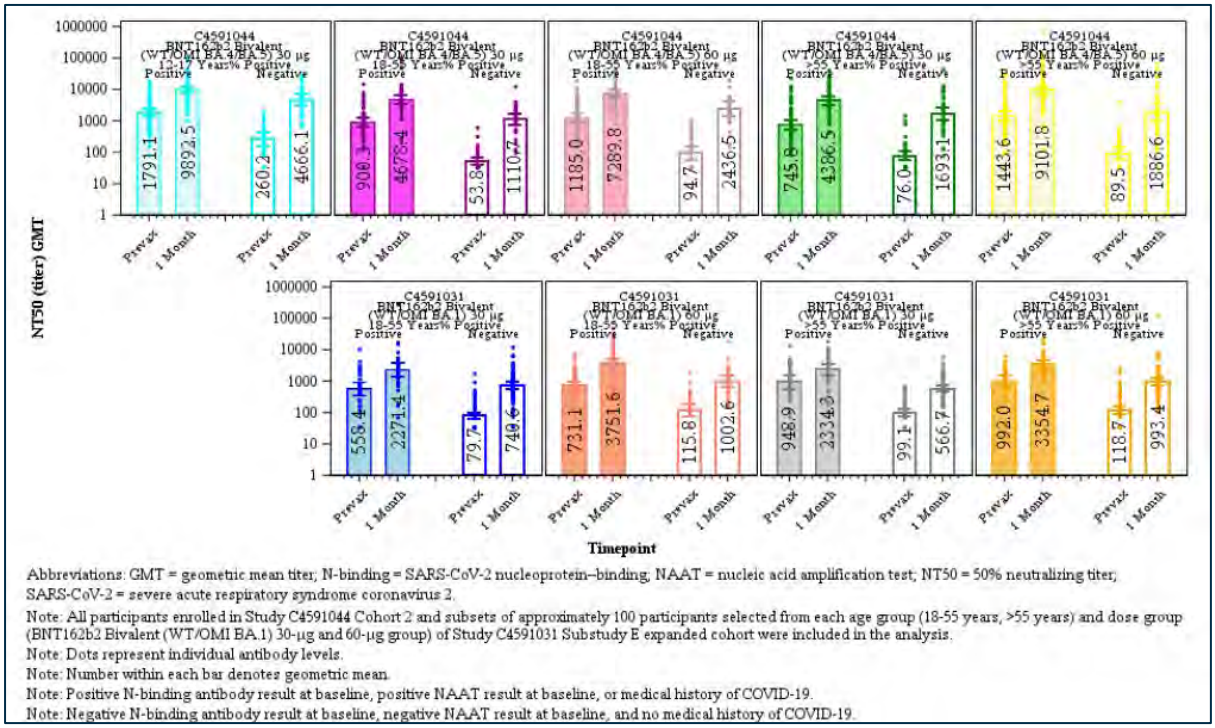
Table 35. Geometric Mean Titers, by Subgroup – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

				Vaccine Group (as Randomized)			
				C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	All	Prevax	104	1105.8 (835.1, 1464.3)	N/A	N/A
			1 Month	105	8212.8 (6807.3, 9908.7)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	78	1791.1 (1379.6, 2325.3)	N/A	N/A
			1 Month	79	9892.5 (8114.6, 12059.8)	N/A	N/A
		Negative[e]	Prevax	26	260.2 (157.1, 430.9)	N/A	N/A
			1 Month	26	4666.1 (3096.1, 7032.2)	N/A	N/A
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	30 µg/12-17 years	All	Prevax	105	1190.5 (921.8, 1537.5)	N/A	N/A
			1 Month	105	6687.6 (5617.0, 7962.3)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	79	1837.1 (1473.0, 2291.2)	N/A	N/A
		Negative[e]	Prevax	26	318.6 (184.4, 550.4)	N/A	N/A
			1 Month	26	3632.5 (2289.1, 5764.4)	N/A	N/A
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	All	Prevax	105	6863.3 (5587.8, 8430.1)	N/A	N/A
			1 Month	105	23641.3 (20473.1, 27299.8)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[d]	Prevax	79	8685.4 (7062.7, 10680.9)	N/A	N/A
			1 Month	79	25991.8 (22377.5, 30189.8)	N/A	N/A
		Negative[e]	Prevax	26	3356.2 (2106.9, 5346.2)	N/A	N/A
			1 Month	26	17725.2 (12376.4, 25385.7)	N/A	N/A

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Extracted from Table 2, Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023).

Figure 13. Geometric Mean Titers and 95% Confidence Intervals, by Baseline SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay - Omicron BA.4/BA.5 - NT50 - Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort - Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination - Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figure 1, Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023).

Evaluator's comments: The Evaluator finds the results in participants without evidence of infection to be most informative for the reasons summarised in the previous comments. Baseline and post-vaccination neutralising titres to Omicron BA.4/5 were higher in adolescents without infection than in adults without infection as expected, so a direct comparison of GMTs at 1 month does not answer the question of whether the vaccine was more immunogenic in one age group compared to another. Estimated fold rises at 1 month (based on the data shown in Figure 13) for each age group were: 12-17 YOA, 17.9-fold; 18-55 YOA, 20.6-fold; > 55 YOA, 22.3-fold. In adolescents, the 1 month GMT in baseline positive participants was just over double that in baseline negative (9892.5 vs 4666.1 respectively) and as expected, the estimated fold rise was lower (5.5 vs 17.9 respectively). The magnitude of fold rise in baseline positive adolescent participants was roughly similar to that seen in 18-55 YOA (5.2-fold) and > 55 YOA (5.9-fold) participants. The Evaluator concludes that for Omicron BA.4/5 neutralising responses, BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg produces similarly robust immune responses as in the older age groups. For Omicron BA.1 neutralising responses in adolescents without infection, based on the data shown in Table 2 of the Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023), the estimated fold rise was 11.4-fold and for reference strain, 5.3-fold; again broadly similar to those for the older age groups. Comparative data is shown in Figure 6 (Omicron BA.1) and Figure 9 (reference strain) of the Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023).

14.1.4. Geometric fold rises

Exact GMFRs were presented in section 2.5.1.2 of the Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_lmmunogenicity Data (15/01/2023) and were slightly different to those estimated in the previous comments given only paired results were included for the precise calculation of GMFRs.

In adolescents without evidence of infection, for Omicron BA.4/5, Omicron BA.1 and reference strain, exact GMFRs were 17.8, 11.2 and 5.3 respectively (compared to 17.9, 11.4 and 5.3 as estimated previously).

Evaluator's comments: These GMFRs include more precise data, which were very similar to those previously estimated in the previous Evaluator's comments, hence there are no changes to those previous conclusions.

14.1.5. Seroresponse rates

Seroresponse rates in adolescents with and without evidence of infection for Omicron BA.4/5, Omicron BA.1 and reference strain are shown in Table 36. The source table also included data for the 2 adult age groups.

Table 36. Number (%) of Participants Achieving Seroresponse, by Subgroup – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

				Vaccine Group (as Randomized)			
				C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)		C4591031 BNT162b2 Bivalent (WT/OMI BA.1)	
Assay	Dosage/Age Group	Subgroup	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	30 µg/12-17 years	All	1 Month	104	69 (66.3) (56.4, 75.3)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[e]	1 Month	78	44 (56.4) (44.7, 67.6)	N/A	N/A
		Negative[f]	1 Month	26	25 (96.2) (80.4, 99.9)	N/A	N/A
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	30 µg/12-17 years	All	1 Month	105	67 (63.8) (53.9, 73.0)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[e]	1 Month	79	43 (54.4) (42.8, 65.7)	N/A	N/A
		Negative[f]	1 Month	26	24 (92.3) (74.9, 99.1)	N/A	N/A
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	30 µg/12-17 years	All	1 Month	105	43 (41.0) (31.5, 51.0)	N/A	N/A
		Baseline SARS-CoV-2 status					
		Positive[e]	1 Month	79	26 (32.9) (22.7, 44.4)	N/A	N/A
		Negative[f]	1 Month	26	17 (65.4) (44.3, 82.8)	N/A	N/A

Abbreviations: LLOQ = lower limit of quantitation; N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

a. Protocol-specified timing for blood sample collection.

b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.

c. n = Number of participants with seroresponse for the given assay at the given sampling time point.

d. Exact 2-sided CI, based on the Clopper and Pearson method.

e. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Extracted from Table 6, Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023).

Evaluator's comments: Seroresponse rates in adolescents without prior evidence of infection for Omicron BA.4/5, Omicron BA.1 and reference strain were 96.2%, 92.3% and 65.4% respectively. In adults 18-55 YOA without evidence of infection, they were 81.8%, 72.7% and 81.8% respectively. In adults > 55 YOA without evidence of infection, they were 90.0%, 92.5% and 75.0% respectively. As expected, seroresponse rates in baseline positive participants were lower across age groups, reflective of a higher baseline titre even though 1 month titres were higher than in baseline negative participants. Seroresponse rates represent the proportion of participants with a ≥ 4-fold rise in titre from baseline, so provide complementary information to GMFRs. Taking the GMT and GMFR results into account, the Evaluator concludes that BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg produces a similarly robust immune response in adolescents to adults, especially against the Omicron variants relative to reference strain. There was no comparator group given BNT162b2 30 µg as a booster though, so whether BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg is any better than a monovalent booster is unable to be commented on.

14.2. Immunogenicity results for Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 combined (data cutoff 12/10/2022 [Cohort 2] and 31/10/2022 [Cohort 3])

These results were initially provided by email from the Sponsor in non-eCTD format on 19/01/2023 (TRIM: D22-5052381), following the Round 1 CER, in a study report named, 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023)'. They were later provided in eCTD format.

The study design for Cohort 2 was shown in Table 4 and for Cohort 3 in Table 5. Of note, recruitment into Cohort 2 was randomised 1:1 to BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg or BNT162b2 bivalent (WT/OMI BA.4/BA.5) 60 µg and observer-blind, whereas Cohort 3 was open-label. The data considered in this section were combined from both cohorts into each age group (18-55 YOA and > 55 YOA). The reference group included participants from Study C4591031 Substudy E.

14.2.1. Statistical analyses

The **primary immunogenicity objectives** included a number of statistical tests in relation to testing the superiority and/or non-inferiority of neutralising titres and seroresponses between participants **> 55 YOA** from Study C4591044 Cohort 2 and Cohort 3 (who received BNT162b2 30 µg) compared to historical controls from Study C4591031 Substudy E (who received BNT162b2 30 µg). The model-based GMR calculation used a linear regression model that included terms for baseline neutralising titre and comparison group. The calculation of difference in seroresponse rates was stratified by baseline neutralising titre category (< median or ≥ median). 'The **secondary objectives** of GMTs, GMFRs, and percentages of participants with seroresponse, along with the 95% CIs, were provided for each group and were summarized by baseline SARS-CoV-2 infection status and sex.'

In participants **18-55 YOA** from Study C4591044 Cohort 2 and Cohort 3, the **primary immunogenicity objective** was to assess the noninferiority with respect to level of neutralising titre and seroresponse rate of the 'anti-Omicron BA.4/BA.5 immune response induced by BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg in the 18 through 55-year age group relative to the anti-Omicron immune response elicited by BNT162b2 Bivalent (WT/Omicron BA.4/BA.5) 30 µg in the > 55-year age group.' (i.e. an internal comparison from Study C4591044 that doesn't involve the reference group). '**Noninferiority based on GMR** was declared if the lower limit of the 2-sided 95% CI for the GMR was greater than 0.67; **noninferiority based on seroresponse** was declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was > -10%.'

14.2.2. Immunogenicity population

'This part of the immunogenicity analysis included approximately 300 randomized participants per vaccine group. All participants 18 through 55, and > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups from Study C4591044 Cohort 2 and Cohort 3 were included. All participants in the > 55 years of age group in C4591031 Substudy E expanded cohort who received BNT162b2 30 µg and met the evaluability criteria were selected as the reference group. Because of substantially lower prior infection rate in C4591031 Substudy E due to the study having been conducted earlier in 2022 than C4591044, the reference group has a lower baseline infection rate than the groups in C4591044 Cohort 2 and Cohort 3.'

'The evaluable immunogenicity population for participants with or without evidence of infection up to 1 month after study vaccination included a total of 297 and 286 participants 18 through 55 and > 55 years in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg groups, respectively, and 289 for participants > 55 years in the BNT162b2 30 µg group. The evaluable immunogenicity population without evidence of infection up to 1 month after study vaccination included a total of 77 and 105 for participants 18 through 55 and > 55 years in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg groups, respectively, and 238 for participants > 55 years in the BNT162b2 30 µg group.'

'There were 17 exclusions for participants 18 through 55 and 20 exclusions for participants > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg groups from the evaluable immunogenicity population, with the majority being due to not having at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination.'

14.2.3. Demographics

Participant demographics for the study and reference groups are shown in Table 37. Notable features were:

- The majority of participants were White (over 78% in each group).
- The median age in the 18-55 YOA study group was 41.0 years, in the > 55 YOA study group was 65.0 years and in the > 55 YOA reference group was 66.0 years.
- Median time from last dose of BNT162b2 30 µg was ~ 11 months in the 2 study groups but only ~ 6 months in the reference group.
    - The majority of participants in the study groups received their study vaccine dose within ≥ 9 to ≤ 12 months, whereas in the reference group it was between ≥ 5 to < 7 months.
- Positive baseline SARS-CoV-2 status was seen in 71.7% and 61.5% of participants in the 18-55 YOA and > 55 YOA study groups respectively but in only 14.2% of the > 55 YOA reference group.

Table 37. Demographic Characteristics – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)		
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg
	18-55 Years (N[a]=297) n[b] (%)	>55 Years (N[a]=286) n[b] (%)	>55 Years (N[a]=289) n[b] (%)
Sex			
Male	104 (35.0)	129 (45.1)	134 (46.4)
Female	193 (65.0)	157 (54.9)	155 (53.6)
Race			
White	239 (80.5)	224 (78.3)	254 (87.9)
Black or African American	25 (8.4)	47 (16.4)	18 (6.2)
American Indian or Alaska Native	0	3 (1.0)	0
Asian	30 (10.1)	8 (2.8)	12 (4.2)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	2 (0.7)
Multiracial	3 (1.0)	3 (1.0)	3 (1.0)
Ethnicity			
Hispanic/Latino	39 (13.1)	37 (12.9)	54 (18.7)
Non-Hispanic/non-Latino	256 (86.2)	247 (86.4)	235 (81.3)
Not reported	2 (0.7)	2 (0.7)	0
Age at vaccination (years)			
Mean (SD)	39.2 (9.75)	65.6 (6.74)	66.3 (6.47)
Median	41.0	65.0	66.0
Min, max	(18, 55)	(56, 87)	(56, 87)
Baseline SARS-CoV-2 status			
Positive[c]	213 (71.7)	176 (61.5)	41 (14.2)
Negative[d]	84 (28.3)	110 (38.5)	246 (85.1)
Missing	0	0	2 (0.7)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months[e])			
n	297	286	289
Mean (SD)	10.8 (1.65)	11.2 (1.33)	6.8 (1.41)
Median	11.3	11.5	6.3
Min, max	(5.4, 13.0)	(5.5, 12.9)	(5.3, 13.0)
≥5 to <7 Months	13 (4.4)	3 (1.0)	224 (77.5)
≥7 to <9 Months	26 (8.8)	15 (5.2)	40 (13.8)
≥9 to ≤12 Months	184 (62.0)	182 (63.6)	24 (8.3)
>12 Months	74 (24.9)	86 (30.1)	1 (0.3)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (days)			
n	297	286	289
Mean (SD)	302.8 (46.33)	312.7 (37.16)	190.1 (39.59)
Median	315.0	322.0	175.0
Min, max	(152, 365)	(153, 362)	(147, 365)
<150 Days	0	0	2 (0.7)
150-209 Days	15 (5.1)	6 (2.1)	224 (77.5)
210-269 Days	42 (14.1)	27 (9.4)	47 (16.3)
270-365 Days	240 (80.8)	253 (88.5)	16 (5.5)
Body mass index (BMI)			
Underweight (<18.5 kg/m^2)	4 (1.3)	6 (2.1)	4 (1.4)
Normal weight (≥18.5-24.9 kg/m^2)	83 (27.9)	63 (22.0)	80 (27.7)
Overweight (≥25.0-29.9 kg/m^2)	97 (32.7)	100 (35.0)	100 (34.6)
Obese (≥30.0 kg/m^2)	113 (38.0)	117 (40.9)	105 (36.3)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
e. Month was calculated as 28 days.

Source: Table 3, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: The **> 55 YOA** reference group is vastly different to the > 55 YOA study group and in the Evaluator's opinion is not suitable for valid statistical comparisons. The major differences relate to the immune status at enrolment, which arise from: (1) non-contemporaneous recruitment, with the reference group being enrolled earlier in 2022 than the study groups (evident from the data cutoff dates of 16/05/2022 vs 12/10/2022 [Cohort 2] and 31/10/2022 [Cohort 3] respectively). This was reflected by a large difference in the proportions who were baseline SARS-CoV-2 positive between the study group (61.5%) and reference group (14.2%). Even with some control for baseline titres, those who were baseline positive for SARS-CoV-2 infection in the study group would have had a higher chance of multiple prior infections and/or exposure to a different range (e.g. newer) variant(s) (including Omicron BA.4/5) than in the reference group. (2) interval between the prior BNT162b2 30 µg dose and the 4th dose (~ 11 months for the study group vs ~ 6 months for the reference group), which was reflected in higher baseline titres in the reference group.

The quantitative and qualitative differences that arise in participants > 55 YOA would be expected to cause differential responses in neutralisation to Omicron BA.4/5, Omicron BA.1 and/or reference strain from re-vaccination that could not be overcome by stratification or simple statistical adjustment. Hence, the Evaluator will focus in the subsequent sections on examining the descriptive immunogenicity analyses for those > 55 YOA. Emphasis will be placed on whether the point estimates are similar to those previously reported from the Cohort 2 participants, with the expectation being that the 95% CIs will be narrower given triple the number of subjects.

For those **18-55 YOA** from Study C4591044, the primary immunogenicity objective was a test of non-inferiority of immune responses compared to those aged > 55 YOA. This will be less subject to interference from pre-existing differences in immunity through exposure to SARS-CoV-2; however, there could be residual confounding due to age-related differences (e.g. behavioural) in temporal exposure to SARS-CoV-2 and/or to different variant(s). There were no controls 18-55 YOA given BNT162b2 30 µg in the present report for Study C4591044.

14.2.4. Noninferiority of Anti-Omicron BA.4/5 Immune Response in 18 Through 55 Years to > 55 Years Based on Geometric Mean Ratio

'In the evaluable immunogenicity population **with or without prior evidence of infection** up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titers for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg group to > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg group was 0.98 (2-sided 95% CI: 0.83, 1.16)'. Hence, the criterion for non-inferiority (i.e. lower bound of the 2-sided 95% CI > 0.67) was met.

'In the evaluable immunogenicity population **without prior evidence of infection** up to 1 month after study vaccination, model-based GMR of Omicron BA.4/BA.5 neutralizing titers for participants 18 through 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg group) to participants > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg was 1.00 (2-sided 95% CI: 0.71, 1.41).' Hence, the criteria for non-inferiority were also met for this subgroup.

14.2.5. Noninferiority of Anti-Omicron BA.4/5 Immune Response in Participants 18 Through 55 Years to > 55 Years Based on Difference in Seroresponse Rate

'In the evaluable immunogenicity population **with or without prior evidence of infection** up to 1 month after study vaccination, 61.2% of participants 18 through 55 years and 66.7% of participants > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups achieved seroresponse to Omicron BA.4/BA.5. The adjusted difference in percentages of participants with seroresponse to Omicron BA.4/BA.5 between 18 through 55 years of age and > 55 years of age in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups was -3.03 % (95% CI: -9.68, - 3.63). Hence, the criterion to declare noninferiority was met.

In relation to the analysis in participants **without prior evidence of infection**, the Sponsor stated that, 'Differences in seroresponse rate… were similar to those in the evaluable immunogenicity population with or without prior evidence of infection up to 1 month after study vaccination.'; however, the data were not shown in the Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_lmmunogenicity and Safety Data report (18/01/2023).

14.2.6. Geometric Mean Titres (Combined Cohort 2 [Group 2 and Group 4] and Cohort 3)

GMTs for Omicron BA.4/5 and reference strain neutralisation from pre-vaccination and 1 month post-vaccination, for the 2 study groups and the reference group, stratified by baseline SARS-CoV-2 status, are shown in Table 38. The source table additionally presented data stratified by sex. The same data are represented graphically in Figure 14.

These data can be compared with those in Table 18 and Table 22, which showed data for the 2 study groups (stratified by baseline SARS-CoV-2 status) for the smaller number of subjects following enrolment of Cohort 2 (but not Cohort 3). These later data represent ~ 300 participants per study group compared to ~ 100 per study group as shown in Table 22.

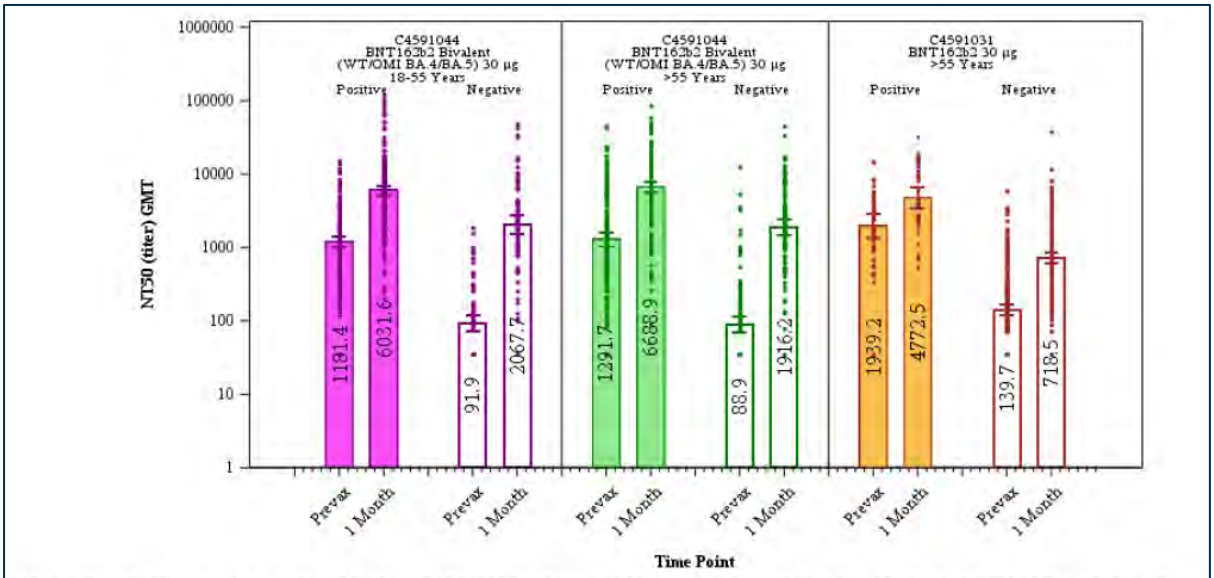
Table 38. Geometric Mean Titers, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	Prevax	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)	278	205.4 (170.3, 247.7)
		1 Month	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)	282	938.9 (802.3, 1098.8)
	Baseline SARS-CoV-2 status							
	Positive[d]	Prevax	210	1181.4 (1005.3, 1388.3)	174	1291.7 (1027.5, 1623.8)	40	1939.2 (1326.0, 2835.8)
		1 Month	213	6031.6 (5203.9, 6991.0)	176	6688.9 (5664.4, 7898.8)	40	4772.5 (3413.9, 6671.9)
	Negative[e]	Prevax	84	91.9 (71.5, 118.1)	110	88.9 (69.8, 113.4)	236	139.7 (118.0, 165.3)
		1 Month	84	2067.7 (1530.2, 2793.9)	108	1916.2 (1489.5, 2465.1)	240	718.5 (617.5, 836.0)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	Prevax	296	4017.3 (3430.7, 4704.1)	284	3690.6 (3082.2, 4419.0)	287	2699.9 (2291.7, 3180.9)
		1 Month	296	16323.3 (14686.5, 18142.6)	286	16250.1 (14499.2, 18212.4)	289	10415.5 (9366.7, 11581.8)
	Baseline SARS-CoV-2 status							
	Positive[d]	Prevax	213	7068.6 (6251.9, 7992.0)	174	8082.1 (6843.6, 9544.8)	41	14247.2 (10299.1, 19708.6)
		1 Month	212	19076.6 (17056.5, 21336.0)	176	21273.3 (18604.2, 24325.3)	41	21444.4 (17318.3, 26553.5)
	Negative[e]	Prevax	83	942.3 (705.6, 1258.3)	110	1068.0 (835.9, 1364.6)	244	2054.8 (1749.9, 2412.8)
		1 Month	84	11014.6 (8793.9, 13796.0)	110	10560.6 (8827.1, 12634.5)	246	9286.4 (8296.8, 10394.0)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Extracted from Table 6, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Figure 14. GMTs and 95% CIs, by Baseline SARS-CoV-2 Status: SARS-CoV-2 Neutralization Assay – Omicron BA.4/BA.5 – NT50 – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.

Note: Dots represent individual antibody levels.

Note: Number within each bar denotes geometric mean.

Note: Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.

Note: Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Figure 1, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: The GMTs from participants in the expanded Study C4591044 Cohort 2 and Cohort 3 combined plus Study C4591031 Substudy E (Table 38) show a broadly consistent pattern to those previously evaluated in Table 18 and Table 22; however, the latter data show systematically higher results in all 3 studied groups (both pre- and post-vaccination, in baseline SARS-CoV-2 positive and negative participants, and for Omicron BA.4/5 and reference strain). The time between prior (3rd) dose of BNT162b2 30 µg and 4th dose of BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg or BNT162b2 30 µg was broadly similar in all instances (around 11 months for BNT162b2 bivalent [WT/OMI BA.4/BA.5] 30 µg recipients and around 6 months for BNT162b2 30 µg recipients). While the 95% CIs for the earlier data were wider (reflecting fewer participants), improved data precision would seem to be an unlikely explanation for an increase in GMTs across the board.

14.2.7. Geometric Mean Fold Rises (Combined Cohort 2 [Group 2 and Group 4] and Cohort 3)

These data were presented in the text of section 2.2.3.2 of the 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023)' rather than in tables.

14.2.7.1. Omicron BA.4/5 neutralisation

'GMFR from before study vaccination to 1 month after study vaccination were higher for participants in both vaccine groups who were **baseline negative** compared with those who

were **baseline positive** (BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg: 18 to 55 years: 22.5 vs 5.1, > 55 years: 21.5 vs 5.2; BNT162b2 30 µg: 5.1 vs 2.4) for SARS-CoV-2. Within baseline positive or baseline negative groups, GMFRs at 1 month after study vaccination were higher for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg groups compared with the BNT162b2 30 µg group. GMFR across both sexes were similarly high across all age groups and doses.'

14.2.7.2. Reference strain neutralisation

'GMFRs from before study vaccination to 1 month after study vaccination were generally higher for participants in both vaccine groups who were **baseline negative** compared with those who were **baseline positive** (BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg: 18 to 55 years: 11.6 vs 2.7, > 55 years: 9.9 vs 2.7; BNT162b2 30 µg: 4.5 vs 1.5) for SARS-CoV-2 reference strain. Within baseline positive or baseline negative groups, GMFRs at 1 month after study vaccination were higher for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group compared with the BNT162b2 30-µg group, possibly due to longer interval from last dose and higher prevaccination titers in the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group.'

Evaluator's comments: The generally lower GMFRs in the reference group largely reflect a shorter time between the prior (3rd) dose of BNT162b2 30 µg and the 4th study dose in the reference group compared to the BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg study groups (about 6 months vs 11 months respectively). The data can be compared to the earlier data from smaller numbers of participants prior to enrolment of Study C4591044 Cohort 3 (see Table 19 and Table 23). Although the GMTs at the latter time point seemed systematically higher in almost all subgroups studied, these differences were ironed out by the GMFRs. Hence the GMFRs described in this section of the CER were very similar to those at the earlier timepoints as shown in Table 19 and Table 23. Notwithstanding the Evaluator's comments in the previous section of the CER, data from the expanded cohorts in Study C4591044 and Study C4591031 Substudy E reinforce the conclusions made earlier (see section 7.2.1.15) about clinical efficacy / immunology.

14.2.8. Seroresponses (Combined Cohort 2 [Group 2 and Group 4] and Cohort 3)

Seroresponse rates at 1 month after study vaccination are shown in Table 39. The source table additionally shows data for gender based subgroups, where results were similar to the overall groups. These data can be compared to the earlier data for Cohort 2 shown in Table 21 (i.e. when there were approximately ~ 100 participants per age group, compared to the ~ 300 per age group shown here).

Table 39. Number (%) of Participants Achieving Seroresponse, by Subgroup – BNT162b2 Bivalent 30-µg Groups of Study C4591044 Cohort 2/3 Combined and BNT162b2 30-µg Group of Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)					
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg				C4591031 BNT162b2 30 µg	
			18-55 Years		>55 Years		>55 Years	
Assay	Subgroup	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.4/BA.5 - NT50 (titer)	All	1 Month	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)
	Baseline SARS-CoV-2 status							
	Positive[e]	1 Month	210	108 (51.4) (44.5, 58.4)	174	95 (54.6) (46.9, 62.1)	39	11 (28.2) (15.0, 44.9)
	Negative[f]	1 Month	84	72 (85.7) (76.4, 92.4)	108	93 (86.1) (78.1, 92.0)	232	116 (50.0) (43.4, 56.6)
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)	All	1 Month	295	130 (44.1) (38.3, 49.9)	284	130 (45.8) (39.9, 51.8)	287	138 (48.1) (42.2, 54.0)
	Baseline SARS-CoV-2 status							
	Positive[e]	1 Month	212	63 (29.7) (23.7, 36.4)	174	49 (28.2) (21.6, 35.5)	41	5 (12.2) (4.1, 26.2)
	Negative[f]	1 Month	83	67 (80.7) (70.6, 88.6)	110	81 (73.6) (64.4, 81.6)	244	132 (54.1) (47.6, 60.5)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 Cohort 2/3 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and all participants >55 years of age from Study C4591031 Substudy E expanded cohort BNT162b2 30-µg group who met evaluability criteria were included in the analysis.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
f. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Extracted from Table 7, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: The seroresponses against Omicron BA.4/5 and reference strain among BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg recipients from the expanded cohorts shown in Table 39 were very similar to those previously evaluated in Cohort 2 (Table 21). The current data adds seroresponse rates in the BNT162b2 30 µg control group from Study C4591031 Substudy E (age > 55 years), which are lower for both Omicron BA.4/5 and reference strain neutralisation; however, this is to be expected given that baseline titres were higher in this group for both baseline positive and negative participants (see Table 38) in line with the shorter

time between 3rd and 4th doses (~ 6 months vs ~ 11 months). Overall, these data reinforce the Evaluator's previous conclusions about seroresponses (given the larger numbers and narrower CIs) but don't provide any further new information.

14.3. Safety analysis for Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 combined (data cutoff 12/10/2022 [Cohort 2] and 31/10/2022 [Cohort 3])

'Available safety data as of 12 October 2022 for Cohort 2 (Group 2 and Group 4) and 31 October 2022 for Cohort 3 are summarized below for all participants 18 through 55 (n=313) and > 55 years of age (n=306) who received a 30-µg dose of BNT162b2 Bivalent (WT/OMI BA.4/BA.5). These data included local reactions and systemic events recorded in the e-diary for 7 days post vaccination and AEs reported through 1 month post vaccination.'

14.3.1. Safety population

The safety population is shown in Table 40 and follow-up times after study vaccination are shown in Table 41. 'Median follow-up time after study vaccination to the data cutoff or withdrawal date across vaccine groups was 1.5 months, and most participants had follow-up time from ≥ 1 to < 2 months (99.8%).'

Table 40. Safety Population – Cohort 2 and Cohort 3 Combined

	Vaccine Group (as Administered)		
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		
	18-55 Years n[a]	>55 Years n[a]	Total n[a] (%)
Randomized[b]			620
Vaccinated	313	306	619 (99.8)
Safety population	313	306	619 (99.8)
HIV-positive	1	0	1 (0.2)
Excluded from safety population			1 (0.2)
Reason for exclusion			
Participant did not receive study intervention			1 (0.2)

a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.

Source: Table 8, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Table 41. Follow-up Time After Study Vaccination – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		
	18-55 Years (N^a=313) n^b (%)	>55 Years (N^a=306) n^b (%)	Total (N^a=619) n^b (%)
Participants (%) with length of follow-up of:			
<1 Month	1 (0.3)	0	1 (0.2)
≥1 Month to <2 months	312 (99.7)	306 (100.0)	618 (99.8)
Mean (SD)	1.5 (0.12)	1.5 (0.09)	1.5 (0.11)
Median	1.5	1.5	1.5
Min, max	(0.3, 1.8)	(1.3, 1.8)	(0.3, 1.8)

Note: Follow-up time was calculated from the study vaccination to the cutoff date or withdrawal date, whichever date was earlier.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

Source: Table 9, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: There were more than 300 people in each age group who contributed safety data, almost all of whom had > 1 month follow-up, with a median of 1.5 month's follow-up.

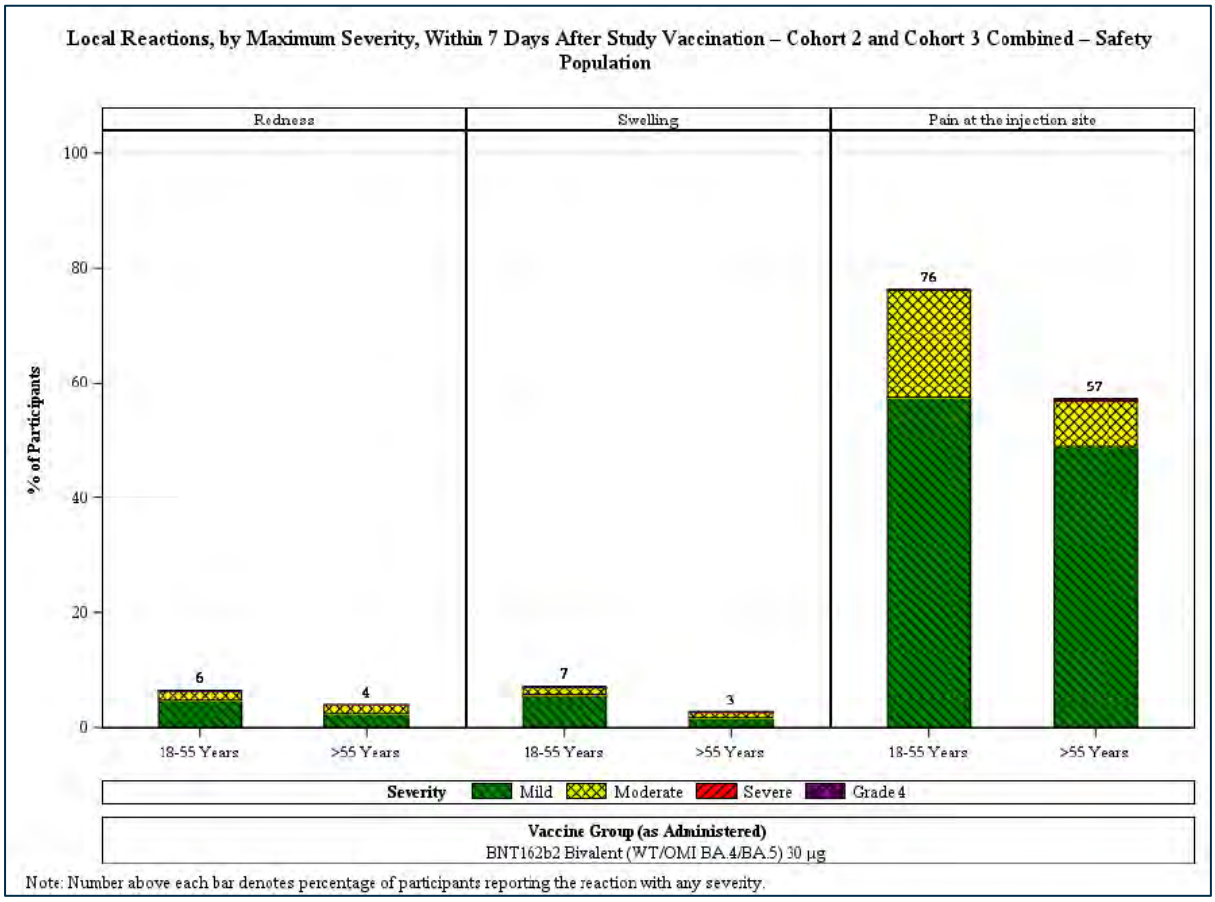
14.3.2. Reactogenicity

14.3.2.1. Local reactions

Local reactions were more common in the 18-55 YOA group than the > 55 YOA group as shown in Figure 15. There were no Grade 4 reactions reported in either age group. 'The median onset for all local reactions was 1 to 2.5 days, and all reactions resolved within a median duration of 1 to 2 days after onset. No clinically meaningful differences in local reactions were observed by sex or baseline SARSCoV-2 status subgroups.'

These data can be compared with the earlier data from the initial enrolment of ~ 200 participants into Cohort 2 (i.e. Group 2 and Group 4) that were shown in Figure 11.

Figure 15. Local Reactions, by Maximum Severity, Within 7 Days After Study Vaccination – Cohort 2 and Cohort 3 Combined – Safety Population



Source: Figure 4, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

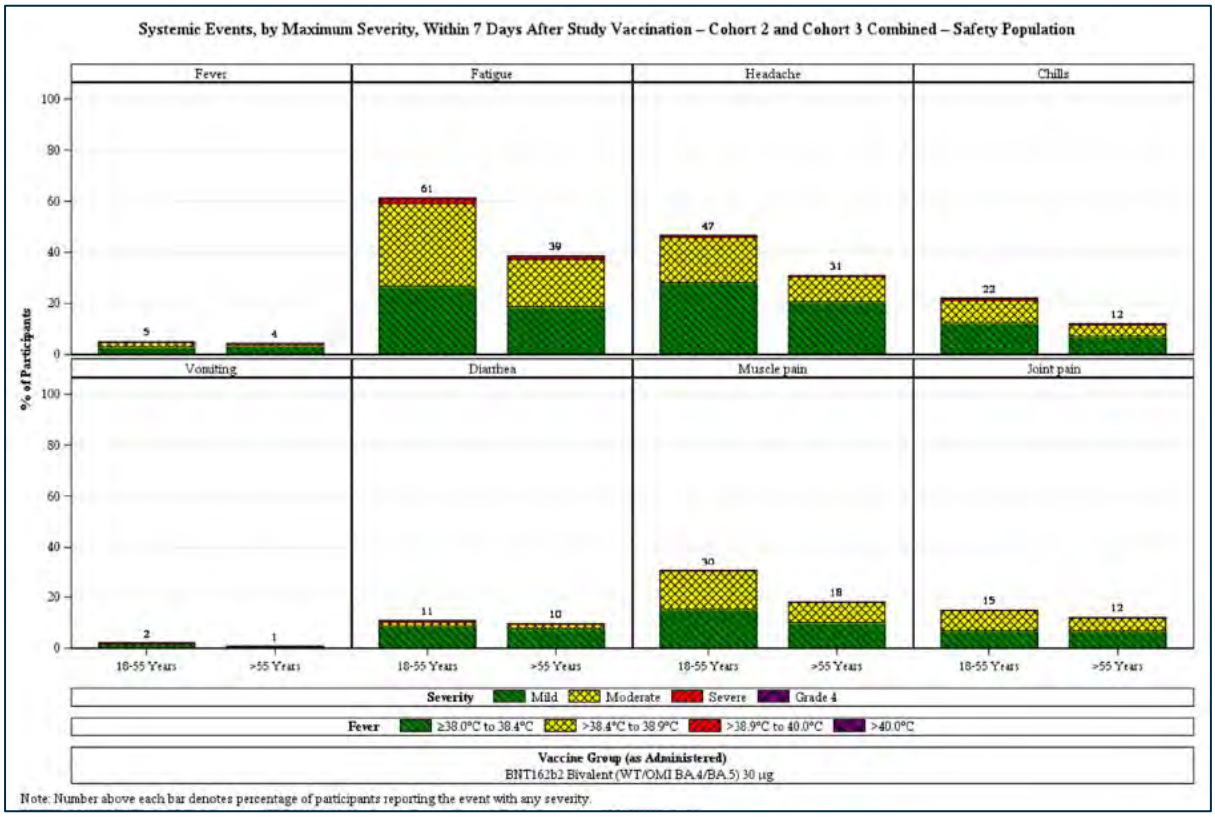
Evaluator's comments: Frequencies, severities and durations of local reactions were very consistent with the preliminary data shown in Figure 11. The Evaluator has no new conclusions about the safety profile from these data.

14.3.2.2. Systemic events

'The incidence and/or severity of most systemic events was higher in participants 18 through 55 years of age who received the 30-µg dose level of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) than > 55 years of age.' as shown in Figure 16. There were no Grade 4 systemic events in either group. 'The median onset for all systemic events was 2 to 3.5 days, and all events resolved within a median duration of 1 to 2 days after onset. No clinically meaningful differences in systemic events were observed by sex or baseline SARSCoV-2 status subgroups.'

These data can be compared with the earlier data from the initial enrolment of ~ 200 participants into Cohort 2 (i.e. Group 2 and Group 4) that were shown in Figure 12.

Figure 16. Systemic Events, by Maximum Severity, Within 7 Days After Study Vaccination – Cohort 2 and Cohort 3 Combined – Safety Population



Source: Figure 5, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: Frequencies, severities and durations of systemic reactions were very consistent with the preliminary data shown in Figure 12. The Evaluator has no new conclusions about the safety profile from these data.

14.3.3. Adverse events

14.3.3.1. Summary of adverse events

'An overview of AEs reported from study vaccination through 1 month after study vaccination is shown' in Table 42. There were no life-threatening AEs, withdrawals due to AEs, or deaths reported. No clinically meaningful differences were seen in subgroups.

'Any AE' was observed in 6.1% of participants 18-55 YOA and 6.9% of participants > 55 YOA (compared to 2.9% and 3.8% respectively in the preliminary data [Table 31]), 'Related AEs' in 3.8% and 2.0% respectively (vs 1.0% and 0.9% respectively), 'Severe AEs' in 0.3% and 0.7% (vs 0.0% vs 0.9% respectively), and 'SAEs' in 0.3% (1 participant) and 0.7% (2 participants) (vs 0.0% and 0.9% [1 participant] respectively.

Table 42. Number (%) of Participants Reporting at Least 1 Adverse Event From Study Vaccination Through 1 Month After Study Vaccination – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)	
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30µg	
Adverse Event	18-55 Years (N[a]=313) n[b] (%)	>55 Years (N[a]=306) n[b] (%)
Any adverse event	19 (6.1)	21 (6.9)
Related[c]	12 (3.8)	6 (2.0)
Severe	1 (0.3)	2 (0.7)
Life-threatening	0	0
Any serious adverse event	1 (0.3)	2 (0.7)
Related[c]	0	0
Severe	1 (0.3)	2 (0.7)
Life-threatening	0	0
Any nonserious adverse event	18 (5.8)	20 (6.5)
Related[c]	12 (3.8)	6 (2.0)
Severe	0	0
Life-threatening	0	0
Any adverse event leading to withdrawal	0	0
Related[c]	0	0
Severe	0	0
Life-threatening	0	0
Death	0	0

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Assessed by the investigator as related to the study intervention.

Source: Table 10, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: The frequencies of 'Any AE' and 'Any related AE' at 1 month were higher following enrolment of Cohort 2 and Cohort 3 (~ 600 participants total) than they were following enrolment of Cohort 2 (~ 200 participants total); however, the frequencies of Severe AEs and SAEs were similar. As previously, there were no life-threatening AEs, withdrawals due to AEs, or deaths reported. The Evaluator will be interested to see which SOCs and PTs reflect these increased frequencies of AEs (see subsequent sections). There were 2 additional SAEs compared to the preliminary data, one in each age group.

14.3.3.2. Analysis of adverse events

The Sponsor presented a summary of all AEs (regardless of relatedness to IP) in Table 11 of the 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023)'. These can be compared to the preliminary data for Cohort 2 that were described on page 88 of this CER, particularly in Table 13 of the '1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report'.

Evaluator's comments: As mentioned in the previous Evaluator's comments, there were higher frequencies of 'Any AE' in these recent data compared to the preliminary data. Surprisingly, in the preliminary data, there were no AEs in the SOC of 'General disorder and administration site conditions' (largely reactogenicity related events), whereas these were reported in 1.3% of participants 18-55 YOA and 0.7% of participants > 55 YOA in these latter data. AEs in the SOC of 'Musculoskeletal and connective tissue disorders' (also largely related to reactogenicity) were also relatively under-represented in the preliminary data, being observed in 0.0% of participants 18-55 YOA and 1.9% of participants > 55 YOA, compared to 0.3% and 2.3% respectively in the latter data. Other SOCs with AEs reported affecting ≥ 1.0% of participants in either age group in the latter data were: 'Blood and lymphatic system disorders' in 2.2% of 18-55 YOA and 0.3% of > 55 YOA (including the PT 'Lymphadenopathy' in 1.6% and 0.3% respectively [0.97% overall]); 'Gastrointestinal disorders' in 0.3% and 1.0% respectively; 'Infections and infestations' in 1.0% and 0.0% respectively; 'Psychiatric disorders' in 0.0% and 1.0% respectively; and 'Skin and subcutaneous tissue disorders' in 0.3% and 1.0% respectively. Although the frequencies of 'Any AEs' were higher in the later data, these appeared to be distributed across reactogenicity-related AEs (some of which appeared relatively under-represented in the preliminary data) and sporadically elsewhere. The Evaluator expects the analysis of related AEs (below) to provide more insight. Of note, 'Lymphadenopathy' is quoted at a frequency of 'Uncommon (≥ 1/1,000 to < 1/100) in Table 2 of the PI and occurred at a frequency of 0.97% in adults here. The frequency of 'Lymphadenopathy' in adolescents was 0.0% (as shown in Table 13 of the '1 Month Post Dose Safety and Immunogenicity (Sentinel) Data, Study C4591044 Cohort 2 report'), hence overall it has been noted at a frequency of < 1/100. Pending further consideration of relatedness (below), the frequencies and distribution of 'any AE' are not concerning and are consistent with those presented in the PI.

Immediate adverse events

The only prior immediate adverse event occurring after enrolment of Cohort 2 was in a 12-17 YOA participant (see section 8.5.8.3). There was one additional immediate AE that occurred with enrolment of Cohort 3. 'One (0.3%) participant in the 18 through 55 years of age group reported immediate AEs of injection site erythema, injection site pain, and injection site swelling (n = 1, each) within 30 minutes of study vaccination'.

Evaluator's comments: The additional immediate events described above were not severe and involved AEs captured in the PI.

Severe or life-threatening adverse events

The 3 reports of severe events were all SAEs and are considered further below. There were no life-threatening events.

Related adverse events

'AEs assessed as related by the investigator were reported by 12 (3.8%) participants and 6 (2.0%) participants in the 18 to 55 years of age and > 55 years of age group, respectively' (Table 43).

Table 43. Number (%) of Participants Reporting at Least 1 Related Adverse Event From Study Vaccination Through 1 Month After Study Vaccination, by System Organ Class and Preferred Term – Cohort 2 and Cohort 3 Combined – Safety Population

	Vaccine Group (as Administered)			
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30µg			
	18-55 Years (N[a]=313)		>55 Years (N[a]=306)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any adverse event	12 (3.8)	(2.0, 6.6)	6 (2.0)	(0.7, 4.2)
Blood and lymphatic system disorders	6 (1.9)	(0.7, 4.1)	1 (0.3)	(0.0, 1.8)
Lymphadenopathy	5 (1.6)	(0.5, 3.7)	1 (0.3)	(0.0, 1.8)
Lymphadenitis	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Gastrointestinal disorders	1 (0.3)	(0.0, 1.8)	1 (0.3)	(0.0, 1.8)
Diarrhoea	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Frequent bowel movements	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
General disorders and administration site conditions	4 (1.3)	(0.3, 3.2)	2 (0.7)	(0.1, 2.3)
Fatigue	2 (0.6)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)
Injection site pain	2 (0.6)	(0.1, 2.3)	1 (0.3)	(0.0, 1.8)
Chills	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Injection site erythema	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Injection site swelling	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Pyrexia	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Infections and infestations	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Oral herpes	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Nervous system disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Headache	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Cough	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Skin and subcutaneous tissue disorders	1 (0.3)	(0.0, 1.8)	2 (0.7)	(0.1, 2.3)
Erythema	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Pruritus	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Urticaria	1 (0.3)	(0.0, 1.8)	0	(0.0, 1.2)
Vascular disorders	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)
Lymphoedema	0	(0.0, 1.2)	1 (0.3)	(0.0, 1.8)

Note: MedDRA (v25.1) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any adverse event," n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.

Source: Table 12, Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023).

Evaluator's comments: For each age group, the frequency of related AEs by PT was ≤ 0.3 (i.e. no more than 1 participant) for each individual PT and most AEs reflected reactogenicity-related

events, with the exception of the following (all in the 18-55 YOA group): 'Lymphadenopathy' (1.6%), 'Fatigue' (0.6%), 'Injection site pain' (0.6%). There are no new safety issues and there are no new considerations for the PI.

14.3.4. Deaths

'No deaths were reported from study vaccination through 1 month after vaccination.'

14.3.5. Serious adverse events

There were 3 SAEs. One (in participant C4591001 s47F, who was enrolled into Cohort 2) was previously considered in section 8.4.1.3, Table 32 and section 12.1.1.2. It was deemed not related to IP by the Investigator and the Evaluator.

Limited details were provided in the 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data report (18/01/2023)' regarding the other 2 SAEs as follows:

- 'A s47F, s47F participant s4 7F years of age, reported a severe SAE of worsening of s47F on Day s47F after vaccination reported as resolved within 14 days. The event was assessed by the investigator as not related to study intervention.'
- 'A s47F, s47F participant s4 7F years of age reported a severe SAE of hypotension with onset on Day s47F after vaccination, resolving within 1 day. The event was assessed by the investigator as not related to study intervention.'

Evaluator's comments: **EvQset5.** The Evaluator notes 2 additional SAEs following enrolment of Cohort 3, as briefly described in section 3.2.3.4 of the document titled 'Study C4591044 Cohort 2 (Group 2 and 4) and Cohort 3 Combined_1MPD_Immunogenicity and Safety Data' (section 2.5 of eCTD submission e006875 [0003]). One was a s4 7F year old s47F with s47F The other was a s4 7F year old s47F with s47F. Please provide detailed participant narratives for those 2 additional SAEs.

14.3.6. Discontinuations due to adverse events

'There were no discontinuations due to AEs from study vaccination through 1 month after vaccination.'

14.3.7. Adverse events of special interest

'No protocol-specified AESI (myocarditis and pericarditis) were reported and no AEs of anaphylaxis/hypersensitivity, appendicitis, or Bell's palsy were reported up to 1 month after vaccination.'

14.3.8. Surveillance of COVID-19 cases

The Sponsor stated there were 8 cases of COVID-19, 4 in each age group. None were severe. No participants reported MIS-A signs or symptoms after study vaccination.

14.4. Presentations on safety for the US FDA VRBPAC meeting on 26/01/2023

The US FDA held a meeting of the VRBPAC on 26/01/2023[15] with the following discussion topics in relation to future periodic vaccination campaigns:

> ***Simplification* of COVID-19 vaccine use:**
>
> • *Immunization schedule*: Please discuss and provide input on simplifying the immunization schedule to authorize or approve a two-dose series in certain young children, and in older adults and persons with compromised immunity, and only one dose in all other individuals.
>
> AND
>
> ***Periodic update* to COVID-19 vaccines:**
>
> • *Vaccine composition*: Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine composition, including to the currently authorized or approved vaccines to be available for use in the U.S. in the fall of 2023.

The meeting considered presentations by representatives of the FDA, CDC, NIAID, Pfizer, Moderna and Novavax.[16] Included were two presentations on safety (one from the CDC and one from the FDA), as described in the sections that follow.

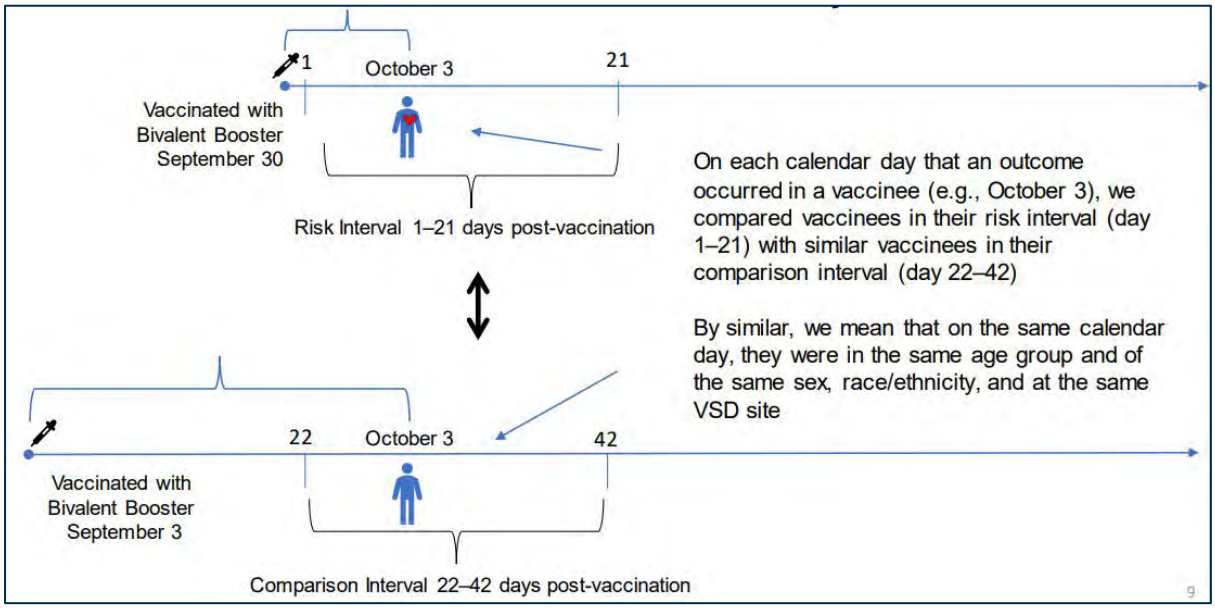
14.4.1. CDC representative's presentation

A CDC representative presented results from a review of Vaccine Safety Datalink (VSD), which includes electronic health record data on ~ 12.5 million individuals across 9 integrated healthcare organisations.[17]

The investigators utilised 'innovative' methodology of rapid cycle analysis (RCA) with near real-time surveillance data and primarily compared event rates for ischaemic stroke in the 21 day interval following vaccination with COMIRNATY Original/Omicron BA.4-5 to those in 'vaccinated concurrent comparators' who were in their 22 to 42 day interval following vaccination (with the aim of reducing a number of biases that may be more apparent with unvaccinated controls)[18] (Figure 17). Supplemental analyses were done using unvaccinated/un-boosted comparators. All analyses were adjusted for age, sex, race/ethnicity, VSD site, calendar time (days) and seasonality (time). A 'signal' was defined if P-value < 0.01 (1-sided).

[15] See https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-january-26-2023-meeting-announcement (accessed on 1/02/2023).
[16] Presentations are listed at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-january-26-2023-meeting-announcement#event-materials (accessed 1/02/2023).
[17] Available from: https://www.fda.gov/media/164811/download (accessed 1/02/2023).
[18] Protocol available from: https://www.cdc.gov/vaccinesafety/pdf/COVID19-RCA-Protocol-1342-508.pdf (accessed 2/02/2023).

Figure 17. Vaccinee with outcome in the risk interval and a concurrent comparator "bivalent vaccinated individuals only"



Source: Slide 9 of the CDC presentation titled 'COVID-19 mRNA bivalent booster vaccine safety', VRBPAC 26/01/2023, available from https://www.fda.gov/media/164811/download (accessed 1/02/2023).

In the period 28/08/2022 through 7/01/2023, there were 549,943 COMIRNATY Original/Omicron BA.4-5 vaccinations, 285,706 Moderna mRNA bivalent vaccinations and 1,298,400 influenza vaccinations. Results of the primary analysis are shown in Table 44 and of the supplemental analysis in Table 45. Results of a post-signal analysis (stratified by concomitant receipt/non-receipt of influenza vaccination) are shown in Table 46 (of note, this only involved review of a 'small subset of charts'.

Table 44. Bivalent RCA concurrent comparator analyses of ischemic strokes during 1–21-day Risk Interval versus 22–42-day Comparison Interval*

				Nominal analysis		Sequential analysis	
Age group (years)	Vaccine	Risk events (N)	Comp events (N)	Adjusted Rate Ratio	95% Confidence Interval	1-sided p-value	Signal? 1-sided p <0.01
18–64	Pfizer	33	23	1.34	0.77–2.36	0.183	no
	Moderna	11	13	0.65	0.27–1.52	0.89	no
65+	**Pfizer**	**130**	**92**	**1.47**	**1.11–1.95**	**0.005**	**yes**
	Moderna	57	49	1.12	0.75–1.67	0.323	no

Source: Slide 11 of the CDC presentation titled 'COVID-19 mRNA bivalent booster vaccine safety', VRBPAC 26/01/2023, available from https://www.fda.gov/media/164811/download (accessed 1/02/2023). * Data through Jan 8, 2023.

Table 45. Ischemic strokes during the 1–21-day interval comparing bivalent boosted vs. un-boosted concurrent comparators (but eligible for bivalent booster)*

Age group (years)	Interval (days)	Comparators	Vaccine	Risk events (N)	Comp events (N)	Adjusted Rate Ratio	95% Confidence Interval	P-value (2-sided)
65+	1–21	Not bivalent boosted	Pfizer	134	1510	1.07	0.89–1.28	0.483

Source: Slide 18 of the CDC presentation titled 'COVID-19 mRNA bivalent booster vaccine safety', VRBPAC 26/01/2023, available from https://www.fda.gov/media/164811/download (accessed 1/02/2023). * Analyses only included outcomes through December 10, 2022.

Table 46. Ischemic stroke incidence during days 1–21 compared with days 22–42, among ≥65 years with and without simultaneous influenza vaccination*

Analytic population	Cases in 1–21-day Risk Interval (N=103)	Cases in 22–42-day Comparison Interval (N=82)	Adjusted Rate Ratio** (95% CI)	P-value
Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine	40	20	**2.00 (1.18–3.48)**	**0.010**
Bivalent Pfizer + same day standard dose flu vaccine	3	4	0.75 (0.14–3.63)	0.727
Bivalent Pfizer without any same day flu vaccine	60	58	1.03 (0.72–1.49)	0.855

Source: Slide 21 of the CDC presentation titled 'COVID-19 mRNA bivalent booster vaccine safety', VRBPAC 26/01/2023, available from https://www.fda.gov/media/164811/download (accessed 1/02/2023). * Analyses only included outcomes through December 10, 2022. * Analyses only include vaccination data through November 5, 2022, and stroke outcome data through December 17, 2022. ** Adjusted by 5-year age groups.

In their **interpretation** of the data, the investigators noted:

- The statistical signal persisted for 7 weeks, with slow attenuation in the rate ratio from 1.92 to 1.47 but continuing to meet the statistical criteria for a signal.
- Temporal clustering evaluation found a significant cluster 11-22 days post-vaccination.
- Based on the small subset of charts reviewed, most confirmed cases had concomitant high-dose or adjuvanted influenza vaccination.
    - Separate analyses did not detect an elevated risk ratio for stroke after influenza vaccine alone (data not shown).
- Supplemental analyses suggest comparison interval (22–42 days) rates were lower than expected (RR 0.76 [95% CI: 0.60, 0.95]).

The following **caveats** were also noted by the investigators (verbatim):

- Small numbers of strokes and imprecise rate ratios limit some analyses.
    - Reduced follow-up time after Moderna booster due to distribution delays.
    - Concomitant flu vaccine analyses limited by small numbers.
- Difficult to interpret temporal clustering during risk and comparison intervals.
- Possible unmeasured confounding.
    - Results may be influenced by confounders that vary over time.

    - Do early adopters of bivalent booster vaccine have greater risk of near-term cardiovascular events?
        - Same trend has not been observed for acute myocardial infarctions.
        - Potential impact of differential vaccine availability after EUA (Pfizer > Moderna).
- Possible role of SARS-CoV-2 infection before booster?
    - Background incidence of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake.
- Analysis excluded cases with COVID-19 diagnosis or positive test in prior 30 days, although asymptomatic infections and home antigen tests are not consistently documented in electronic health record; however, Kaiser Permanente Northern California chart reviews did not find recent SARS-CoV-2 infection or exposure.

Finally, the investigators stated that, 'CDC and FDA are engaged in epidemiologic analyses regarding co-administration of COVID-19 mRNA bivalent booster and flu vaccines'.

Evaluator's comments: A safety signal was found relating to an increased risk of ischaemic stroke following boosting with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg that was sustained over the final 7 weeks of the observation period. The statistical significance was dependent on the 'innovative methods' used to select 'vaccinated concurrent comparators' as controls (i.e. not seen when using unvaccinated/un-boosted controls) and was restricted to vaccinees ≥ 65 YOA *and* those receiving concomitant age-appropriate influenza vaccination. A signal was not seen among the smaller number of Moderna mRNA bivalent vaccine recipients, in whom a supplemental analysis stratified by concomitant receipt/non-receipt of influenza vaccine was not performed. There were a number of factors that could confound the analysis that were acknowledged by the investigators and in addition to those listed above, the Evaluator notes the geographical restriction and relatively fewer number of vaccinees compared to the FDA data presented in section 14.4.2. It should be possible to repeat this analysis using the same methods on subsequent data, both in the same setting or expanded/other settings. The Evaluator is unable to determine from the data presented whether a definite safety signal is present.

14.4.2. FDA representative's presentations

An FDA representative presented results of their own review of Center's for Medicare & Medicaid Services (CMS) data through December 2022, which included experience with 4,265,244 COMIRNATY Original/Omicron BA.4-5 vaccinations of adults ≥ 65 YOA.[19] There were an additional 3,042,074 recipients of Moderna's bivalent vaccine in that age group.

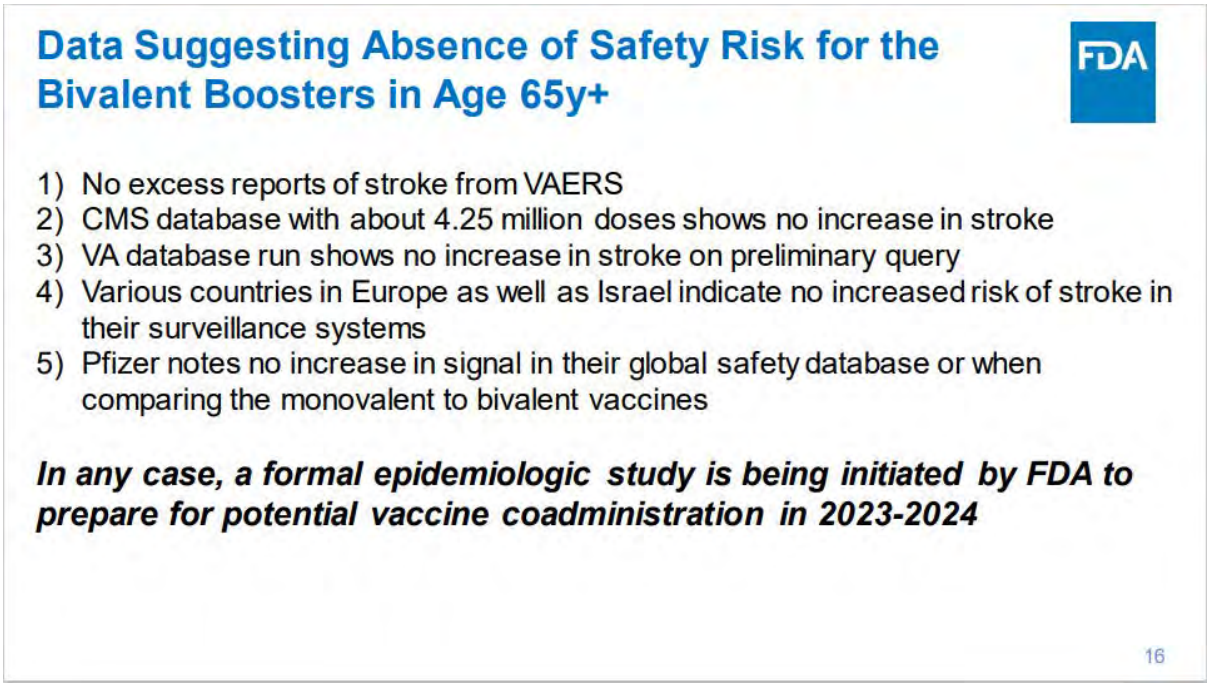
Utilising methodology of RCA near real-time surveillance of that CMS data, the FDA found no increased risk of non-haemorrhagic stroke (compared to historical rates) in the paediatric, adult 18-64 YOA or elderly ≥ 65 YOA populations.

Nor was a signal seen in the elderly sub-population who received concomitant COMIRNATY Original/Omicron BA.4-5 plus influenza vaccination (38% of the 4,265,244 Medicare recipients), or the 78% of Medicare recipients who received influenza vaccination within ± 42 days.

The FDA representative's conclusions in relation to non-haemorrhagic stroke risk following bivalent Omicron BA.4/5 mRNA vaccination in the context of other available data are shown in Figure 18.

[19] Available from: https://www.fda.gov/media/164815/download (accessed 1/02/2023).

Figure 18. Data suggesting absence of safety risk for the bivalent booster in age 65y+



Source: Slide 16 of the FDA presentation titled 'Update on Original COVID-19 Vaccine and COVID-19 Vaccine, Bivalent Effectiveness and Safety', VRBPAC 26/01/2023, available from https://www.fda.gov/media/164815/download (accessed 1/02/2023).

Evaluator's comments: The FDA has considered results from a larger dataset than was considered by the CDC, in the context of data from other sources, and was unable to corroborate the signal for an increased risk of ischaemic stroke. Both the CDC and FDA have noted there will be ongoing surveillance, including a formal epidemiologic study to be initiated by the FDA to prepare for potential vaccine coadministration in 2023-2024. The Evaluator is interested in the Sponsor's interpretation of the CDC's presentation and whether they have any specific plans in surveillance for a signal of ischaemic stroke. **EvQset5:** Please provide an interpretation of the potential safety signal for an increased risk of ischaemic stroke following boosting with BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg that was identified by the US Centers for Disease Control in their presentation to the FDA's VRBPAC meeting on 26/01/2023. Please outline any plans the Sponsor has for ongoing surveillance of this potential safety signal.

14.5. Evaluator's overall conclusions on clinical efficacy

These conclusions should be read in the context of the previous conclusions regarding immunogenicity in adult participants that were presented in section 7.5.1.

14.5.1. Adolescents 12-17 YOA

The descriptive analysis of immunogenicity presented in section 14.1 suggests a similarly robust immune response from BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg against Omicron BA.4/5 as seen in adults. GMTs and GMFRs against Omicron BA.1 were lower but seroresponses were relatively preserved. Seroresponse to reference strain in participants without evidence of infection were seen in 65.4% of participants. Direct comparison of results with adults was hampered by a higher proportion of adolescents with evidence of prior infection (that may additionally involve a different number and/or variants for the prior infection[s]) as well as a ~ 2 month shorter interval (~ 8 months compared to ~ 10 months) between the prior vaccine

dose and the study booster dose. There were no real world data available to the Evaluator at the time of the Round 2 report.

14.5.2. Adults 18-55 YOA and > 55 YOA

Immunogenicity data from an expanded number of adult participants (approximately triple the number) were available for evaluation in the Round 2 CER. The Evaluator found the superiority and non-inferiority statistical testing to be non-convincing given systematic differences between the recruitment of study participants given BNT162b2 bivalent (WT/OMI BA.4/BA.5) 30 µg and controls given BNT162b2 30 µg; hence focussed instead on the descriptive immunogenicity results. The pattern of those results (GMTs, GMFRs and seroresponses) was broadly in line with the previous data and reinforce the conclusions made earlier.

14.6. Evaluator's overall conclusions on clinical safety

These conclusions should be read in the context of the previous conclusions regarding clinical safety in adult participants that were presented in section 8.8.

There were no new safety concerns or considerations raised following the inclusion of Cohort 3 safety data, in line with the evaluation in section 14.3 and associated Evaluator's comments in that section. A potential safety signal for an increased risk of ischaemic stroke in the 21 days following vaccination was identified in individuals ≥ 65 YOA who received concomitant influenza vaccination. This was found by the US CDC using 'innovative methods' in the selection of controls but was not corroborated by the FDA in their analysis of a larger dataset using more conventional methods or through a review of data from other sources. This potential signal requires further study and monitoring.

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

Unchanged from section 9.1; however, with reduced uncertainty in relation to immunogenicity results in adolescents 12-17 YOA.

15.2. Second round assessment of risks

Unchanged from section 9.2; however, the uncertainty surrounding a potential safety signal of non-ischemic stroke in individuals ≥ 65 YOA receiving concomitant adjuvanted influenza vaccine (evaluated in section 14.4) is noted.

15.3. Second round assessment of benefit-risk balance

Taking together the previous assessment of benefit-risk balance (section 9.3), along with the additional consideration of the further immunogenicity data (section 15.1) and real-world safety data (section 15.2), the Evaluator continues to find the benefit-risk assessment to be **favourable**.

16. Second round recommendation regarding authorisation

Based on the evaluation of the clinical data, the Evaluator recommends approval of COMIRNATY Original/Omicron BA.4-5 *as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older*.

The Evaluator notes the decisions made by the Delegate on 20/01/2023 'to provisionally register medicine(s), to approve product information, and to impose conditions under the Therapeutic Goods Act 1989' (TRIM ref: D23-5055082).

The Evaluator agrees with the clinical conditions imposed by the Delegate in their recommendation to provisionally register the medicine, which were:

- An update of the Australian PI via a future submission is required for inclusion of adolescent immunogenicity data in 12-17 years old age group based on the Study C4591044. This may be undertaken after Clinical Evaluation Report (Round 2) by the TGA for the current submission PM-2022-05306-1-2 has been issued to the Sponsor.
- Final Clinical Study Report for the Study C4591044 is to be provided to the TGA when it becomes available to the Sponsor.

The Evaluator notes the Sponsor's commitment to further monitor the potential risk of ischaemic stroke in individuals over 65 YOA.

17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

The Evaluator notes the clinical condition imposed by the Delegate in relation to the PI (section 16). Otherwise, no further comments.

17.2. Second round comments on draft CMI (clinical aspects)

No further comments.

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

No further comments.

18. References

Link-Gelles R, Ciesla AA, Fleming-Dutra KE, et al. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection - Increasing Community Access to Testing Program, United States, September-November 2022. MMWR Morb Mortal Wkly Rep. 2022;71(48):1526-1530. Published 2022 Dec 2. doi:10.15585/mmwr.mm7148e1.

Surie D, DeCuir J, Zhu Y, et al. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19-Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years - IVY Network, 18 States, September 8-November 30, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(5152):1625-1630. Published 2022 Dec 30. doi:10.15585/mmwr.mm715152e2.

Tenforde MW, Weber ZA, Natarajan K, et al. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19-Associated Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults - VISION Network, Nine States, September-November 2022. MMWR Morb Mortal Wkly Rep. 2022;71(5152):1616-1624. Published 2022 Dec 30. doi:10.15585/mmwr.mm715152e1.

19. Supporting information, tables and figures

19.1. Clinical pharmacology study synopses

Not applicable.

19.2. Other supporting tables and figures

Table 47. Other sponsors' COVID-19 vaccines that have been provisionally approved by the TGA

Effective date	Sponsor	Name	Type
a. 19 January 2022 b. 9 June 2022 c. 22 July 2022	Biocelect Pty Ltd on behalf of Novavax Inc	NUVAXOVID (NVX-CoV2373) a. For individuals aged 18 years and over b. Booster dose for individuals aged 18 years and over c. For individuals aged 12 years and over	Protein vaccine
a. 9 August 2021 b. 3 September 2021 c. 7 December 2021 d. 17 February 2022 e. 19 July 2022 f. 19 October 2022	Moderna Australia Pty Ltd	SPIKEVAX (elasomeran) a. For individuals aged 18 years and over b. For individuals aged 12 years and over c. Booster dose for individuals aged 18 years and over d. For individuals aged 6 years and over e. For individuals aged 6 months and over f. Booster dose for individuals aged 12 years and over	mRNA
29 August 2022	Moderna Australia Pty Ltd	SPIKEVAX Bivalent Original/Omicron (elasomeran/imelasomeran) Booster dose for individuals aged 18 years and over	mRNA
25 June 2021	Janssen-Cilag Pty Ltd	COVID-19 Vaccine Janssen For individuals aged 18 years and over	Viral vector
a. 15 February 2021 b. 8 February 2022	AstraZeneca Pty Ltd	VAXZEVRIA (previously COVID-19 Vaccine AstraZeneca) a. For individuals aged 18 years and over b. Booster dose for individuals aged 18 years and over	Viral vector

Source: Accessed from https://www.tga.gov.au/products/covid-19/covid-19-vaccines/covid-19-vaccine-provisional-registrations on 21/11/2022 (last updated 28/10/2022).

19.2.1. Study C4591044 – Study design

Table 48. Study C4591044 Objectives, Estimands and Endpoints - Primary Safety

Objectives	Estimands	Endpoints
Primary Safety		
Cohort 1: To describe the safety and tolerability profile of BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Cohort 2: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55, and >55 years of age, and BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 60 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Cohort 2 + Cohort 3 combined: To describe the safety and tolerability profile of BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants receiving 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following the study vaccination • Systemic events for up to 7 days following the study vaccination • AEs from the study vaccination through 1 month after the study vaccination • SAEs from the study vaccination through 6 months after the study vaccination	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

Table 49. Study C4591044 Objectives, Estimands and Endpoints - Primary Immunogenicity

Objectives	Estimands	Endpoints
Primary Immunogenicity		
Cohort 1: To describe the immune response to BNT162b5 Bivalent (WT/OMI BA.2) 30 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg given as a second booster dose to COVID-19 vaccine–experienced participants 18 through 55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.2)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 4 + Cohort 3/ Group 2 combined: To demonstrate the superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg compared to after BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) to 1 month after BNT162b2, given as a second booster dose in BNT162b2-experienced participants • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority with respect to level of neutralizing titer and with respect to seroresponse rate of the anti-Omicron BA.4/BA.5 immune response after BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg given as a second booster dose to BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the Omicron (BA.4/BA.5)–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age • The difference in percentages of participants with seroresponse to the Omicron BA.4/BA.5 strain at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) given as a second booster dose in BNT162b2-experienced participants 18 through 55 years of age compared to participants >55 years of age	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers
Cohort 2: To describe the immune response to BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg or 60 µg and BNT162b2 Bivalent (WT/OMI BA.1) 30 µg[d] or 60 µg[d] given as a second booster dose to BNT162b2-experienced participants 12 through 17, 18 through 55[d], and >55[d] years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 Omicron (BA.1)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022. For legend, see text below Table 50.

Table 50. Study C4591044 Objectives, Estimands and Endpoints - Secondary Immunogenicity

Objectives	Estimands	Endpoints
Secondary Immunogenicity		
Cohort 2/Group 4 + Cohort 3/Group 2 combined: To demonstrate the noninferiority of the anti–reference-strain immune response after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose in BNT162b2-experienced participants >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMR of the reference-strain–neutralizing titers at 1 month after BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) and at 1 month after BNT162b2 given as a second booster dose in BNT162b2-experienced participants	• SARS-CoV-2 reference-strain[b]–neutralizing titers
Cohort 2/Group 2 + Cohort 3/Group 1 combined and Cohort 2/Group 4 + Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (WT/ OMI BA.4/BA.5) 30 µg compared to BNT162b2 30 µg[c] given as a second booster dose to BNT162b2-experienced participants 18 through 55 and >55 years of age.	In participants complying with the key protocol criteria (evaluable participants): • GMT at each time point for each strain-specific neutralizing titer • GMFR from before the study vaccination to each subsequent time point for each strain-specific neutralizing titer • Percentages of participants with seroresponse[a] at each time point following vaccination for each strain-specific neutralizing titer	• SARS-CoV-2 Omicron (BA.4/BA.5)–neutralizing titers • SARS-CoV-2 reference-strain[b]–neutralizing titers

a. Seroresponse is defined as achieving a ≥4-fold rise from the baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
b. Reference strain is also referred to as the Wild Type or ancestral strain (Wuhan-Hu-1; USA-WA1/2020).
c. The participants >55 years of age from C4591031 Substudy E expanded cohort who received BNT162b2 30 µg as a second booster dose will be used as comparator group for this objective.
d. A subset of approximately 100 participants in each age group (18 through 55 years of age, >55 years of age) and dose group (30 µg, 60 µg) from C4591031 Substudy E expanded cohort who received BNT162b2 Bivalent (WT/OMI BA.1) 30 µg or 60 µg as a second booster dose will be selected for this objective. The subset selected from C4591031 Substudy E will include similar percentage of participants with baseline positive SARS-CoV-2 infection status as the groups in Cohort 2 of this study, whenever feasible.
e. If the COVID-19 illness visit is conducted as an in-person visit, a blood sample will be taken for this assessment. No blood samples will be obtained for remote (telehealth) COVID-19 illness visits.

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022.

Table 51. Study C4591044 Objectives, Estimands and Endpoints - Exploratory

Objectives	Estimands	Endpoints
Exploratory		
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe confirmed COVID-19 and severe COVID-19 cases in each vaccine and age group.		• Confirmed COVID-19 cases • Confirmed severe COVID-19 cases • Strain sequencing of COVID-19 cases
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to SARS-CoV-2 infection at the time of the COVID-19 illness visit[e] and at the convalescent visit.		• SARS-Cov-2–neutralizing titers previously specified for the respective cohorts
Cohort 1, Cohort 2, and Cohort 2 + Cohort 3 combined: To describe the immune response to emerging VOCs.		• SARS-CoV-2–neutralizing titers for VOCs not already specified
Cohort 2: To describe the cell-mediated immune response, and additional humoral immune response parameters, to the reference strain[b] and Omicron in a subset of participants with PBMC samples collected.		

Source: C4591044 Protocol Amendment 2 Clean Copy, 24Aug2022. For legend, see text below Table 50.

19.2.1. Supportive data – variant neutralisation

Table 52. Variants Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants >55 Years of Age

	Vaccine Group (as Randomized)	
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg	C4591031 BNT162b2 30 µg
	n[a] (%)	n[a] (%)
Randomized[b]	39 (100.0)	40 (100.0)
All-available immunogenicity population	38 (97.4)	40 (100.0)
Excluded from all-available immunogenicity population	1 (2.6)	0
Reason for exclusion		
Did not have at least 1 valid and determinate immunogenicity result after study vaccination	1 (2.6)	0
Evaluable immunogenicity population	36 (92.3)	40 (100.0)
Participants without evidence of infection up to 1 month after the study vaccination[c]	17 (43.6)	20 (50.0)
Excluded from evaluable immunogenicity population	3 (7.7)	0
Reason for exclusion[d]		
Did not have at least 1 valid and determinate immunogenicity result within 28-42 days after the study vaccination	3 (7.7)	0

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. n = Number of participants with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
c. Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
d. Participants may have been excluded for more than 1 reason.

Source: Table 1, 1 Month Post Dose Immunogenicity Data – New Variants, Study C4591044 Cohort 2 (Sentinel Group) report.

Table 53. Geometric Mean Titers, by Baseline SARS-CoV-2 Status – New Variants Neutralization – Subset of Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Participants >55 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)			
			C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30 µg		C4591031 BNT162b2 30 µg	
Assay	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 FFRNT - Omicron BA.4.6 - NT50 (titer)	All	Prevax	36	91.5 (52.5, 159.7)	40	101.1 (58.9, 173.5)
		1 Month	36	968.2 (623.3, 1503.9)	40	232.2 (149.3, 361.1)
	Positive[d]	Prevax	19	281.6 (159.5, 497.2)	20	283.4 (142.6, 563.2)
		1 Month	19	1564.4 (938.2, 2608.5)	20	586.9 (346.9, 993.0)
	Negative[e]	Prevax	17	26.1 (14.9, 45.6)	20	36.1 (20.4, 63.6)
		1 Month	17	566.3 (280.8, 1142.0)	20	91.9 (59.8, 141.1)
SARS-CoV-2 FFRNT - Omicron BA.2.75.2 - NT50 (titer)	All	Prevax	36	31.1 (20.1, 48.3)	40	48.0 (29.1, 79.0)
		1 Month	36	209.5 (131.6, 333.5)	40	99.3 (62.4, 158.1)
	Positive[d]	Prevax	19	62.0 (32.5, 118.0)	20	125.5 (62.1, 253.9)
		1 Month	19	325.9 (183.0, 580.5)	20	264.5 (146.3, 478.0)
	Negative[e]	Prevax	17	14.4 (10.1, 20.6)	20	18.3 (12.1, 27.7)
		1 Month	17	127.9 (61.5, 265.8)	20	37.3 (25.1, 55.4)
SARS-CoV-2 FFRNT - Omicron BQ.1.1 - NT50 (titer)	All	Prevax	36	30.8 (18.5, 51.3)	40	31.4 (21.4, 45.9)
		1 Month	36	266.5 (171.2, 415.0)	40	58.1 (39.2, 86.1)
	Positive[d]	Prevax	19	74.4 (34.7, 159.4)	20	59.6 (35.0, 101.5)
		1 Month	19	444.4 (259.4, 761.3)	20	132.2 (82.5, 212.0)
	Negative[e]	Prevax	17	11.5 (9.2, 14.5)	20	16.5 (11.0, 24.8)
		1 Month	17	150.5 (77.2, 293.4)	20	25.5 (17.4, 37.4)
SARS-CoV-2 FFRNT - Omicron XBB - NT50 (titer)	All	Prevax	36	18.2 (13.3, 24.8)	40	27.1 (18.9, 38.8)
		1 Month	36	89.8 (60.4, 133.5)	40	41.4 (27.5, 62.3)
	Positive[d]	Prevax	19	26.8 (16.2, 44.2)	20	54.6 (32.5, 92.0)
		1 Month	19	130.9 (80.0, 214.3)	20	98.5 (58.0, 167.3)
	Negative[e]	Prevax	17	11.8 (9.0, 15.4)	20	13.4 (10.3, 17.5)
		1 Month	17	58.9 (31.6, 109.9)	20	17.4 (12.6, 24.1)

Abbreviations: FFRNT = fluorescent focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Approximately forty participants (20 baseline SARS-CoV-2 positive status and 20 negative status) were selected from >55 years age group in Study C4591044 Cohort 2 BNT162b2 Bivalent (WT/OMI BA.4/BA.5) 30-µg group and from Study C4591031 Substudy E expanded cohort (>55 years) BNT162b2 30-µg group.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.

Source: Table 3, 1 Month Post Dose Immunogenicity Data – New Variants, Study C4591044 Cohort 2 (Sentinel Group) report.

19.2.2. Real-world effectiveness data

Table 54. Characteristics of patients with SARS-CoV-2 tests conducted at national pharmacy testing program locations (N = 360,626) — Increasing Community Access to Testing program, United States, September–November 2022

Characteristic	SARS-CoV-2 test result (col. %)		Number and type of mRNA COVID-19 vaccine doses received* before test date, no. (row %)					
	Positive (case-patients)	Negative (control-patients)	Unvaccinated	2 monovalent doses	3 monovalent doses	4 monovalent doses†	≥2 monovalent doses	≥2 monovalent plus bivalent booster
SARS-CoV-2 status§								
Positive (case-patients)	121,687 (100)	0 (—)	28,874 (24)	36,429 (30)	41,409 (34)	9,175 (8)	87,013 (72)	5,800 (5)
Negative (control-patients)	0 (—)	238,939 (100)	72,010 (30)	72,352 (30)	65,122 (27)	12,981 (5)	150,455 (63)	16,474 (7)
Time frame of test								
Sep 14–Oct 29, 2022	98,729 (81)	194,150 (81)	81,876 (28)	88,392 (30)	88,768 (30)	19,425 (7)	196,585 (67)	14,418 (5)
Oct 30–Nov 11, 2022	22,958 (19)	44,789 (19)	19,008 (28)	20,389 (30)	17,763 (26)	2,731 (4)	40,883 (60)	7,856 (12)
Age group, yrs								
18–49	75,012 (62)	171,125 (72)	81,296 (33)	82,488 (34)	71,881 (29)	0 (—)	154,369 (63)	10,472 (4)
50–64	29,896 (25)	43,179 (18)	14,366 (20)	19,688 (27)	22,580 (31)	11,055 (15)	53,323 (73)	5,386 (7)
≥65	16,779 (14)	24,635 (10)	5,222 (13)	6,605 (16)	12,070 (29)	11,101 (27)	29,776 (72)	6,416 (15)
Sex								
Female	68,487 (56)	150,790 (63)	57,988 (26)	66,662 (30)	66,983 (31)	13,661 (6)	147,306 (67)	13,983 (6)
Male	53,029 (44)	87,644 (37)	42,818 (30)	41,915 (30)	39,245 (28)	8,486 (6)	89,646 (64)	8,209 (6)
Other	171 (0.1)	505 (0.2)	78 (12)	204 (30)	303 (45)	9 (1)	516 (76)	82 (12)
Race and ethnicity								
Black or African American, non-Hispanic	15,881 (13)	39,592 (17)	20,759 (37)	19,729 (36)	11,190 (20)	2,321 (4)	33,240 (60)	1,474 (3)
Hispanic or Latino	22,694 (19)	48,109 (20)	22,074 (31)	25,281 (36)	19,408 (27)	2,141 (3)	46,830 (66)	1,899 (3)
Other, non-Hispanic	14,583 (12)	25,453 (11)	7,796 (19)	10,552 (26)	16,811 (42)	2,240 (6)	29,603 (74)	2,637 (7)
White, non-Hispanic	60,315 (50)	110,191 (46)	40,756 (24)	46,158 (27)	53,483 (31)	14,654 (9)	114,295 (67)	15,455 (9)
Unknown	8,214 (7)	15,594 (7)	9,499 (40)	7,061 (30)	5,639 (24)	800 (3)	13,500 (57)	809 (3)
HHS testing site region¶								
Region 1	8,705 (7)	15,181 (6)	5,088 (21)	5,653 (24)	9,005 (38)	1,943 (8)	16,601 (70)	2,197 (9)
Region 2	13,533 (11)	19,672 (8)	7,698 (23)	8,918 (27)	12,151 (37)	2,199 (7)	23,268 (70)	2,239 (7)
Region 3	9,802 (8)	17,519 (7)	7,090 (26)	7,618 (28)	8,564 (31)	1,957 (7)	18,139 (66)	2,092 (8)
Region 4	24,059 (20)	57,781 (24)	28,092 (34)	26,615 (33)	18,942 (23)	4,525 (6)	50,082 (61)	3,666 (4)
Region 5	25,382 (21)	44,689 (19)	19,072 (27)	20,873 (30)	20,740 (30)	4,403 (6)	46,016 (66)	4,983 (7)
Region 6	12,601 (10)	31,708 (13)	14,127 (32)	15,290 (35)	10,892 (25)	2,140 (5)	28,322 (64)	1,860 (4)
Region 7	3,451 (3)	6,715 (3)	3,004 (30)	3,318 (33)	2,735 (27)	537 (5)	6,590 (65)	572 (6)
Region 8	3,060 (3)	5,423 (2)	1,485 (18)	2,861 (34)	2,973 (35)	527 (6)	6,361 (75)	637 (8)
Region 9	18,771 (15)	35,126 (15)	14,080 (26)	15,321 (28)	17,755 (33)	3,433 (6)	36,509 (68)	3,308 (6)
Region 10	2,323 (2)	5,125 (2)	1,148 (15)	2,314 (31)	2,774 (37)	492 (7)	5,580 (75)	720 (10)
SVI, mean (SD)**	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
History of self-reported SARS-CoV-2 positive test result								
None	95,378 (78)	136,420 (57)	59,380 (26)	63,497 (27)	73,538 (32)	18,420 (8)	155,455 (67)	16,963 (7)
Positive >90 days before current test	26,309 (22)	102,519 (43)	41,504 (32)	45,284 (35)	32,993 (26)	3,736 (3)	82,013 (64)	5,311 (4)
SARS-CoV-2 test type								
Rapid NAAT††	39,729 (33)	84,511 (35)	33,055 (27)	44,280 (36)	34,218 (28)	6,281 (5)	84,779 (68)	6,406 (5)
Laboratory-based NAAT§§	81,958 (67)	154,428 (65)	67,829 (29)	64,501 (27)	72,313 (31)	15,875 (7)	152,689 (65)	15,868 (7)
Self-reported one or more chronic underlying condition¶¶								
No	94,236 (77)	187,842 (79)	85,207 (30)	86,234 (31)	81,463 (29)	13,581 (5)	181,278 (64)	15,593 (6)
Yes	27,451 (23)	51,097 (21)	15,677 (20)	22,547 (29)	25,068 (32)	8,575 (11)	56,190 (72)	6,681 (9)
For persons who received only monovalent mRNA doses, no. of mos since most recent dose								
2–3	3,718 (3)	7,540 (3)	0 (—)	1,966 (17)	3,446 (31)	5,846 (52)	11,258 (100)	0 (—)
4–5	7,188 (6)	12,284 (6)	0 (—)	2,907 (15)	5,517 (28)	11,048 (57)	19,472 (100)	0 (—)
6–7	6,110 (5)	11,396 (5)	0 (—)	4,002 (23)	9,061 (52)	4,443 (25)	17,506 (100)	0 (—)
≥8	69,592 (60)	118,304 (53)	0 (—)	99,906 (53)	87,943 (47)	47 (0.03)	187,896 (100)	0 (—)

Abbreviations: HHS = U.S. Department of Health and Human Services; ICATT = Increasing Community Access to Testing program; NAAT = nucleic acid amplification test; SVI = social vulnerability index.

* Only month and year of receipt were reported for each vaccination dose from some participating pharmacies; therefore, the number of months between a vaccine dose and testing is a whole number calculated as the difference between the month and year of testing and the month and year of the vaccine dose. Persons reporting an mRNA booster dose on or after September 1, 2022, were assumed to have received a bivalent dose because no monovalent mRNA doses were authorized for use as booster doses at that time. For doses received in the same month or the month before SARS-CoV-2 testing, an additional question was asked to specify whether the dose was received ≥2 weeks before testing, and only doses received ≥2 weeks before testing were included.

† Persons aged <50 years without moderate or severe immunocompromise were not eligible for a fourth monovalent (second booster) dose. Because of timing of authorization, not enough persons ≥8 months from the fourth dose (second monovalent booster) were available to include in analyses.

§ SARS-CoV-2 status after the most recent vaccine dose received.

¶ Regions defined by HHS and include only states and territories with ICATT sites. U.S. Virgin Islands (Region 2) and Federated States of Micronesia, Guam, Marshall Islands, Northern Mariana Islands, Palau, and American Samoa (Region 9) were not included because they did not have pharmacies participating in ICATT. https://www.hhs.gov/about/agencies/iea/regional-offices/index.html

** SVI is a tool that uses U.S. Census Bureau data on 16 social factors to rank social vulnerability by U.S. Census Bureau tract. The scale is from 0 to 1; higher SVIs represent more vulnerable communities. Tests with missing SVI data (<1% of total) were excluded from all analyses. https://www.atsdr.cdc.gov/placeandhealth/svi/data_documentation_download.html

†† Rapid NAAT was performed on-site on self-collected nasal swabs using ID Now (Abbott Diagnostics Scarborough Inc.) and Accula (Thermo Fisher Scientific).

§§ Laboratory-based NAAT was performed on self-collected nasal swabs at contracted laboratories using a variety of testing platforms.

¶¶ Underlying conditions included on the survey were heart conditions, high blood pressure, overweight or obesity, diabetes, current or former smoker, kidney failure or end stage renal disease, cirrhosis of the liver, chronic lung disease (such as chronic obstructive pulmonary disease, moderate to severe asthma, cystic fibrosis, or pulmonary embolism).

Source: https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7148e1-H.pdf (accessed 8/12/2022).

19.2.3. Study C4591044 Cohort 2

Table 55. Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years				>55 Years			
	30 µg		30 µg		60 µg		30 µg		60 µg	
Local Reaction	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])
Redness[d]										
Any	107	6 (5.6) (2.1, 11.8)	102	6 (5.9) (2.2, 12.4)	110	12 (10.9) (5.8, 18.3)	105	3 (2.9) (0.6, 8.1)	101	7 (6.9) (2.8, 13.8)
Mild	107	4 (3.7) (1.0, 9.3)	102	5 (4.9) (1.6, 11.1)	110	6 (5.5) (2.0, 11.5)	105	1 (1.0) (0.0, 5.2)	101	4 (4.0) (1.1, 9.8)
Moderate	107	2 (1.9) (0.2, 6.6)	102	1 (1.0) (0.0, 5.3)	110	5 (4.5) (1.5, 10.3)	105	2 (1.9) (0.2, 6.7)	101	3 (3.0) (0.6, 8.4)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Swelling[d]										
Any	107	8 (7.5) (3.3, 14.2)	102	7 (6.9) (2.8, 13.6)	110	17 (15.5) (9.3, 23.6)	105	2 (1.9) (0.2, 6.7)	101	9 (8.9) (4.2, 16.2)
Mild	107	6 (5.6) (2.1, 11.8)	102	5 (4.9) (1.6, 11.1)	110	7 (6.4) (2.6, 12.7)	105	1 (1.0) (0.0, 5.2)	101	5 (5.0) (1.6, 11.2)
Moderate	107	2 (1.9) (0.2, 6.6)	102	2 (2.0) (0.2, 6.9)	110	10 (9.1) (4.4, 16.1)	105	1 (1.0) (0.0, 5.2)	101	4 (4.0) (1.1, 9.8)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Pain at the injection site[e]										
Any	107	75 (70.1) (60.5, 78.6)	102	81 (79.4) (70.3, 86.8)	110	103 (93.6) (87.3, 97.4)	105	59 (56.2) (46.2, 65.9)	102	72 (70.6) (60.7, 79.2)
Mild	107	45 (42.1) (32.6, 52.0)	102	65 (63.7) (53.6, 73.0)	110	59 (53.6) (43.9, 63.2)	105	53 (50.5) (40.5, 60.4)	102	54 (52.9) (42.8, 62.9)
Moderate	107	29 (27.1) (19.0, 36.6)	102	16 (15.7) (9.2, 24.2)	110	44 (40.0) (30.8, 49.8)	105	6 (5.7) (2.1, 12.0)	102	18 (17.6) (10.8, 26.4)
Severe	107	1 (0.9) (0.0, 5.1)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	102	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	102	0 (0.0, 3.6)
Any local reaction[f]	107	75 (70.1) (60.5, 78.6)	102	85 (83.3) (74.7, 90.0)	110	103 (93.6) (87.3, 97.4)	105	60 (57.1) (47.1, 66.8)	102	73 (71.6) (61.8, 80.1)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. Reactions reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.

Note: Grade 4 reactions were classified by the investigator or medically qualified person.

a. N = number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.

b. n = Number of participants with the specified characteristic.

c. Exact 2-sided CI, based on the Clopper and Pearson method.

d. Mild: >2.0 to 5.0 cm; moderate: >5.0 to 10.0 cm; severe: >10.0 cm; Grade 4: necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).

e. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe pain at the injection site.

f. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

Source: p41 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 56. Onset Days for Local Reactions, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
Local Reaction	**30 µg**	**30 µg**	**60 µg**	**30 µg**	**60 µg**
Redness					
n[a]	6	6	12	3	7
Mean (SD)	1.7 (0.52)	2.5 (1.05)	2.4 (0.67)	2.7 (0.58)	2.7 (0.95)
Median	2.0	2.5	2.0	3.0	2.0
Min, max	(1, 2)	(1, 4)	(2, 4)	(2, 3)	(2, 4)
Swelling					
n[a]	8	7	17	2	9
Mean (SD)	1.5 (0.53)	2.0 (0.82)	2.1 (0.83)	2.0 (0.00)	1.9 (0.60)
Median	1.5	2.0	2.0	2.0	2.0
Min, max	(1, 2)	(1, 3)	(1, 5)	(2, 2)	(1, 3)
Pain at the injection site					
n[a]	75	81	103	59	72
Mean (SD)	1.5 (0.60)	1.5 (0.55)	1.4 (0.50)	1.7 (0.52)	1.6 (0.55)
Median	1.0	1.0	1.0	2.0	2.0
Min, max	(1, 4)	(1, 3)	(1, 3)	(1, 3)	(1, 3)
Any local reaction[b]					
n[a]	75	85	103	60	73
Mean (SD)	1.5 (0.60)	1.5 (0.57)	1.4 (0.50)	1.8 (0.54)	1.6 (0.62)
Median	1.0	1.0	1.0	2.0	2.0
Min, max	(1, 4)	(1, 3)	(1, 3)	(1, 3)	(1, 4)

Note: Day of onset is the first day the specified reaction was reported.
Note: Reactions reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis.
a. n = Number of participants reporting the specified reaction, with each participant counted only once per reaction.
b. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

Source: p56 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 57. Duration (Days) From First to Last Day of Local Reactions – Cohort 2 – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
Local Reaction	30 µg	30 µg	60 µg	30 µg	60 µg
Redness					
n[a]	6	6	12	3	7
Mean (SD)	2.5 (0.55)	1.5 (0.84)	2.6 (1.16)	2.0 (1.73)	1.9 (0.90)
Median	2.5	1.0	3.0	1.0	2.0
Min, max	(2, 3)	(1, 3)	(1, 4)	(1, 4)	(1, 3)
Swelling					
n[a]	8	7	17	2	9
Mean (SD)	1.9 (0.99)	1.4 (0.79)	2.1 (0.93)	1.5 (0.71)	1.7 (0.71)
Median	1.5	1.0	2.0	1.5	2.0
Min, max	(1, 3)	(1, 3)	(1, 4)	(1, 2)	(1, 3)
Pain at the injection site					
n[a]	75	81	103	59	72
Mean (SD)	2.4 (1.15)	2.4 (1.57)	2.6 (1.29)	1.7 (1.03)	2.3 (1.56)
Median	2.0	2.0	2.0	1.0	2.0
Min, max	(1, 5)	(1, 11)	(1, 6)	(1, 6)	(1, 9)

Note: Duration was calculated in days as the difference from the start of the first reported reaction to the resolution of the last reported reaction, inclusive.
Note: Reactions were recorded in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. Reactions reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis. The resolution date for reactions ongoing on the last day of e-diary completion was recorded on the participant's case report form.
a. n = Number of participants reporting the specified reaction on any of the 7 days.

Source: p58 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 58. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population (part 1)

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years			>55 Years				
	30 µg		30 µg		60 µg		30 µg		60 µg	
Systemic Event	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])
Fever										
Any	107	10 (9.3) (4.6, 16.5)	102	5 (4.9) (1.6, 11.1)	110	13 (11.8) (6.4, 19.4)	105	8 (7.6) (3.3, 14.5)	101	14 (13.9) (7.8, 22.2)
≥38.0°C to 38.4°C	107	7 (6.5) (2.7, 13.0)	102	2 (2.0) (0.2, 6.9)	110	8 (7.3) (3.2, 13.8)	105	6 (5.7) (2.1, 12.0)	101	8 (7.9) (3.5, 15.0)
>38.4°C to 38.9°C	107	2 (1.9) (0.2, 6.6)	102	3 (2.9) (0.6, 8.4)	110	3 (2.7) (0.6, 7.8)	105	2 (1.9) (0.2, 6.7)	101	4 (4.0) (1.1, 9.8)
>38.9°C to 40.0°C	107	1 (0.9) (0.0, 5.1)	102	0 (0.0, 3.6)	110	2 (1.8) (0.2, 6.4)	105	0 (0.0, 3.5)	101	2 (2.0) (0.2, 7.0)
>40.0°C	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Fatigue[d]										
Any	107	72 (67.3) (57.5, 76.0)	102	64 (62.7) (52.6, 72.1)	110	76 (69.1) (59.6, 77.6)	105	41 (39.0) (29.7, 49.1)	101	54 (53.5) (43.3, 63.5)
Mild	107	27 (25.2) (17.3, 34.6)	102	31 (30.4) (21.7, 40.3)	110	27 (24.5) (16.8, 33.7)	105	21 (20.0) (12.8, 28.9)	101	24 (23.8) (15.9, 33.3)
Moderate	107	45 (42.1) (32.6, 52.0)	102	31 (30.4) (21.7, 40.3)	110	48 (43.6) (34.2, 53.4)	105	19 (18.1) (11.3, 26.8)	101	26 (25.7) (17.6, 35.4)
Severe	107	0 (0.0, 3.4)	102	2 (2.0) (0.2, 6.9)	110	1 (0.9) (0.0, 5.0)	105	1 (1.0) (0.0, 5.2)	101	4 (4.0) (1.1, 9.8)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Headache[d]										
Any	107	54 (50.5) (40.6, 60.3)	102	45 (44.1) (34.3, 54.3)	110	50 (45.5) (35.9, 55.2)	105	31 (29.5) (21.0, 39.2)	101	36 (35.6) (26.4, 45.8)
Mild	107	28 (26.2) (18.1, 35.6)	102	33 (32.4) (23.4, 42.3)	110	30 (27.3) (19.2, 36.6)	105	23 (21.9) (14.4, 31.0)	101	21 (20.8) (13.4, 30.0)
Moderate	107	26 (24.3) (16.5, 33.5)	102	12 (11.8) (6.2, 19.6)	110	19 (17.3) (10.7, 25.7)	105	8 (7.6) (3.3, 14.5)	101	14 (13.9) (7.8, 22.2)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	1 (1.0) (0.0, 5.4)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Chills[d]										
Any	107	25 (23.4) (15.7, 32.5)	102	15 (14.7) (8.5, 23.1)	110	30 (27.3) (19.2, 36.6)	105	13 (12.4) (6.8, 20.2)	101	23 (22.8) (15.0, 32.2)
Mild	107	19 (17.8) (11.0, 26.3)	102	9 (8.8) (4.1, 16.1)	110	19 (17.3) (10.7, 25.7)	105	7 (6.7) (2.7, 13.3)	101	12 (11.9) (6.3, 19.8)
Moderate	107	6 (5.6) (2.1, 11.8)	102	6 (5.9) (2.2, 12.4)	110	10 (9.1) (4.4, 16.1)	105	6 (5.7) (2.1, 12.0)	101	11 (10.9) (5.6, 18.7)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the study vaccination.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.

Source: p59 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 59. Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population (part 2)

	Vaccine Group (as Administered)									
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)									
	12-17 Years		18-55 Years			>55 Years				
	30 µg		30 µg		60 µg		30 µg		60 µg	
Systemic Event	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])
Vomiting[e]										
Any	107	3 (2.8) (0.6, 8.0)	102	2 (2.0) (0.2, 6.9)	110	2 (1.8) (0.2, 6.4)	105	1 (1.0) (0.0, 5.2)	101	3 (3.0) (0.6, 8.4)
Mild	107	3 (2.8) (0.6, 8.0)	102	1 (1.0) (0.0, 5.3)	110	1 (0.9) (0.0, 5.0)	105	1 (1.0) (0.0, 5.2)	101	2 (2.0) (0.2, 7.0)
Moderate	107	0 (0.0, 3.4)	102	1 (1.0) (0.0, 5.3)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	1 (1.0) (0.0, 5.4)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Diarrhea[f]										
Any	107	7 (6.5) (2.7, 13.0)	102	14 (13.7) (7.7, 22.0)	110	14 (12.7) (7.1, 20.4)	105	9 (8.6) (4.0, 15.6)	101	7 (6.9) (2.8, 13.8)
Mild	107	7 (6.5) (2.7, 13.0)	102	10 (9.8) (4.8, 17.3)	110	13 (11.8) (6.4, 19.4)	105	9 (8.6) (4.0, 15.6)	101	6 (5.9) (2.2, 12.5)
Moderate	107	0 (0.0, 3.4)	102	3 (2.9) (0.6, 8.4)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	1 (1.0) (0.0, 5.4)
Severe	107	0 (0.0, 3.4)	102	1 (1.0) (0.0, 5.3)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
New or worsened muscle pain[d]										
Any	107	28 (26.2) (18.1, 35.6)	102	32 (31.4) (22.5, 41.3)	110	46 (41.8) (32.5, 51.6)	105	21 (20.0) (12.8, 28.9)	101	23 (22.8) (15.0, 32.2)
Mild	107	12 (11.2) (5.9, 18.8)	102	18 (17.6) (10.8, 26.4)	110	24 (21.8) (14.5, 30.7)	105	13 (12.4) (6.8, 20.2)	101	13 (12.9) (7.0, 21.0)
Moderate	107	16 (15.0) (8.8, 23.1)	102	14 (13.7) (7.7, 22.0)	110	21 (19.1) (12.2, 27.7)	105	8 (7.6) (3.3, 14.5)	101	9 (8.9) (4.2, 16.2)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	1 (1.0) (0.0, 5.4)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
New or worsened joint pain[d]										
Any	107	13 (12.1) (6.6, 19.9)	102	17 (16.7) (10.0, 25.3)	110	27 (24.5) (16.8, 33.7)	105	12 (11.4) (6.0, 19.1)	101	15 (14.9) (8.6, 23.3)
Mild	107	9 (8.4) (3.9, 15.4)	102	10 (9.8) (4.8, 17.3)	110	13 (11.8) (6.4, 19.4)	105	7 (6.7) (2.7, 13.3)	101	6 (5.9) (2.2, 12.5)
Moderate	107	4 (3.7) (1.0, 9.3)	102	7 (6.9) (2.8, 13.6)	110	13 (11.8) (6.4, 19.4)	105	5 (4.8) (1.6, 10.8)	101	8 (7.9) (3.5, 15.0)
Severe	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	1 (0.9) (0.0, 5.0)	105	0 (0.0, 3.5)	101	1 (1.0) (0.0, 5.4)
Grade 4	107	0 (0.0, 3.4)	102	0 (0.0, 3.6)	110	0 (0.0, 3.3)	105	0 (0.0, 3.5)	101	0 (0.0, 3.6)
Any systemic event[g]	107	86 (80.4) (71.6, 87.4)	102	77 (75.5) (66.0, 83.5)	110	90 (81.8) (73.3, 88.5)	105	59 (56.2) (46.2, 65.9)	101	64 (63.4) (53.2, 72.7)
Use of antipyretic or pain medication[h]	107	36 (33.6) (24.8, 43.4)	102	30 (29.4) (20.8, 39.3)	110	57 (51.8) (42.1, 61.4)	105	31 (29.5) (21.0, 39.2)	101	39 (38.6) (29.1, 48.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis; the severity of these events is based on the grading scale in the adverse event section of the case report form.
Note: Grade 4 events were classified by the investigator or medically qualified person.

a. N = number of participants reporting at least 1 yes or no response for the specified event after the study vaccination.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
g. Any systemic event: any fever, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
h. Severity was not collected for use of antipyretic or pain medication.

Source: p59 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 60. Onset Days for Systemic Events, Within 7 Days After the Study Vaccination – Cohort 2 – Safety Population

	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
Systemic Event	30 µg	30 µg	60 µg	30 µg	60 µg
Fever					
n[a]	10	5	13	8	14
Mean (SD)	1.9 (0.32)	2.0 (0.00)	2.1 (0.28)	2.4 (1.06)	1.9 (0.36)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 2)	(2, 2)	(2, 3)	(2, 5)	(1, 2)
Fatigue					
n[a]	72	64	76	41	54
Mean (SD)	1.7 (0.70)	1.8 (0.67)	1.7 (0.47)	2.0 (1.07)	1.9 (0.71)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 4)	(1, 5)	(1, 2)	(1, 7)	(1, 5)
Headache					
n[a]	54	45	50	31	36
Mean (SD)	2.2 (0.92)	1.9 (1.13)	2.0 (1.12)	2.0 (0.80)	2.1 (1.05)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 6)	(1, 7)	(1, 6)	(1, 5)	(1, 6)
Chills					
n[a]	25	15	30	13	23
Mean (SD)	2.1 (1.09)	2.5 (1.60)	2.1 (0.37)	2.1 (0.64)	1.9 (0.34)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 6)	(1, 7)	(2, 4)	(1, 4)	(1, 2)
Vomiting					
n[a]	3	2	2	1	3
Mean (SD)	3.7 (2.89)	3.0 (1.41)	3.0 (1.41)	2.0 (NE)	3.0 (1.73)
Median	2.0	3.0	3.0	2.0	2.0
Min, max	(2, 7)	(2, 4)	(2, 4)	(2, 2)	(2, 5)
Diarrhea					
n[a]	7	14	14	9	7
Mean (SD)	2.9 (1.35)	3.0 (1.80)	2.9 (1.49)	2.7 (1.22)	4.4 (1.72)
Median	3.0	2.0	2.5	2.0	4.0
Min, max	(1, 5)	(1, 6)	(1, 6)	(1, 5)	(2, 7)
New or worsened muscle pain					
n[a]	28	32	46	21	23
Mean (SD)	2.3 (0.90)	2.3 (1.08)	2.0 (0.86)	2.6 (1.47)	2.3 (1.02)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 5)	(1, 7)	(1, 6)	(1, 7)	(1, 6)
New or worsened joint pain					
n[a]	13	17	27	12	15
Mean (SD)	2.6 (1.33)	2.2 (1.47)	2.1 (0.87)	3.1 (1.83)	2.2 (0.77)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(2, 6)	(1, 7)	(1, 6)	(1, 7)	(2, 5)
Any systemic event[b]					
n[a]	86	77	90	59	64
Mean (SD)	1.8 (0.84)	1.7 (0.91)	1.7 (0.82)	2.1 (1.34)	2.0 (0.96)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 5)	(1, 7)	(1, 6)	(1, 7)	(1, 7)
Use of antipyretic or pain medication					
n[a]	36	30	57	31	39
Mean (SD)	2.0 (0.41)	2.0 (1.27)	2.1 (1.05)	2.3 (1.19)	2.1 (1.00)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	(1, 4)	(1, 7)	(1, 7)	(1, 7)	(1, 6)

Abbreviation: NE = not estimable.
Note: Day of onset is the first day the specified event was reported.
Note: Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis.
a. n = Number of participants reporting the specified event, with each participant counted only once per event.
b. Any systemic event: any fever, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.

Source: p88 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

Table 61. Duration (Days) From First to Last Day of Systemic Events – Cohort 2 – Safety Population

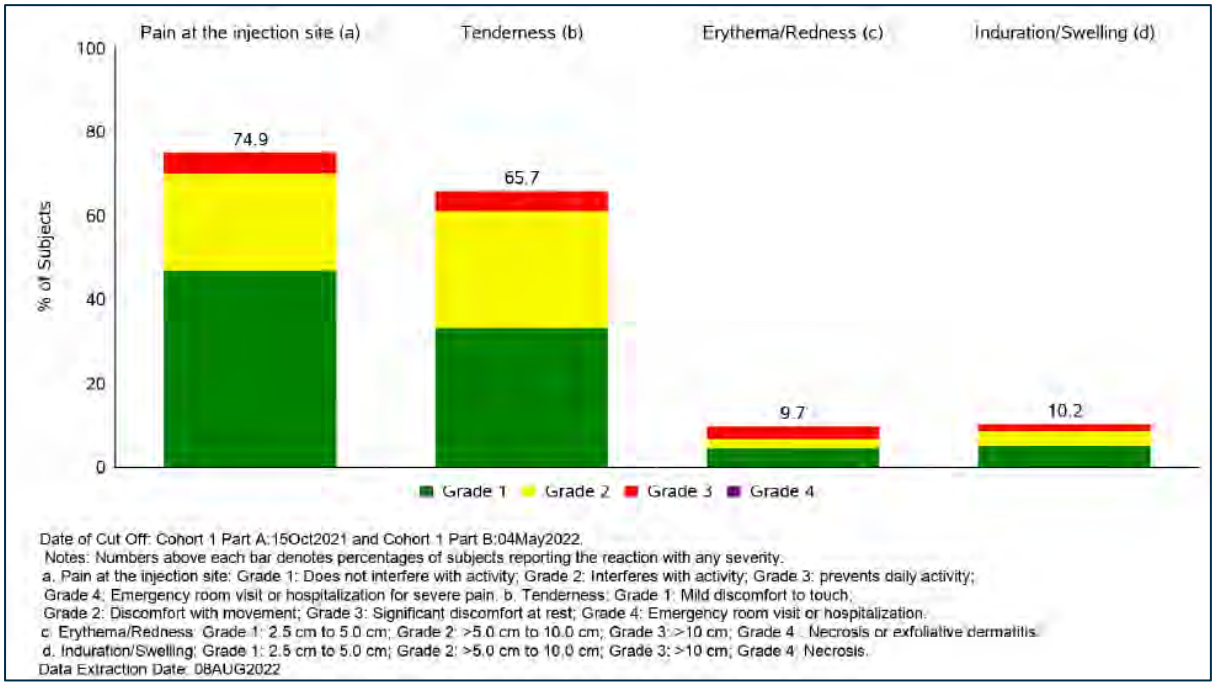
	Vaccine Group (as Administered)				
	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)				
	12-17 Years	18-55 Years		>55 Years	
Systemic Event	30 µg	30 µg	60 µg	30 µg	60 µg
Fever					
n[a]	10	5	13	8	14
Mean (SD)	1.1 (0.32)	1.0 (0.00)	1.0 (0.00)	1.1 (0.35)	1.1 (0.36)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 2)	(1, 1)	(1, 1)	(1, 2)	(1, 2)
Fatigue					
n[a]	72	64	76	41	54
Mean (SD)	2.3 (2.33)	2.3 (2.09)	2.3 (1.76)	2.4 (2.28)	2.1 (1.95)
Median	1.0	1.0	1.5	2.0	1.0
Min, max	(1, 14)	(1, 13)	(1, 7)	(1, 14)	(1, 8)
Headache					
n[a]	54	45	50	31	36
Mean (SD)	2.1 (1.75)	2.1 (1.69)	2.6 (2.08)	1.5 (0.89)	2.3 (2.20)
Median	1.0	1.0	2.0	1.0	2.0
Min, max	(1, 8)	(1, 7)	(1, 9)	(1, 4)	(1, 11)
Chills					
n[a]	25	15	30	13	23
Mean (SD)	1.5 (1.05)	1.6 (1.30)	1.3 (0.92)	1.2 (0.38)	1.5 (1.34)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 5)	(1, 6)	(1, 5)	(1, 2)	(1, 7)
Vomiting					
n[a]	3	2	2	1	3
Mean (SD)	1.0 (0.00)	1.5 (0.71)	1.5 (0.71)	1.0 (NE)	1.0 (0.00)
Median	1.0	1.5	1.5	1.0	1.0
Min, max	(1, 1)	(1, 2)	(1, 2)	(1, 1)	(1, 1)
Diarrhea					
n[a]	7	14	14	9	7
Mean (SD)	2.6 (2.82)	2.2 (2.04)	2.2 (1.63)	1.4 (1.01)	1.3 (0.49)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 8)	(1, 8)	(1, 5)	(1, 4)	(1, 2)
New or worsened muscle pain					
n[a]	28	32	46	21	23
Mean (SD)	1.3 (1.16)	1.7 (1.38)	1.2 (0.51)	1.7 (1.35)	1.0 (0.21)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 7)	(1, 6)	(1, 3)	(1, 5)	(1, 2)
New or worsened joint pain					
n[a]	13	17	27	12	15
Mean (SD)	1.5 (1.39)	1.2 (0.44)	1.3 (0.72)	3.4 (4.64)	1.1 (0.35)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 6)	(1, 2)	(1, 4)	(1, 14)	(1, 2)
Use of antipyretic or pain medication					
n[a]	36	30	57	31	39
Mean (SD)	1.7 (1.37)	2.0 (2.31)	1.8 (1.53)	1.6 (1.20)	1.9 (1.69)
Median	1.0	1.0	1.0	1.0	1.0
Min, max	(1, 6)	(1, 13)	(1, 7)	(1, 6)	(1, 9)

Abbreviation: NE = not estimable.
Note: Duration was calculated in days as the difference from the start of the first reported event to the resolution of the last reported event, inclusive.
Note: Events and use of antipyretic or pain medication were recorded in the electronic diary (e-diary) from Day 1 through Day 7 after the study vaccination. Events reported as adverse events in the case report form within 7 days after the study vaccination were also included in the analysis. The resolution date for events ongoing on the last day of e-diary completion was recorded on the participant's case report form.
a. n = Number of participants reporting the specified event on any of the 7 days.

Source: p88 of the C4591044_C2_1MPD_Full_Safety_Final_TLF_Bundle_22Nov22.pdf file

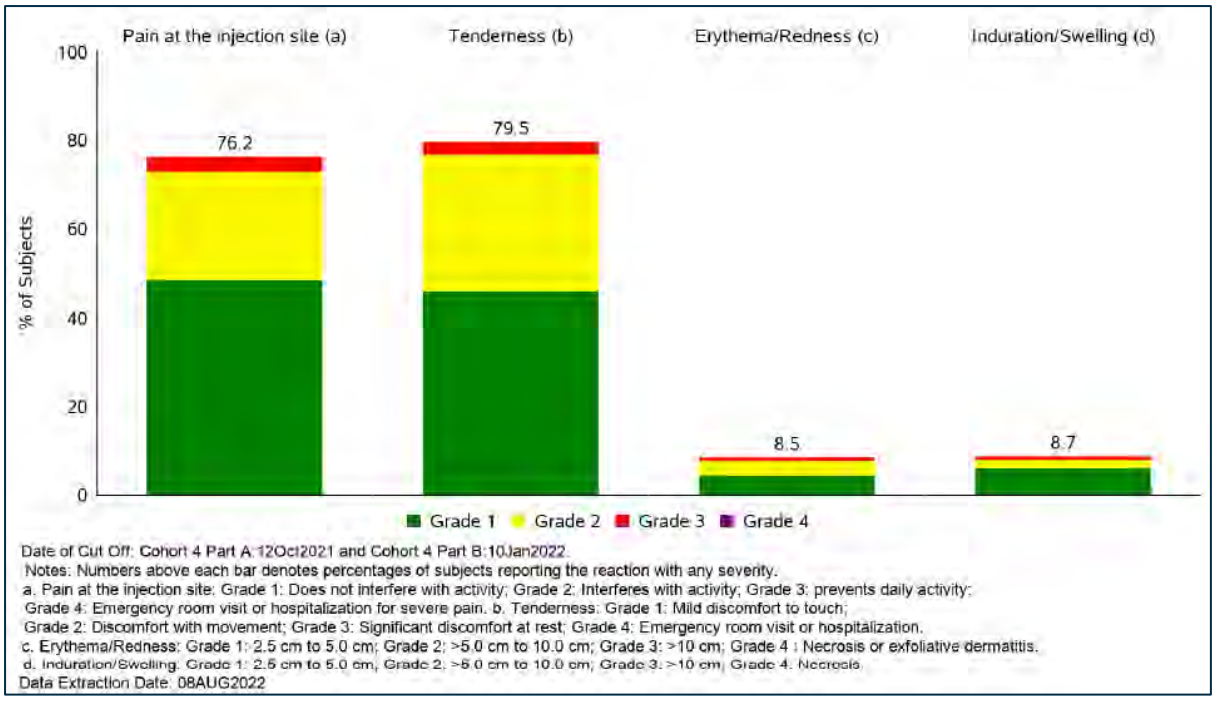
19.2.4. Study BNT162-17 – VoC safety data Alpha Delta

Figure 19. Local Reactions, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 1 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.1.7 + B.1.617.2) - Reactogenicity Set



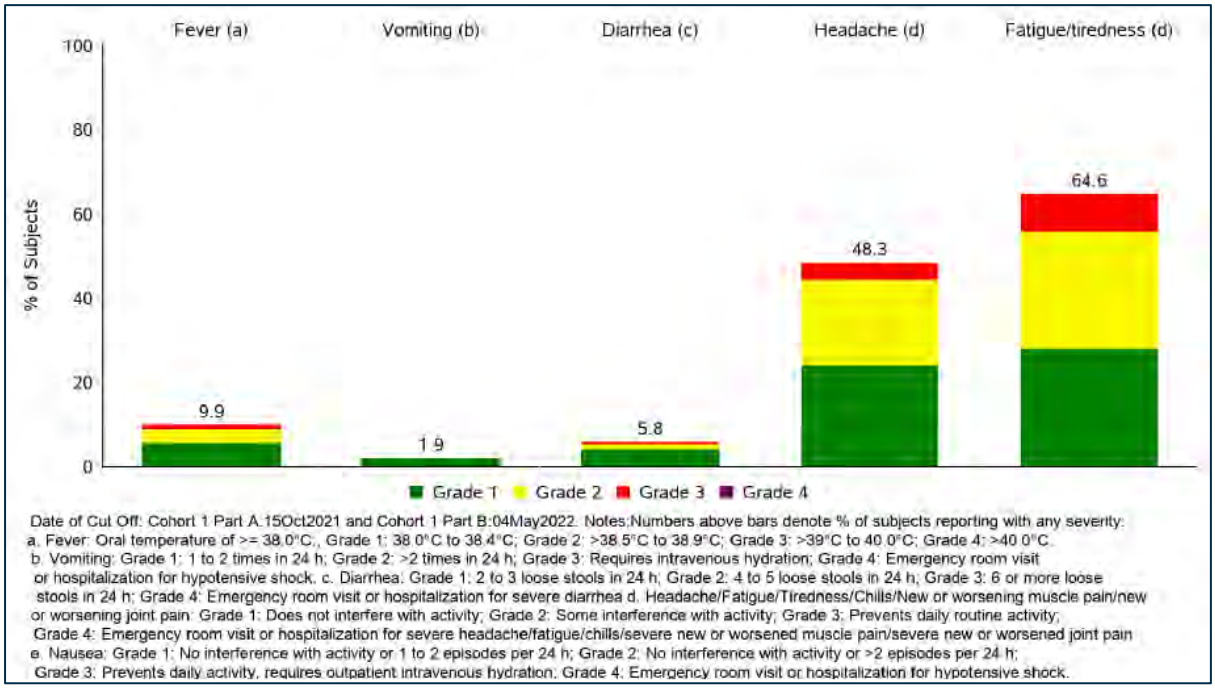
Source: Figure 1, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

Figure 20. Local Reactions, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.617.2) - Reactogenicity Set



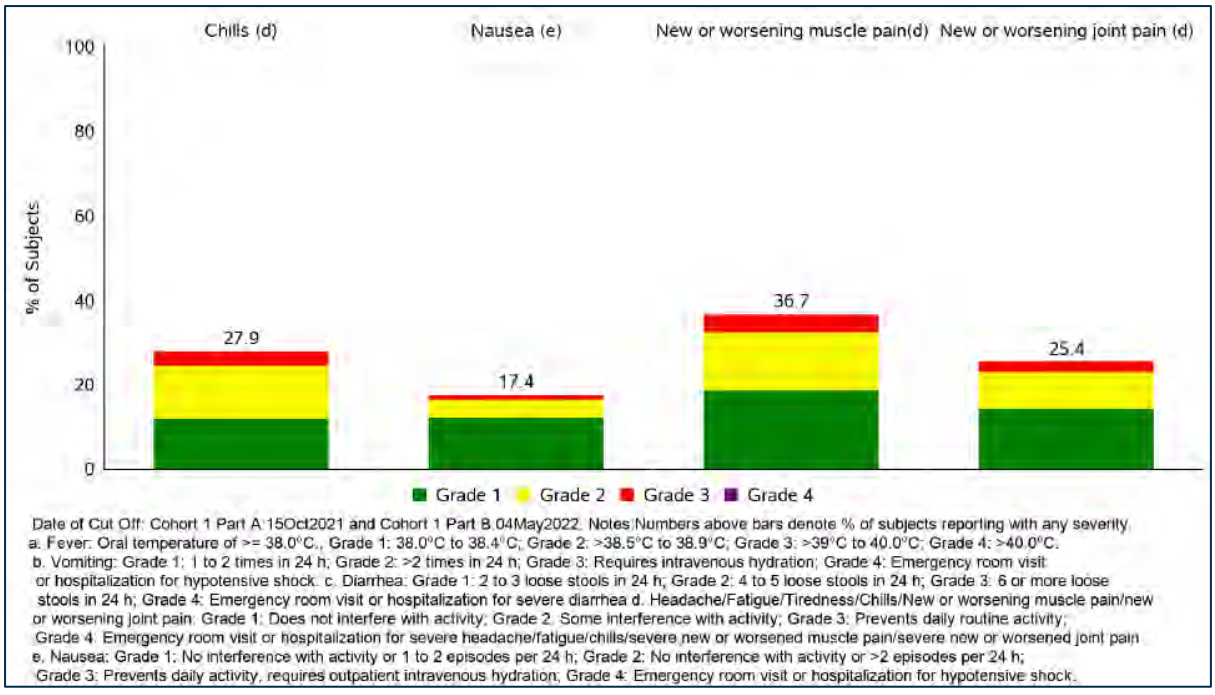
Source: Figure 2, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

Figure 21. Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 1 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.1.7 + B.1.617.2) - Reactogenicity Set – Part 1



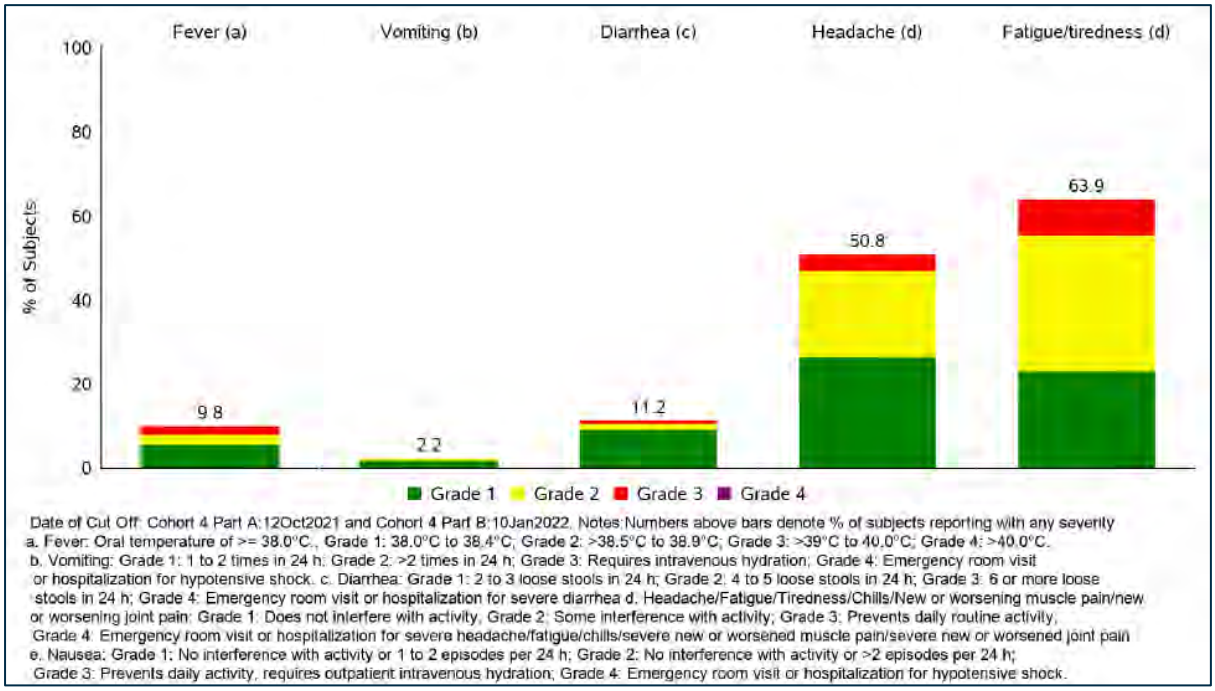
Source: Figure 3, Part 1, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

Figure 22. Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination- Cohort 1 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.1.7 + B.1.617.2) - Reactogenicity Set – Part 2



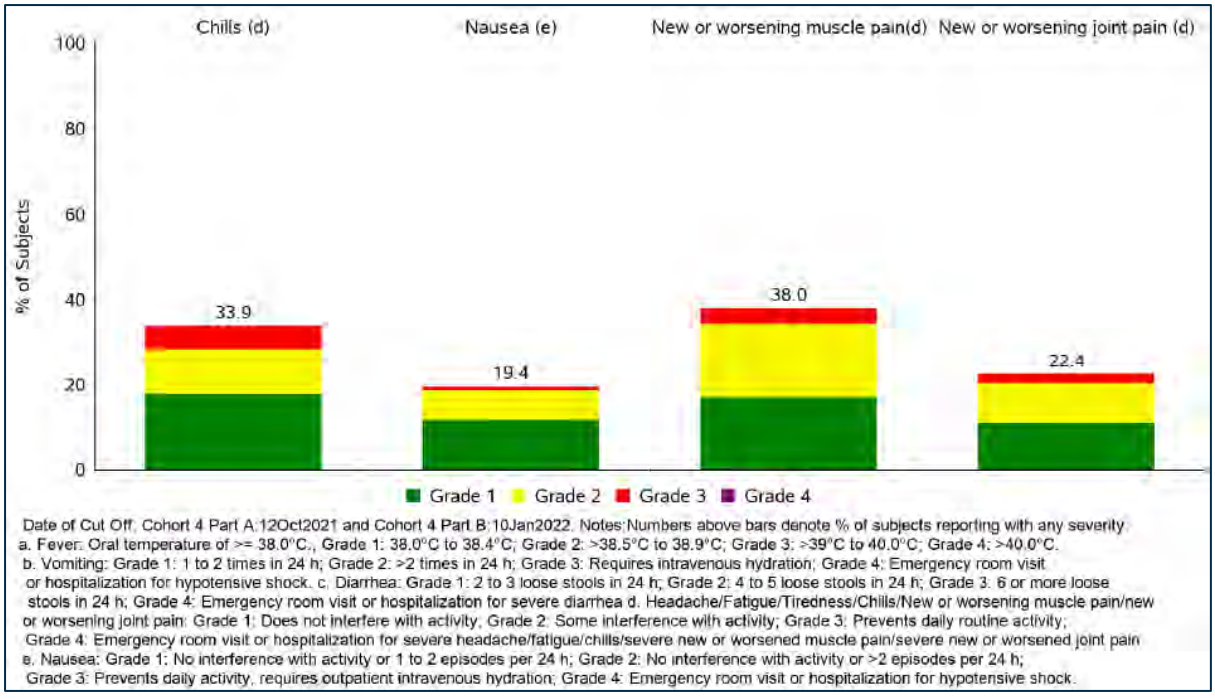
Source: Figure 3, Part 2, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

Figure 23. Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.617.2) - Reactogenicity Set – Part 1



Source: Figure 4, Part 1, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

Figure 24. Systemic Events, by Maximum Severity, Within 7 Days of Study Vaccination - Cohort 4 Participants 18 to 85 Years of Age (Part A and Part B: Booster Dose, Dose 3) - BNT162b2 (B.1.617.2) - Reactogenicity Set – Part 2



Source: Figure 4, Part 2, Clinical Overview – VOC Safety Summary (Alpha and Delta Variant).

19.2.5. Post-marketing surveillance of safety data

19.2.5.1. US CDC review of v-safe and VAERS safety data (31/08/2022 to 23/10/2022)

Table 62. Demographic and vaccination characteristics of persons aged ≥12 years* who reported receipt of a bivalent Pfizer-BioNTech or Moderna COVID-19 vaccine booster dose to v-safe† — United States, August 31–October 23, 2022

Characteristic	Vaccine, no. (%)		
	Pfizer-BioNTech n = 122,953	Moderna n = 89,006	Total N = 211,959
Sex			
Female	77,913 (63.4)	56,651 (63.7)	**134,564 (63.5)**
Male	44,031 (35.8)	31,697 (35.6)	**75,728 (35.7)**
Unknown	1,009 (0.8)	658 (0.7)	**1,667 (0.8)**
Age group, yrs			
12–17	1,464 (1.2)	NA	**1,464 (0.7)**
18–49	41,022 (33.4)	27,570 (31.0)	**68,592 (32.4)**
50–64	34,947 (28.4)	24,262 (27.3)	**59,209 (27.9)**
≥65	45,520 (37.0)	37,174 (41.8)	**82,694 (39.0)**
Ethnicity			
Hispanic	6,967 (5.7)	4,765 (5.4)	**11,732 (5.5)**
Non-Hispanic	112,895 (91.8)	82,009 (92.1)	**194,904 (92.0)**
Unknown	3,091 (2.5)	2,232 (2.5)	**5,323 (2.5)**
Race			
American Indian or Alaska Native	441 (0.4)	328 (0.4)	**769 (0.4)**
Asian	6,884 (5.6)	4,750 (5.3)	**11,634 (5.5)**
Black or African American	6,574 (5.4)	4,583 (5.2)	**11,157 (5.3)**
Native Hawaiian or other Pacific Islander	241 (0.2)	145 (0.2)	**386 (0.2)**
White	102,535 (83.4)	74,984 (84.3)	**177,519 (83.8)**
Multiracial	2,518 (2.1)	1,667 (1.9)	**4,185 (2.0)**
Other	1,873 (1.5)	1,262 (1.4)	**3,135 (1.5)**
Unknown	1,887 (1.5)	1,287 (1.5)	**3,174 (1.5)**
Total no. of COVID-19 vaccine doses received			
2	86 (0.1)	52 (0.1)	**138 (0.1)**
3	4,919 (4.0)	3,186 (3.6)	**8,105 (3.8)**
4	57,603 (46.9)	38,638 (43.4)	**96,241 (45.4)**
5	59,807 (48.6)	46,616 (52.4)	**106,423 (50.2)**
6	538 (0.4)	514 (0.6)	**1,052 (0.5)**
Vaccine co-administration§			
Yes	51,713 (42.1)	32,737 (36.8)	**84,450 (39.8)**
No	71,240 (57.9)	56,269 (63.2)	**127,509 (60.2)**

Abbreviation: NA = not applicable.

* On August 31, 2022, the Food and Drug Administration authorized bivalent formulations of Moderna and Pfizer-BioNTech COVID-19 vaccines for use as a single booster dose ≥2 months after completing primary or booster vaccination, Pfizer-BioNTech for persons aged ≥12 years and Moderna for persons aged ≥18 years. In v-safe, a bivalent booster dose was defined as an age-appropriate mRNA dose administered on or after August 31, 2022, for registrants who completed a primary series (2 doses of Pfizer-BioNTech, Moderna, or Novavax COVID-19 vaccine or 1 dose of Janssen).

† Includes registrants who completed at least one survey during days 0–7 postvaccination.

§ Other vaccines administered during the same visit.

Source: Table 1, US CDC's 'Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged =12 Years — United States, August 31–October 23, 2022'. See https://www.cdc.gov/mmwr/volumes/71/wr/mm7144a3.htm (accessed on 5/12/2022).

Table 63. Adverse reactions and health impacts reported to v-safe for persons aged ≥12 years* who received a bivalent Pfizer-BioNTech or Moderna COVID-19 vaccine booster dose — United States, August 31–October 23, 2022

	% Reporting reaction/health impact after vaccination, by age group, yrs†				
Event	12–17 n = 1,464	18–49 n = 68,592	50–64 n = 59,209	≥65 n = 82,694	Total N = 211,959
Any injection site reaction	**68.7**	**72.9**	**62.0**	**49.7**	**60.8**
Itching	4.6	8.9	7.8	6.9	7.8
Pain	66.9	70.5	58.8	45.0	57.3
Redness	8.5	10.8	9.1	7.6	9.1
Swelling or hardness	13.7	18.4	14.7	9.9	14.0
Any systemic reaction	**59.8**	**67.9**	**55.2**	**43.5**	**54.8**
Abdominal pain	6.4	5.5	3.6	2.1	3.6
Myalgia	33.6	41.3	29.0	20.3	29.6
Chills	19.6	20.6	13.7	9.1	14.2
Fatigue	45.2	53.1	40.0	30.0	40.4
Fever	26.3	23.7	16.6	10.2	16.4
Headache	36.3	42.8	31.5	19.7	30.6
Joint pain	14.5	21.7	16.8	11.1	16.1
Nausea	12.4	12.9	7.9	4.5	8.2
Diarrhea	3.0	6.7	5.4	3.8	5.2
Rash	1.4	1.3	1.1	0.9	1.1
Vomiting	2.5	1.2	0.6	0.4	0.7
Any health impact	**26.8**	**24.2**	**17.3**	**11.6**	**17.3**
Unable to perform normal daily activities	18.4	19.8	14.7	10.6	14.8
Unable to attend school or work	15.6	11.3	6.0	1.6	6.1
Needed medical care	1.2	0.9	0.7	0.8	0.8
Telehealth	0.2	0.3	0.2	0.2	0.3
Clinic	0.8	0.4	0.3	0.3	0.3
Emergency visit	0.1	0.1	0.1	0.1	0.1
Hospitalization	0	0	0	0	0

* On August 31, 2022, the Food and Drug Administration authorized bivalent formulations of Moderna and Pfizer-BioNTech COVID-19 vaccines for use as a single booster dose ≥2 months after completing primary or booster vaccination, Pfizer-BioNTech for persons aged ≥12 years and Moderna for adults aged ≥18 years. In v-safe, a bivalent booster was defined as an age-appropriate mRNA dose administered on or after August 31, 2022, for registrants who completed a primary series (2 doses of Pfizer-BioNTech, Moderna, or Novavax COVID-19 vaccine or 1 dose of Janssen).
† Percentage of registrants who reported a reaction or health impact at least once during days 0–7 postvaccination.

Source: Table 2, US CDC's 'Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged =12 Years — United States, August 31–October 23, 2022'. See https://www.cdc.gov/mmwr/volumes/71/wr/mm7144a3.htm (accessed on 5/12/2022).

Table 64. Events* reported to the Vaccine Adverse Event Reporting System for persons aged ≥12 years† after receipt of a bivalent Pfizer-BioNTech or Moderna COVID-19 vaccine booster dose — United States, August 31–October 23, 2022

Adverse events	Vaccine, no. reporting (%)		
	Pfizer-BioNTech	Moderna	Total§
Total	2,928	2,615	5,542
Vaccination errors¶	**877 (30.0)**	**1,037 (39.7)**	**1,913 (34.5)**
Error without adverse health event	717 (81.8)	972 (93.7)	1,688 (88.2)
Error with adverse health event**	160 (18.2)	65 (6.3)	225 (11.8)
Error with nonserious health event††	157 (17.9)	61 (5.9)	218 (11.4)
Error with serious health event	3 (0.3)	4 (0.4)	7 (0.4)
Nonserious reports§§,¶¶	**2,762 (94.3)**	**2,530 (96.8)**	**5,291 (95.5)**
Headache	343 (12.4)	285 (11.3)	628 (11.9)
Fatigue	318 (11.5)	257 (10.2)	575 (10.9)
Fever	299 (10.8)	262 (10.4)	561 (10.6)
Pain	293 (10.6)	231 (9.1)	524 (9.9)
Chills	254 (9.2)	205 (8.1)	459 (8.7)
Pain in extremity	209 (7.8)	167 (6.6)	376 (7.1)
Nausea	213 (7.7)	144 (5.7)	357 (6.8)
Dizziness	212 (7.7)	135 (5.3)	347 (6.6)
Injection site pain	138 (5.0)	121 (4.8)	259 (4.9)
COVID-19	169 (6.1)	89 (3.5)	258 (4.9)
Serious reports*,†††	**166 (5.7)**	**85 (3.3)**	**251 (4.5)**
Allergic reaction/Anaphylaxis	6	2	8
Appendicitis	4	1	5
Arrythmia	8	5	13
Atrial fibrillation	5	4	9
Atrioventricular node block, second or third degree	2	0	2
Supraventricular tachycardia	0	1	1
Other	1	0	1
COVID-19	14	6	20
Death§§§	27	9	36
Dyspnea	4	1	5
Fall	1	6	7
Guillain-Barré syndrome	2	0	2
Hypertension, acute	7	3	10
Pericarditis¶¶¶	1	3	4
Pneumonia	6	1	7
Seizure	6	0	6
Thrombotic event	20	11	31
Stroke or transient ischemic attack	12	5	17
Pulmonary embolism	5	5	10
Other	3	1	4
Chest pain, not otherwise specified	9	3	12
Myocardial infarction	5	3	8
Myocarditis****	3	2	5

Abbreviations: MedDRA PT = Medical Dictionary for Regulatory Activities preferred term; VAERS = Vaccine Adverse Event Reporting System.

* Signs and symptoms in VAERS reports are assigned MedDRA PTs by VAERS staff members. Each VAERS report might be assigned more than one MedDRA PT, which can include normal diagnostic findings. A MedDRA PT does not indicate a medically confirmed diagnosis.

† On August 31, 2022, the Food and Drug Administration authorized bivalent formulations of Moderna and Pfizer-BioNTech COVID-19 vaccines for use as a single booster dose ≥2 months after completing primary or booster vaccination, Pfizer-BioNTech for persons aged ≥12 years and Moderna for adults aged ≥18 years.

§ One report was for a person who received both Moderna and Pfizer-BioNTech bivalent booster doses at the same visit and did not experience an adverse health event.

¶ Vaccine administration or handling errors.

** The most common MedDRA PTs among reports of vaccination error included incorrect product formulation administered, incorrect dose administered, underdose, and wrong product administered.

†† Adverse health events coded for reports with nonserious vaccination errors included arthralgia, headache, injection site erythema, injection site swelling, fever, pain, and pain in extremity.

§§ Excluding vaccination error MedDRA PTs.

¶¶ Includes the top 10 most frequently coded MedDRA PTs among nonserious reports.

*** VAERS reports are classified as serious if any of the following are reported: hospitalization, prolongation of hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death. Serious reports to VAERS were reviewed by CDC physicians to form preliminary clinical impressions. https://www.meddra.org/how-to-use/basics/hierarchy

††† Because of the small number of serious reports, percentages are not provided for serious report events. Other clinical impressions included acute pancreatitis, acute respiratory failure, aneurysm, arm pain, arthralgia, aseptic meningitis, bilateral pleural effusion, cellulitis, chronic anemia, compression fracture, confusion, contact dermatitis, costochondritis, erythema nodosum, fever, glaucoma, hearing loss, leukocytoplastic vasculitis, lower extremity weakness, lymphadenopathy, migraine, myalgia, pancreatitis, pericardial and pleural effusions, pericardial tamponade, pylephlebitis, rhabdomyolysis, unspecified bradycardia, unspecified tachycardia, transverse myelitis, vertigo, and vision loss.

§§§ For reports of death, cause of death was available for four reports: cardiac arrest, dementia, metastatic prostate cancer, and myocardial infarction.

¶¶¶ All four reports of pericarditis have been verified by medical record review.

**** Three of the five reports of myocarditis have been verified by medical record review.

Source: Table 2, US CDC's 'Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged =12 Years — United States, August 31–October 23, 2022'. See https://www.cdc.gov/mmwr/volumes/71/wr/mm7144a3.htm (accessed on 5/12/2022).

19.2.6. First round comments on draft PI (clinical aspects)

Table 65. First round comments on draft PI and CMI (clinical aspects)

Section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). For the full list of excipients, see Section 6.1 List of excipients.
***Evaluator's comments*:** Typo, 'riltozinameran' should be replaced with 'famtozinameran'.
Section 4.2 Dose and method of administration / Dosage / Booster dose in individuals ***Booster dose in individuals 12 years of age and older*** A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older. COMIRNATY Original/Omicron BA.4-5 may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another COVID-19 vaccine. The decision when and for whom to implement a booster dose should be made based on available vaccine safety and immunogenicity data (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations.
***Evaluator's comments*:** The first 2 paragraphs are confusing and appear to present contradictory advice for the reasons discussed in section 1.5. **EvQset3**: The Evaluator is seeking clarification in the form of a rolling question (see section 12.1.1.3).
Section 4.4 Special warnings and precautions for use / General recommendations / *Myocarditis and pericarditis* The section of highlighted text that appears in the corresponding subsection of the PI for COMIRNATY Original/Omicron BA.1 (below) has been omitted from the proposed PI without any annotation.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. Cases have occurred following first and second vaccinations and following booster doses. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not exclusively in younger males. There have been reports in females. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis, including atypical presentations. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a booster dose of COMIRNATY or COMIRNATY Original/Omicron BA.1 has not yet been characterised.

For further details, please refer to the relevant clinical guidelines developed by the Australian Technical Advisory Group on Immunisation.

Evaluator's comments: The risks of myocarditis and pericarditis after a booster dose of COMIRNATY Original/Omicron BA.1 and COMIRNATY Original/Omicron BA.4-5 can be similarly characterised (see section 8.7.1) and these sections of the PI should be the same.

- Please insert a statement in the relevant section of the PI that says, 'The risks of myocarditis and pericarditis after a booster dose of COMIRNATY or COMIRNATY Original/Omicron BA.4-5 have not yet been characterised.

'Section 4.8 Adverse effects (undesirable effects) / Summary of safety profile / COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran) / ***Participants 12 years of age and older – after bivalent Omicron BA.4-5 booster dose***

The corresponding section of the PI for COMIRNATY Original/Omicron BA.1 includes two similar subsections to the one proposed below, based on the age groups > 55 YOA (n = 305) and 18-55 YOA (n = 315), and the frequencies of the commonest reactions is presented in the text. Presumably 2 subsections were chosen as the frequencies varied across age groups and this allowed frequencies for both age groups to be shown. The subsection below does not include the number of months post-Dose 3 and nor are the frequencies of reactions provided.

Participants 12 years of age and older – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591044 (Cohort 2), 316 individuals older than 12 years of age who had completed 3 doses of COMIRNATY, received a booster (fourth dose) of COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms) xx months after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after the COMIRNATY booster (third dose). The most frequent adverse reactions in participants older than 12 years of age were injection site pain, fatigue, headache, myalgia, chills and arthralgia. No new adverse reactions were identified for COMIRNATY Original/Omicron BA.4-5 .

COMIRNATY (tozinameran)

Commented [YCKM1]: Reference: BNT162b2 Bivalent (Wild Type/Omicron BA.4/BA.5) COVID-19 Vaccine - 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data - Study C4591044 Cohort 2 (November 2022) Section 2.3.1 and Table 7

Commented [YCKM2]: Reference: BNT162b2 Bivalent (Wild Type/Omicron BA.4/BA.5) COVID-19 Vaccine - 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data - Study C4591044 Cohort 2 (November 2022) Section 2.4 Table 15

Evaluator's comments: The missing data will need to be provided and cross-checked by the TGA prior to a final decision on provisional registration.

Section 4.8 Adverse effects (undesirable effects) / Summary of safety profile / COMIRNATY (tozinameran)

The subsection below does not appear in the PI for COMIRNATY Original/Omicron BA.1 (which is only approved for individuals ≥ 18 YOA); however, has been reinstated (verbatim) from the same section of the PI for COMIRNATY Original.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long term safety follow-up in Study C4591001, 2,260 adolescents (1,131 COMIRNATY 30 micrograms; 1,129 placebo) were 12 to 15 years of age. Of these, 1,559 adolescents (786 COMIRNATY and 773 placebo) have been followed for ≥ 4 months after the second dose of COMIRNATY. The safety evaluation in Study C4591001 is ongoing.

The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).

Evaluator's comments: This information is relevant to the proposed indication for COMIRNATY Original/Omicron BA.4/5, being for individuals ≥ 12 YOA rather than ≥ 18 YOA for COMIRNATY Original/Omicron BA.1.

- The Evaluator supports the addition of this subsection.

Section 4.8 Adverse effects (undesirable effects) / Tabulated list of adverse reactions from clinical studies / Table 2: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial: Individuals 12 years of age and older

The corresponding table of the PI for COMIRNATY Original/Omicron BA.1 (below) shows 'Myocarditis' and 'Pericarditis' listed on a row under the 'System organ class' of 'Nervous system disorders' [sic], with a frequency of 'Not known (cannot be estimated from the available data)'. It also lists both 'Nausea' (SOC = 'Gastrointestinal disorders') and 'Malaise' (SOC = 'General disorders and administration site conditions') with frequencies of 'Uncommon ≥ 1/1000 to < 1/100)'. Table 2 is accompanied by an explanatory footnote as highlighted below.

Table 2: Adverse reactions from COMIRNATY Original/Omicron BA.1 clinical trial: Individuals over 55 years of age

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Psychiatric disorders					
Metabolism and nutrition disorders	Headache				
Nervous system disorders					Myocarditis[a] Pericarditis[a]
Gastrointestinal disorders		Diarrhoea[a]; Vomiting[a]	Nausea		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills;	Pyrexia; Injection site swelling; Injection site redness	Malaise		

a. These adverse reactions were identified in the post-authorisation period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, pain in extremity and asthenia but are still considered adverse reactions.

Table 2 of the proposed PI for COMIRNATY Original/Omicron BA.4-5 does not list myocarditis, pericarditis, nausea or malaise, nor does it contain an explanatory footnote. The listed reactions are all highlighted in yellow.

Table 2: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial: Individuals 12 years of age and older

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Psychiatric disorders					
Metabolism and nutrition disorders	Headache				
Nervous system disorders					
Gastrointestinal disorders		Diarrhoea; Vomiting			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills;	Pyrexia; Injection site swelling; Injection site redness			

Commented [YCKM3]: Reference: BNT162b2 Bivalent (Wild Type/Omicron BA.4/BA.5) COVID-19 Vaccine - 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data - Study C4591044 Cohort 2 (November 2022) Section 2.3.3.2 & 2.4

Evaluator's comments: The approach taken to Table 2 in the PI for COMIRNATY Original/Omicron BA.1 appears to have been to list the very important AEs of myocarditis and pericarditis on the basis of their occurrence in the post-authorisation period and to include an explanatory footnote listing other important AEs that were seen in other COMIRNATY trials but not observed here. The Evaluator agrees with that general approach.

The Evaluator notes that **myocarditis and pericarditis** have already been observed in the post-authorisation period for COMIRNATY Original/Omicron BA.4-5 in the USA (see CDC data quoted

in section 8.7.1) and thinks they should be included in Table 2 of the proposed PI with the same footnote as for the COMIRNATY Original/Omicron BA.1 PI.

The Evaluator is unclear if the **yellow highlights** in Table 2 of the proposed PI indicate data still under review and/or uncertainty regarding different frequencies in different age groups. If there were differences across the age groups, then options would be to include 3 tables (potentially cumbersome) **or** to keep one table that lists the highest frequency seen in one of the 3 age groups with an accompanying footnote that gives the different frequency in the other age group(s). The Evaluator would be satisfied with either option.

- Please add 'Myocarditis' and 'Pericarditis' to Table 2 under an SOC of 'Cardiac disorders' with a frequency of 'Not known (cannot be estimated from the available data)' with an accompanying footnote that reads, 'These adverse reactions were identified in the post-authorisation period.'
- Please clarify the reason for the yellow highlights in Table 2.
- If the frequencies of some reactions very between age groups 12-17, 18-55 and > 55 YOA, then please consider presenting the individual AEs using one of the 2 options proposed above.
- Please include an explanatory statement as a footnote to Table 2 that lists those reactions observed in other COMIRNATY studies (but not listed here) that begins, 'At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591044 Cohort 2: xxx, xxx, etc.'
- Please remove any empty rows from Table 2 (e.g. 'Psychiatric disorders' and 'Nervous system disorders').

Section 5. PHARMACOLOGICAL PROPERTIES / 5.1 Pharmacodynamic properties / Clinical trials / Immunogenicity / COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran) / *Relative vaccine immunogenicity in participants 12 years of age and older – after bivalent Omicron BA.4-5 (second booster dose)*

The proposed text and Tables 4 and 5 in this section are a template awaiting insertion of the relevant data, which begins with an annotation as follows:

COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran)

Relative vaccine immunogenicity in participants 12 years of age and older – after bivalent Omicron BA.4-5 (second booster dose)

In an interim analysis of a subset from Study C4591044 (Cohort 2), xxx individuals 12 years of age and older who had completed a series of 3 doses of COMIRNATY received 1 of the following as a booster dose (fourth dose): COMIRNATY (30 micrograms) or COMIRNATY Original/Omicron BA.4-5 (15/15micrograms). GMRs and seroresponse rates were evaluated at 1 month after COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms) booster vaccination up to a data cut-off date of xxxx, which represents a median of xx months post-booster follow-up. The COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms) booster dose was administered xxx to xxx months (median xxx months) after the third dose.

Commented [YCKM4]: To be update when immunogenicity date with full evaluable immunogenicity population of Cohort 2 becomes available.

BNT162b2 Bivalent (Wild Type/Omicron BA.4/BA.5) COVID-19 Vaccine - 1 Month Post Dose Safety and Immunogenicity (Sentinel) Data - Study C4591044 Cohort 2 (November 2022)
Section 2.1.1 & 2.1.2 provides data forsubset of Cohort 2 (18-55, >55yo)

Evaluator's comments: The Evaluator notes this section is extensive but incomplete for the reasons stated in comment YCKM4.

- The missing data will need to be provided and cross-checked by the TGA prior to a final decision on provisional registration.

Section 5. PHARMACOLOGICAL PROPERTIES / 5.1 Pharmacodynamic properties / Clinical trials / Immunogenicity / COMIRNATY (tozinameran) / *Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses*

This subsection (including text and Table 9) does not appear in the PI for COMIRNATY Original/Omicron BA.1 (which is only approved for individuals ≥ 18 YOA); however, has been reinstated (verbatim) from the same section of the PI for COMIRNATY Original.

Evaluator's comments: This information is relevant to the proposed indication for COMIRNATY Original/Omicron BA.4/5, being for individuals ≥ 12 YOA rather than ≥ 18 YOA for COMIRNATY Original/Omicron BA.1.

- The Evaluator supports the addition of this subsection.

Minor editorial changes

Comparing the proposed PI to the currently approved PI for COMIRNATY Original/Omicron BA.1, there are several recurring MECs that result from:

- Use of 'Omicron BA.4-5' rather than 'Omicron BA.1'.
- Famtozinameran rather than riltozinameran.
- Age group ≥ 12 YOA rather than ≥ 18 YOA.

Evaluator's comments:

- The Evaluator supports all of the MECs listed above.

Notes: The Evaluator compared the proposed PI for COMIRNATY Original/Omicron BA.4-5 (Version: proposed-pi-BA.4/5) to the existing PI for COMIRNATY Original/Omicron BA.1 (Version: pfpcodii11122, dated 14/11/2022) and the existing PI for COMIRNATY Original (Version: pfpcobii11122, dated 14/11/2022).

19.2.7. Study C4591044 Cohort 2 – participants 12-17 years of age

Table 66. Demographic Characteristics – Study C4591044 Cohort 2 and Study C4591031 Substudy E Expanded Cohort – Participants With or Without Evidence of Infection up to 1 Month After Study Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)								
	C4591044 BNT162b2 Bivalent (WT/OMI BA.4/BA.5)					C4591031 BNT162b2 Bivalent (WT/OMI BA.1)			
	12-17 Years	18-55 Years		>55 Years		18-55 Years		>55 Years	
	30 µg (N[a]=105) n[b] (%)	30 µg (N[a]=95) n[b] (%)	60 µg (N[a]=102) n[b] (%)	30 µg (N[a]=102) n[b] (%)	60 µg (N[a]=99) n[b] (%)	30 µg (N[a]=100) n[b] (%)	60 µg (N[a]=100) n[b] (%)	30 µg (N[a]=100) n[b] (%)	60 µg (N[a]=100) n[b] (%)
Sex									
Male	58 (55.2)	40 (42.1)	41 (40.2)	62 (60.8)	45 (45.5)	51 (51.0)	58 (58.0)	57 (57.0)	53 (53.0)
Female	47 (44.8)	55 (57.9)	61 (59.8)	40 (39.2)	54 (54.5)	49 (49.0)	42 (42.0)	43 (43.0)	47 (47.0)
Race									
White	89 (84.8)	75 (78.9)	83 (81.4)	80 (78.4)	89 (89.9)	77 (77.0)	86 (86.0)	89 (89.0)	83 (83.0)
Black or African American	9 (8.6)	9 (9.5)	11 (10.8)	16 (15.7)	8 (8.1)	7 (7.0)	7 (7.0)	7 (7.0)	11 (11.0)
American Indian or Alaska Native	0	0	0	1 (1.0)	0	0	0	0	0
Asian	3 (2.9)	9 (9.5)	8 (7.8)	3 (2.9)	2 (2.0)	14 (14.0)	4 (4.0)	4 (4.0)	5 (5.0)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1.0)	0	2 (2.0)	1 (1.0)	0	0
Multiracial	3 (2.9)	2 (2.1)	0	1 (1.0)	0	0	2 (2.0)	0	1 (1.0)
Not reported	1 (1.0)	0	0	0	0	0	0	0	0
Ethnicity									
Hispanic/Latino	7 (6.7)	12 (12.6)	13 (12.7)	10 (9.8)	11 (11.1)	11 (11.0)	23 (23.0)	18 (18.0)	21 (21.0)
Non-Hispanic/non-Latino	96 (91.4)	82 (86.3)	88 (86.3)	92 (90.2)	85 (85.9)	89 (89.0)	77 (77.0)	82 (82.0)	79 (79.0)
Not reported	2 (1.9)	1 (1.1)	1 (1.0)	0	3 (3.0)	0	0	0	0
Age at vaccination (years)									
Mean (SD)	15.1 (1.39)	39.4 (9.07)	40.2 (9.87)	65.6 (6.21)	63.7 (6.12)	41.2 (9.17)	39.3 (10.43)	67.0 (6.69)	67.3 (7.25)
Median	15.0	40.0	41.0	65.0	63.0	42.0	39.5	66.0	67.0
Min, max	(12, 17)	(19, 55)	(18, 55)	(56, 79)	(56, 85)	(22, 55)	(18, 55)	(56, 85)	(56, 86)
Baseline SARS-CoV-2 status									
Positive[c]	79 (75.2)	62 (65.3)	75 (73.5)	62 (60.8)	67 (67.7)	33 (33.0)	70 (70.0)	36 (36.0)	35 (35.0)
Negative[d]	26 (24.8)	33 (34.7)	27 (26.5)	40 (39.2)	32 (32.3)	67 (67.0)	30 (30.0)	64 (64.0)	65 (65.0)
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (months[e])									
n	105	95	102	102	99	100	100	100	100
Mean (SD)	8.3 (1.24)	10.4 (1.61)	10.5 (1.27)	10.6 (1.26)	10.7 (1.27)	8.8 (1.60)	8.9 (1.56)	7.0 (1.79)	6.9 (1.57)
Median	8.4	10.9	10.8	10.9	10.9	8.6	8.5	6.3	6.3
Min, max	(5.6, 12.0)	(5.5, 12.8)	(6.6, 13.0)	(5.5, 12.9)	(6.6, 13.0)	(5.6, 13.0)	(5.4, 12.3)	(4.7, 11.5)	(5.4, 11.1)
<5 Months	0	0	0	0	0	0	0	1 (1.0)	0
≥5 to <7 Months	11 (10.5)	5 (5.3)	3 (2.9)	1 (1.0)	1 (1.0)	11 (11.0)	5 (5.0)	73 (73.0)	73 (73.0)
≥7 to <9 Months	77 (73.3)	12 (12.6)	9 (8.8)	9 (8.8)	10 (10.1)	55 (55.0)	64 (64.0)	10 (10.0)	12 (12.0)
≥9 to ≤12 Months	17 (16.2)	71 (74.7)	87 (85.3)	87 (85.3)	79 (79.8)	31 (31.0)	29 (29.0)	16 (16.0)	15 (15.0)
>12 Months	0	7 (7.4)	3 (2.9)	5 (4.9)	9 (9.1)	3 (3.0)	2 (2.0)	0	0
Time from the last dose of BNT162b2 (received prior to the study) to the study vaccination (days)									
n	105	95	102	102	99	100	100	100	100
Mean (SD)	233.4 (34.60)	290.9 (45.00)	295.1 (35.61)	296.4 (35.36)	298.3 (35.51)	246.1 (44.88)	248.7 (43.68)	196.3 (50.12)	194.0 (44.04)
Median	234.0	305.0	302.0	306.0	306.0	239.5	239.0	175.5	175.0
Min, max	(157, 335)	(155, 357)	(184, 364)	(153, 362)	(184, 363)	(158, 365)	(151, 343)	(131, 322)	(150, 312)
<150 Days	0	0	0	0	0	0	0	4 (4.0)	0
150-209 Days	17 (16.2)	7 (7.4)	3 (2.9)	3 (2.9)	3 (3.0)	17 (17.0)	14 (14.0)	72 (72.0)	74 (74.0)
210-269 Days	77 (73.3)	18 (18.9)	21 (20.6)	19 (18.6)	20 (20.2)	65 (65.0)	66 (66.0)	10 (10.0)	16 (16.0)
270-365 Days	11 (10.5)	70 (73.7)	78 (76.5)	80 (78.4)	76 (76.8)	18 (18.0)	20 (20.0)	14 (14.0)	10 (10.0)
Body mass index (BMI)									
Number of participants ≥16 years of age[f]	44	95	102	102	99	100	100	100	100
Underweight (<18.5 kg/m^2)	5 (11.4)	1 (1.1)	6 (5.9)	3 (2.9)	1 (1.0)	1 (1.0)	2 (2.0)	0	0
Normal weight (≥18.5-24.9 kg/m^2)	28 (63.6)	38 (40.0)	23 (22.5)	27 (26.5)	22 (22.2)	20 (20.0)	27 (27.0)	22 (22.0)	23 (23.0)
Overweight (≥25.0-29.9 kg/m^2)	8 (18.2)	32 (33.7)	31 (30.4)	33 (32.4)	41 (41.4)	31 (31.0)	30 (30.0)	42 (42.0)	41 (41.0)
Obese (≥30.0 kg/m^2)	3 (6.8)	24 (25.3)	42 (41.2)	39 (38.2)	35 (35.4)	48 (48.0)	41 (41.0)	36 (36.0)	36 (36.0)
Body mass index (BMI) 12-15 years of age/Obese[g]									
Number of participants 12-15 years of age[f]	61	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yes	6 (9.8)								
No	55 (90.2)								

Abbreviations: N/A = not applicable; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All participants enrolled in Study C4591044 Cohort 2 and subsets of approximately 100 participants selected from each age group (18-55 years, >55 years) and dose group (BNT162b2 Bivalent (WT/OMI BA.1) 30-µg and 60-µg group) of Study C4591031 Substudy E expanded cohort were included in the analysis.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations except for BMI.
b. n = Number of participants with the specified characteristic.
c. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
d. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
e. Month was calculated as 28 days.
f. This value is the denominator for the percentage calculations for BMI.
g. For participants 12 through 15 years of age, obesity is defined as a BMI at or above the 95th percentile from the growth chart. Refer to the CDC growth charts at

Source: Table 1, Study C4591044 Cohort 2 Group 1 (Participants 12-17 Years) 1MPD_Immunogenicity Data (15/01/2023).

20. Attachment: additional evaluation material

Not applicable.

21. Information about the evaluator

Not applicable (internal TGA evaluation).

Appendix: study summary and commentary

Not applicable.

Therapeutic Goods Administration

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Nonclinical Evaluation Report

Tozinameran/famtozinameran

[COMIRNATY BIVALENT ORIGINAL/OMICRON BA.4-5]

Submission No: PM-2022-05306-1-2
Sponsor: Pfizer Australia Pty Ltd

December 2022

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New vaccine

Sponsor: Pfizer Australia Pty Ltd

Generic name: **Tozinameran/famtozinameran**

Trade name: **COMIRNATY BIVALENT ORIGINAL/OMICRON BA.4-5 COVID-19 VACCINE**

Dose form and strength: Injection, Suspension; 15/15 µg in 0.3 mL

Drug class: mRNA encapsulated in LNP

Submission No: PM-2022-05306-1-2

Tox file No: E22-636157

TRIM reference: D22-6240013

Date authorised: 22 December 2022

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

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SUMMARY

- Pfizer Australia Pty Ltd has applied for provisional approval of a new bivalent COVID-19 vaccine containing tozinameran and famtozinameran (COMIRNATY ORIGINAL/OMICRON BA.4-5) in lipid nanoparticles (LNP). The Omicron BA.4-5 bivalent vaccine is indicated as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The vaccine dose is 30 µg of mRNA/0.3 mL (15 µg of each mRNA) given intramuscularly (IM) at least 5 months after the completion of COVID-19 vaccine primary series.

- mRNA of the Omicron BA.4-5 variant is manufactured using the same processes as for the original monovalent vaccine (BNT162b2) followed by combining the Omicron BA.4-5 variant mRNA with BNT162b2 mRNA in equal amounts (15 µg each) prior to lipid nanoparticle formation.

- Module 4 comprised of a pharmacology study in mice comparing the immunogenicity of the Omicron BA.4-5 monovalent and the original/Omicron BA.4-5 bivalent vaccines against the Wuhan strain and Omicron BA.1, BA.2 and BA.4-5 and Delta either as part of the primary series of immunisation or as boosters following the primary series of immunisation with the original vaccine (*Study VR-VTR-10976*). To compare immune responses elicited by the original, Omicron BA.1 and Omicron BA.4/BA.5 variant-modified vaccine candidates, mouse sera from the study with the Omicron BA.1 bivalent vaccine (*Study VR-VTR-10944*; Submission PM-2022-03551-1-2) were also tested concurrently with 1 month post third dose sera from the new study in the same pseudovirus neutralisation assay runs. The following summary is based on the Health Canada evaluation report (Appendix 1) and the TGA evaluator's review of immunogenicity data 1 month after the 3rd (booster) dose.

- The original/Omicron BA.4-5 bivalent vaccine as a booster dose after two primary series of the original vaccine (BNT162b2) induced cross-variant neutralisation against the original Wuhan strain, Delta and Omicron lineages BA.1, BA.2, BA.2.12.1 and BA.4-5. Both the BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising antibody (NAb) titres agaisnt all Omicron sublineages tested than the original monovalent vaccine, and higher NAb titres against BA.4-5 than the original/BA.1 bivalent vaccine. Interestingly, NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine than the BA.4-5 monovalent vaccine (see comparison table below), possibly related to the lower BA.4-5 mRNA dose in the bivalent vaccine. The findings suggest that the BA.4-5 monovalent (0.5 µg) could be more effective than the Original/BA.4-5 bivalent vaccine (0.25 + 0.25 µg) in preventing COVID-19 disease caused by Omicron variants (BA.2, BA.4-5).

Neutralising antibody (NAb) titres 1 month after a booster dose of monovalent or bivalent vaccine formulations following a primary series of immunisation with the original vaccine

Vaccines	Variants					
	Wuhan	Delta	BA.1	BA.2	BA2.12.1	BA.4-5
NAb Titre						
Original	70546	17911	1308	1378	973	603
BA.1 monovalent	21998	8454	7575	7030	404	1136
Original/B.1 bivalent	65839	28865	3366	16677	10385	15522
BA.4-5 monovalent	65839	28865	3366	16677	10385	15522
Original/BA.4-5 bivalent	34457	13291	3537	5391	4294	5446
NAb titre ratio						
BA.1 monovalent : Original	0.31	0.47	5.8	5.1	4.2	1.9
Original/BA.1 bivalent : BA.1 monovalent	3.0	2.3	1.0	1.4	1.1	1.1
BA.4-5 monovalent : Original	0.93	1.6	2.6	12	11	26
Original/BA.4-5 bivalent : Original	0.49	0.74	2.7	3.9	4.4	9.0
Original/BA.4-5 bivalent : BA.4-5 monovalent	0.52	0.46	1.1	0.32	0.41	0.35

- Overall, the Original/Omicron BA.4-5 bivalent vaccine as a booster dose induced broader immunogenic responses than the original monovalent vaccine. However, NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine (0.25 + 0.25 μg) than the BA.4-5 monovalent vaccine (0.5 μg).
- There were no protection studies for the Original/Omicron BA.4-5 bivalent vaccine. No toxicity studies on the bivalent vaccine were submitted. This is acceptable since the new mRNA (famtozinameran) uses the same backbone and manufacture platform as tozinameran and there are no changes to vaccine formulation except for the additional mRNA.

CONCLUSIONS AND RECOMMENDATION

- The original/Omicron BA.4-5 bivalent vaccine as a booster dose was immunogenic in mice and induced significantly higher neutralising antibodies against Omicron sublineages than the original monovalent vaccine. However, NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine (0.25 + 0.25 μg) than the BA.4-5 monovalent vaccine (0.5 μg), suggesting that BA.4-5 monovalent vaccine could be a better vaccine candidate against Omicron variants, BA.2 and BA.4-5.
- There are no nonclinical objections to the provisional approval of the original/Omicron BA.4-5 bivalent vaccine.
- The proposed Product Information document accompanying the sponsor's letter of 15 December is acceptable from a nonclinical perspective.
- The Sponsor is requested to provide cellular immunity data of the mouse study when available.

APPENDIX 1 EVALUATION OF NONCLINICAL DATA

The following is based on the Health Canada evaluation (D22-6141024), plus 1 month post dose 3 data, which were not reviewed in the HC report.

PRIMARY PHARMACODYNAMICS

VR-VTR-10976 (PRL-COVID-Ms-2022-06) - Study Report

The objective of this study is to evaluate the immunogenicity and breadth of coverage of BNT162b2 BA.4/BA.5 vaccines as either monovalent or bivalent (1:1 mixture of BNT162b2 and BNT162b2 BA.4/BA.5) formulations in both naïve and BNT162b2-experienced mice.

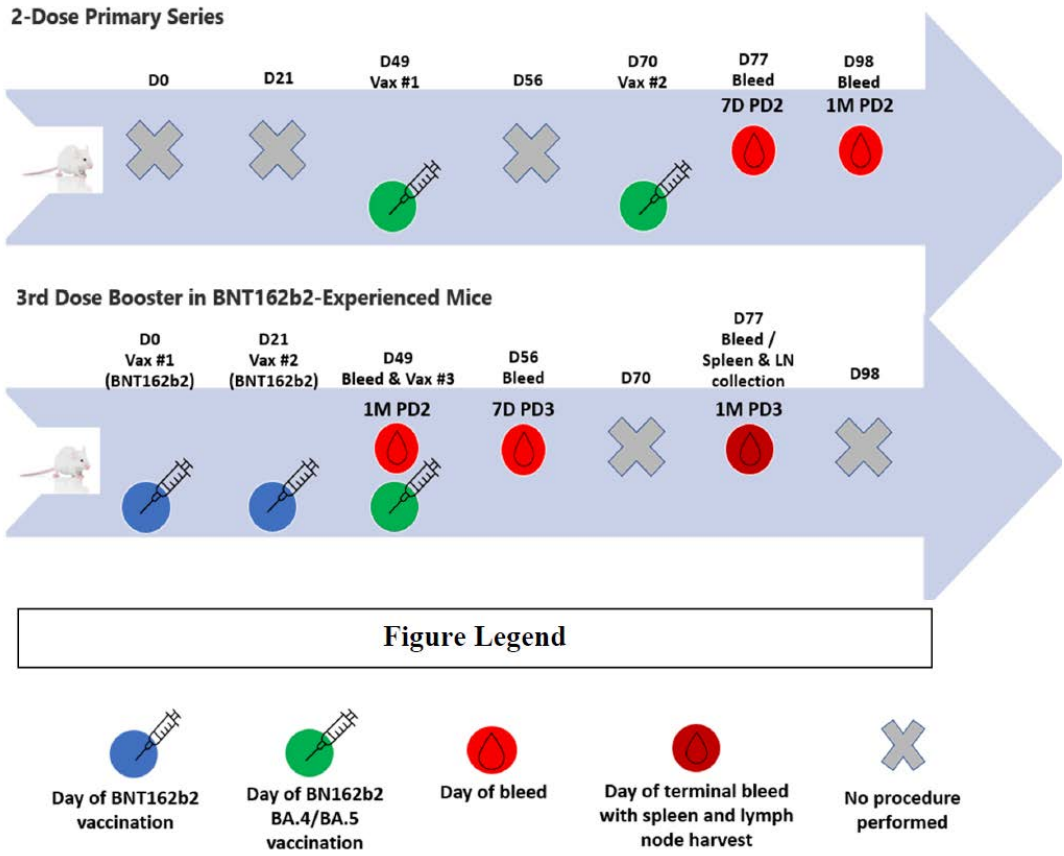
Rationale:

BNT162b2 encodes the full-length SARS-CoV-2 spike glycoprotein in a prefusion conformation and has been highly effective against COVID-19; however, as new SARS-CoV-2 variants of concern (VOCs) emerge, variant-modified vaccines may serve to optimally protect against current and future variants. The mutations of the Omicron BA.4/BA.5 variant were applied to BNT162b2 to generate an Omicron BA.4/BA.5 variant-modified vaccine (BNT162b2 BA.4/BA.5) that was evaluated in mice as both a monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5). formulation. The modRNAs are encapsulated into lipid nanoparticles (LNPs) to protect the modRNA from degradation and to enable delivery of the RNA into host cells after intramuscular (IM) injection.

Study Design:

To assess the impact of a variant-modified BNT162b2 BA.4/BA.5 vaccine on the immune response as a 3rd dose booster, BNT162b2-experienced mice received a booster with either a monovalent or bivalent BA.4/BA.5 vaccine one month after receiving the second dose of BNT162b2 (as part of the standard two-dose series given at Day 0 and Day 21). Sera was collected at multiple time points for evaluation of the neutralising antibody response against the reference strain and Omicron sublineages. Immunogenicity of a 2-dose primary series of the monovalent and bivalent BA.4/BA.5 vaccines was also evaluated in a cohort of naïve mice.

Figure 1. Study design timeline



***Study design*:**

	Group #	N	Vax (Day 0) (µg)	Vax (Day 21) (µg)	Vax (Day 49) (µg)	Vax (Day 70) (µg)	Vaccination (Day of Study)	Bleed (Day of Study)	Tissue harvest
Neg Control	1	5 / 5	X	X	Saline	Saline	49, 70	77 (7DPD2)[a] 98 (1MPD2)	Spleen and LN @ D77 (n=5)
Two dose primary series cohort	2	10	X	X	Omi BA.4/BA.5 P2 (0.5 µg)	Omi BA.4/BA.5 P2 (0.5 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	N/A
	3	10	X	X	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	N/A
(BNT162b2 experienced) 3rd dose booster cohort	4	10	BNT162b2 (0.5)	BNT162b2 (0.5)	Omi BA.4/BA.5 P2 (0.5 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)
	5	10	BNT162b2 (0.5)	BNT162b2 (0.5)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)

a. Tissue harvest performed, spleens and lymph nodes collected.

***Study schedule*:**

Week	Day	Date	Procedure
0	0	25-May-2022	Vax #1 (Groups 4 and 5)
3	21	15-Jun-2022	Vax #2 (Groups 4 and 5)
7	49	13-Jul-2022	Vax #1 (Groups 1-3) Bleed (1MPD2) and Vax #3 (Groups 4 and 5)
8	56	20-Jul-2022	Bleed (7DPD3) (Groups 4 and 5)
10	70	03-Aug-2022	Vax #2 (Groups 1-3)
11	77	10-Aug-2022	Bleed (7DPD2) ® (Groups 1[a]-3)
			Terminal Bleed (Groups 1,[b] 4, 5) **Terminal bleed with Spleen and LN harvest (1MPD3) = (15 of the 25 terminally bled mice)**
14	98	31-Aug-2022	**Terminal Bleed (1MPD2) ® (Groups 1[c]-3)**

Test article:

Item #	Test articles	Description of Antigen	DS Lot #	DP Lot #	DP Matrix	Vials # / Storage
1	Saline	0.9% NaCl	N/A	B2106062	N/A	3 aliquots, RT
2	modRNA BNT162b2 LNP	BNT162b2 V09	00715221-27-DS	00709594-0566-LNP	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C
3	modRNA Omi BA.4/BA.5_P2 LNP	Covid modRNA, pST4-mod_Vac_Omi_BA.4/BA.5_P2	00716042-0096-pVV00880	00717722-0004 F1	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C

Assay readout:

Evaluation and Sample Type	Time Points	Testing Facility
Pseudovirus neutralization test (pVNT) (sera)	49, 56, 77, 98	Pfizer
B and T cell analysis (spleen and LN)	77	Pfizer

Pseudovirus used in the neutralisation assay

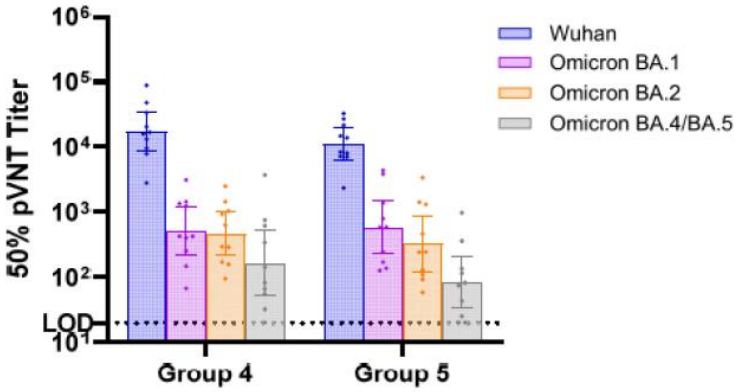
Pseudovirus stocks were generated in HEK-293T cells (ATCC, ref. #CRL-3216) using SARS-CoV-2 spike plasmid DNA and vesicular stomatitis virus (VSV; VSVΔG(G)-GFP virus: Kerafast, ref.# EH1019-PM) for use in the neutralisation assays.

Results:

Immunogenicity

Initial immunization of a 2-dose primary series of BNT162b2 at a 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralising antibody response against the Wuhan strain and substantially lower neutralising titers against Omicron BA.1, BA.2, and BA.4/BA.5 (Figure 2). Consistent with prior studies, BA.4/BA.5 titers were the lowest of the Omicron sublineages tested. Overall, the responses were similar across Group 4 (monovalent booster group) and Group 5 (bivalent booster group), with slightly lower Omicron BA.2 and BA.4/BA.5 titers observed in Group 5.

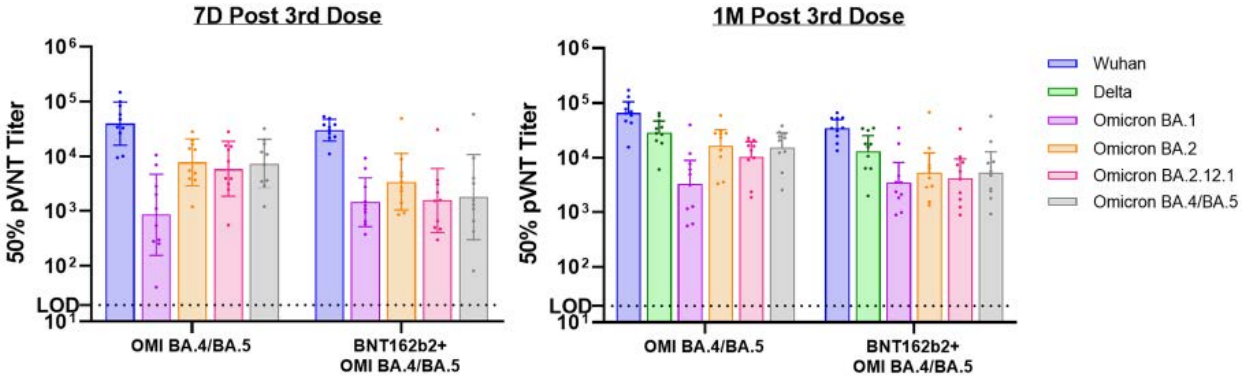
Figure 2. Functional neutralising antibody responses elicited by immunization of naïve mice with 2-doses of BNT162b2 (Groups 4 and 5)



Two groups of 10 female Balb/c mice were immunized IM on Days 0 and 21 with 0.5 µg of BNT162b2. Neutralising antibody responses against pseudovirus of Wuhan reference strain (blue) and Omicron BA.1 (red), BA.2 (orange), and BA.4/BA.5 (purple) variants of concern were measured by pseudovirus neutralisation assay at 1 month post 2nd dose.

Intramuscular immunization of BNT162b2-experienced Balb/c mice with a 0.5 µg dose level of LNP-formulated BA.4/BA.5 variant-modified vaccines as a 3rd dose booster increased neutralising antibody responses against the Wuhan reference strain and Omicron BA.1, BA.2, BA.2.12.1, and BA.4/BA.5 (Figure 3). In the monovalent group, Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5 neutralising titers increased by 2, 2, 17, and 45-fold, respectively, at 7 days post booster compared to 1 month post BNT162b2 Dose 2. A further increase in neutralising antibody responses was observed 1 month post third dose compared to 7 days post third dose. At 1 month post booster, the fold difference compared to 1 month post BNT162b2 Dose 2 increased to 4, 7, 36, and 94 for Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5, respectively. In the bivalent group, Wuhan, Omicron BA.1, BA.2, and BA.4/BA.5 neutralising titers increased by 3, 3, 11, and 22-fold, respectively, 7 days post booster and 3, 6, 17, and 66-fold, respectively, 1 month post booster compared to after BNT162b2 Dose 2. A balanced response against Omicron sublineages was achieved with both monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5) formulations. The monovalent BA.4/BA.5 formulation elicited slightly higher Omicron neutralising titers compared to the bivalent BA.4/BA.5 formulation.

Figure 3. Neutralising antibodies elicited by immunization of BNT162b2-experienced mice with Omicron BA.4/BA.5 variant-modified monovalent and bivalent modRNA vaccines as a 3rd dose booster



	7DPD3					1MPD3					
Vaccine	Wuhan	Omicron				Wuhan	Delta	Omicron			
		BA.1	BA.2	BA.2.12.1	BA.4/BA.5			BA.1	BA.2	BA.2.12.1	BA.4/BA.5
OMI BA.4/BA.5	40174	865	7884	5944	7454	65839	28865	3366	16677	10385	15522
BNT162b2+ OMI BA.4/BA.5	30316	1459	3478	1573	1813	34457	13291	3537	5391	4294	5446

10 Balb/c mice per group were immunized IM on days 0 and 21 with 0.5 µg of BNT162b2; one month following dose 2, mice were boosted with an additional dose of either monovalent vaccine BNT162b2 BA.4/BA.5 (0.5 µg) or bivalent vaccine BNT162b2 + BNT162b2 BA.4/BA.5 (0.25 µg of each). Neutralising antibody responses against the Wuhan reference strain (blue) and Omicron BA.1 (purple), BA.2 (orange), BA.2.12.1 (pink), and BA.4/BA.5 (grey) variants of concern were measured by pseudovirus neutralisation assay at 1 week post 3rd dose and at 1 month post 3rd dose with the addition of the Delta variant (green).

REVIEWER'S COMMENTS:

In the current submission, the Sponsor provided a new murine study (VR-VTR-10976), where the monovalent or bivalent Omicron BA.4/BA.5 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2- experienced Balb/c mice. Sera were collected 1 month following a two dose primary series (vaccinations on Day 0 and Day 21) of the BNT162b2 prototype vaccine and 7 days after a 3rd dose of either a monovalent or bivalent BA.4/BA.5 variant-modified vaccine. Sera were tested with a non-validated SARS-CoV-2 pseudovirus neutralisation assay. Initial immunization of a two dose primary series of BNT162b2 at 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralising antibody response against the Wuhan strain and substantially lower neutralising titers against Omicron BA.1, BA.2, and BA.4/BA.5.

A BA.4/BA.5 booster elicited higher BA.4/BA.5 neutralising titers with a consistent response across Omicron sublineages, suggesting that a BA.4/BA.5-modified vaccine may be more effective overall against Omicron sublineages. The monovalent BA.4/BA.5 formulation induced higher responses to Omicron sublineages than the BA.4/BA.5 bivalent vaccine, however, these responses were better than those induced by the approved BNT162b2 vaccine. In addition, immunogenicity data in mice support that a BA.4/BA.5 bivalent vaccine may give a stronger immune response to BA.5 than the BA.1 bivalent vaccine.

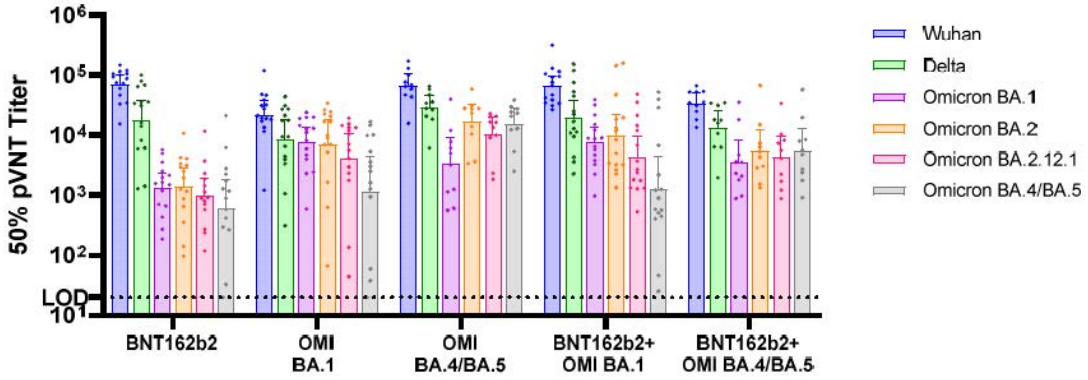
Reviewer's overall conclusion on non-clinical studies

Adding to the previously reviewed information of the already characterized safety profile, these data further demonstrate that no new safety concerns are expected with the use of the bivalent mRNA-based platform.

Additional data (not summarised in the HC evaluation report):

To compare immune responses elicited by Omicron BA.1 and Omicron BA.4/BA.5 variant-modified vaccine candidates, 1 month post third dose mouse sera from PRL-COVID-Ms-2022-01 study (VR-VTR-10944; Submission PM-2022-03551-1-2) were tested concurrently with 1 month post third dose sera from the present study (VR-VTR-10976, Ver 3) in the same pseudovirus neutralisation assay runs. Balb/c mice from both studies (2022-01 and 2022-06) were of a similar age range, were vaccinated and boosted following the same dosing interval, and at the same dose level.

Figure 4. Neutralising antibodies (1 month after the 3rd dose) elicited by immunisation of BNT162b2-experienced mice with Omicron BA.1 and BA.4/BA.5 variant-modified monovalent and bivalent modRNA vaccines as a 3rd Dose Booster



Vaccine	Wuhan	Delta	Omicron			
			BA.1	BA.2	BA.2.12.1	BA.4/BA.5
BNT162b2	70546	17911	1308	1378	973	603
OMI BA.1	21998	8454	7575	7030	4049	1136
OMI BA.4/5	65839	28865	3366	16677	10385	15522
BNT162b2 + OMI BA.1	65389	19206	7652	9855	4380	1294
BNT162b2 + OMI BA.4/BA.5	34457	13291	3537	5391	4294	5446

Balb/c mice were immunised IM on days 0 and 21 with 0.5 µg of BNT162b2; one month following dose 2, mice were boosted with an additional dose of either monovalent Omicron modified vaccine (0.5 µg) or bivalent vaccine (0.25 µg of each; 0.5 µg total) or BNT162b2 prototype vaccine. Omicron BA.1 variant-modified vaccines and BNT162b2 prototype were administered in PRL-COVID-Ms-2022-01 (15 mice per group) and BA.4/BA.5 variant-modified vaccines were administered in PRL-COVID-Ms-2022-06 (10 mice per group). All sera were tested concurrently in the same pseudovirus neutralisation assay runs. Neutralising antibody responses against the Wuhan reference strain (blue), Delta (green), Omicron BA.1 (purple), BA.2 (orange), BA.2.12.1 (pink), and BA.4/BA.5 (grey) variants were measured by pseudovirus neutralisation assay at 1 month post 3rd dose.

Comparison of neutralisation titres (titre ratios) induced by different vaccines

Vaccines	Variants					
	Wuhan	**Delta**	**BA.1**	**BA.2**	**BA2.12.1**	**BA.4-5**
BA.1 monovalent : Original	0.31	0.47	5.8	5.1	4.2	1.9
Original+BA.1 bivalent : BA.1 monovalent	3.0	2.3	1.0	1.4	1.1	1.1
BA.4-5 monovalent : Original	0.93	1.6	2.6	12	11	26
Original+BA.4-5 bivalent : Original	0.49	0.74	2.7	3.9	4.4	9.0
Original+BA.4-5 bivalent : BA.4-5 monovalent	0.52	0.46	1.1	0.32	0.41	0.35

TGA Evaluator's Comments:

- As expected, neutralising titres increased 1 month after the 3rd (booster) dose relative to 1 week after the 3rd dose for all vaccines.
- Both BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising titres to all Omicron sublineages tested than the original monovalent vaccine.
- Both the BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising antibody titres to BA.4-5 than the original/BA.1 bivalent vaccine.
- Neutralising titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine than the BA.4-5 monovalent vaccine.
- Cellular immunity results were not included in the study report and should be provided for review when available.

Protected B when completed

Health Products and Food Branch – Direction générale des produits de santé et des aliments

BIOLOGICS SAFETY AND EFFICACY ASSESSMENT REPORT (BSEAR)

To/À: s22 [redacted], Division Manager, CED-COVID, CVCTB, BRDD		**Control #**	**267502**
		Dossier ID	**HC6-024-e267502**
From/De: s22 [redacted], Clinical Evaluator CED-COVID, CVCTB, BRDD		**Review Target Date**	Expedited review, no target date
		Review Completion Date	2022-10-26
Biologics Safety and Efficacy Assessment Report Type		NDS-CV, expedited review in the context of the COVID-19 pandemic.	
Review Recommendation	A Notice of Compliance (NOC) is recommended.		

Brief Description:

New Drug Submission with flexibilities for designated COVID-19 drug (NDS-CV)

COMIRNATY Bivalent Original & Omicron BA.4/BA.5 mRNA vaccine, for active immunization against COVID-19 disease caused by SARS-CoV-2 virus in persons ≥12 years of age, filed by Pfizer-BioNTech.

Signature Block	*This document is signed electronically in docuBridge by the following people:*
Name and Title	
s22 [redacted], Clinical Evaluator, CED-COVID, CVCTB, BRDD	
s22 [redacted] Division Manager, CED-COVID, CVCTB, BRDD	

Drug Product Information	
Proprietary Name	Comirnaty Original/Omicron BA.4/BA.5 (COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5))
Common Name of the Drug Substance	COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Sponsor/Manufacturer	Pfizer Canada ULC
Therapeutic Classification	Active immunizing agent
Strength(s)	30ug
Dosage form(s)	Multidose vial, suspension
Route(s) of Administration	Dispersion for intramuscular injection

Review Report Information			
Regulatory Project Manager	s22 [redacted], Senior Regulatory Affairs Officer, Office of Regulatory Affairs, CREST, BRDD		
Screening Document Link	HC6-024-e267502 (1.0) Reg Info - Health Product		
Clinical Review Plan Link	*N/A*		
Priority Review (If yes, provide hyperlink to Clinical Assessment Package below)		☐ Yes	☐ No

Review Report Information			
Clinical Assessment Package	*<HYPERLINK>*		
Paediatric Studies Included? (If yes, provide hyperlink to the report below)		☐ Yes	☒ No
Patent Extension Report	*<HYPERLINK>*		
Biostatistical Consultation		☐ Yes	☒ No
Joint Review (e.g., with TPD, MHPD, MDB)		☐ Yes	☒ No
If Joint Review, is BGTD the lead?		☐ Yes	☐ No
Risk Management Plan		☒ Yes	☐ No
Product Monograph Revisions issued		☒ Yes	☐ No
Prescription Drug List Recommendation (determined at the end of the review)		☒ Yes	☐ No
Regulatory Decision Summary Required		☒ Yes	☐ No
Summary Basis of Decision Required		☐ Yes	☒ No
Third Party Information		☐ Yes	☒ No
Instructions (references to parts of the report, or highlighting within the report) for ORA to use to identify third party information or cross references to other files or submissions. ORA will use these instructions to create redacted review reports for sponsors. Reviewers should consult their managers if they are uncertain on the appropriate use of third party information in review reports. Annotation instructions should begin with the following text: "At the time of the finalization of this review, the following instructions can be used to locate third party information." Third party information requires verification product ownership has been transferred in the interval preceding release of this report to the sponsor.			

Submission Tracking Identifiers					
Submission Content	☐ Module 1	☐ Module 2	☐ Module 3	☐ Module 4	☐ Module 5
eCTD Version # and description	**Version #**	**Brief Description of the Transaction**			

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1 DEVELOPMENT OF THE PRODUCT AND ASSESSMENT

Please note the Clinical Executive Summary for the basis of clinical authorization of product. HC6-024-e267502 (1.0) Reg Info - Health Product

2 CANADIAN STATUS/REGULATORY HISTORY

3 INTERNATIONAL REGULATORY STATUS

4 NON-CLINICAL STUDIES

4.1 INTRODUCTION

4.2 TABULAR LISTING OF NON-CLINICAL STUDIES

4.2.1 STUDIES REVIEWED IN THIS BSEAR

VR-VTR-10976	In vivo immunogenicity	BALB/c	BNT162b2 Omicron BA.4/BA.5 variant-modified vaccine	0.5 µg

4.2.2 STUDIES NOT REVIEWED IN THIS BSEAR

Pharmacology - BNT162b2 studies				
R-20-0085	In vivo immunogenicity	BALB/c mice	BNT162b2 (V9)	0.2, 1, 5 µg
R-20-0112	In vivo immunogenicity	BALB/c mice	BNT162a1, BNT162b1, BNT162b2 (V9), BNT162c2	5 µg
R-20-0211	In vitro protein expression	Cell culture	BNT162b2 (V9)	varied
VR-VTR-10741	In vitro protein expression	Cell culture	BNT162b2 (V9)	varied
VR-VTR-10671	In vivo immunogenicity and SARS-CoV-2 challenge	Rhesus macaques	BNT162b2 (V9)	30 and 100 µg
VR-VTR-10944	In vivo immunogenicity	BALB/c	BNT162b2 Omicron BA.1 variant-modified vaccine	0.5 µg

			modified vaccine	
ADME				
PF-07302048 _06Jul20_072424	PK of ALC-0315 and ALC-0159	Wistar Han Rats	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	1 mg/kg
R-20-0072	In vivo distribution	BALB/c mice	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	2 µg
185350	In vivo distribution	Wistar Han Rats	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [^{3}H]-CHE as non-diffusible label	50 µg
01049-20008	In vitro metabolism	CD-1/ICR mouse, Wistar Han and/or Sprague Dawley rat, cynomolgus monkey and	ALC-0315	NA
01049-20009				
01049-20010				
01049-20020			ALC-0159	NA
01049-20021				

		System		
01049-20022		human liver microsomes, S9 fraction, hepatocytes		
PF-07302048 _05Aug20_043725	In vitro and in vivo metabolism	Blood, liver S9 fractions and hepatocytes from CD-1 mouse, Wistar Han rat, cynomolgus monkey and human. In vivo samples from Wistar Han rat plasma, urine, feces, and liver	In vitro: ALC-0315 and ALC-0159 In vivo: modRNA encoding luciferase formulated in LNP comparable to BNT162b2	1 mg/kg modRNA (in vivo samples)
Toxicology – Studies with BNT162b2 variants				
38166	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V8)	100 µg
20GR142	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg
20256434	Development and Reproductive Toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg

4.3 PHARMACOLOGY

4.3.1 PRIMARY PHARMACODYNAMICS

VR-VTR-10976 - Study Report

The objective of this study is to evaluate the immunogenicity and breadth of coverage of BNT162b2 BA.4/BA.5 vaccines as either monovalent or bivalent (1:1 mixture of BNT162b2 and BNT162b2 BA.4/BA.5) formulations in both naïve and BNT162b2-experienced mice.

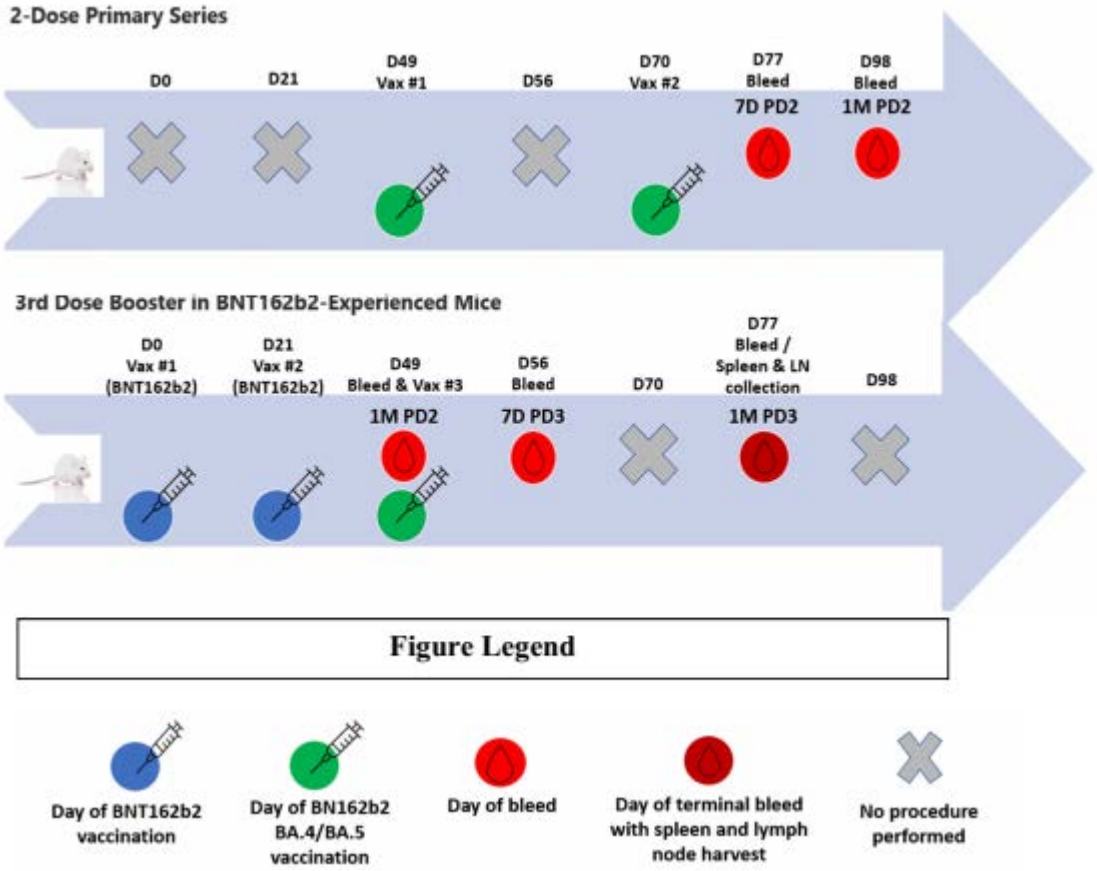
Rationale:

BNT162b2 encodes the full-length SARS-CoV-2 spike glycoprotein in a prefusion conformation and has been highly effective against COVID-19; however, as new SARS-CoV-2 variants of concern (VOCs) emerge, variant-modified vaccines may serve to optimally protect against current and future variants. The mutations of the Omicron BA.4/BA.5 variant were applied to BNT162b2 to generate an Omicron BA.4/BA.5 variant-modified vaccine (BNT162b2 BA.4/BA.5) that was evaluated in mice as both a monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5)

formulation. The modRNAs are encapsulated into lipid nanoparticles (LNPs) to protect the modRNA from degradation and to enable delivery of the RNA into host cells after intramuscular (IM) injection.

Study Design:

To assess the impact of a variant-modified BNT162b2 BA.4/BA.5 vaccine on the immune response as a 3rd dose booster, BNT162b2-experienced mice received a booster with either a monovalent or bivalent BA.4/BA.5 vaccine one month after receiving the second dose of BNT162b2 (as part of the standard two-dose series given at Day 0 and Day 21). Sera was collected at multiple time points for evaluation of the neutralizing antibody response against the reference strain and Omicron sublineages. Immunogenicity of a 2-dose primary series of the monovalent and bivalent BA.4/BA.5 vaccines was also evaluated in a cohort of naïve mice.



	Group #	N	Vax (Day 0) (µg)	Vax (Day 21) (µg)	Vax (Day 49) (µg)	Vax (Day 70) (µg)	Vaccination (Day of Study)	Bleed (Day of Study)	Tissue harvest
Neg Control	1	5 / 5	X	X	Saline	Saline	49, 70	77 (7DPD2)[a] 98 (1MPD2)	Spleen and LN @ D77 (n=5)
Two dose primary series cohort	2	10	X	X	Omi BA.4/BA.5 P2 (0.5 µg)	Omi BA.4/BA.5 P2 (0.5 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	NA
	3	10	X	X	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	NA
(BNT162b2 experienced) 3rd dose booster cohort	4	10	BNT162b2 (0.5)	BNT162b2 (0.5)	Omi BA.4/BA.5 P2 (0.5 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)
	5	10	BNT162b2 (0.5)	BNT162b2 (0.5)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)

a. Tissue harvest performed, spleens and lymph nodes collected.

Week	Day	Date	Procedure
0	0	25-May-2022	Vax #1 (Groups 4 and 5)
3	21	15-Jun-2022	Vax #2 (Groups 4 and 5)
7	49	13-Jul-2022	Vax #1 (Groups 1-3) Bleed (1MPD2) and Vax #3 (Groups 4 and 5)
8	56	20-Jul-2022	Bleed (7DPD3) (Groups 4 and 5)
10	70	03-Aug-2022	Vax #2 (Groups 1-3)
11	77	10-Aug-2022	Bleed (7DPD2) → (Groups 1[a]-3)
			Terminal Bleed (Groups 1,[b] 4, 5) **Terminal bleed with Spleen and LN harvest (1MPD3) = (15 of the 25 terminally bled mice)**
14	98	31-Aug-2022	**Terminal Bleed (1MPD2) → (Groups 1[c]-3)**

Test article:

Item #	Test articles	Description of Antigen	DS Lot #	DP Lot #	DP Matrix	Vials#/ Storage
1	Saline	0.9% NaCl	N/A	B2106062	N/A	3 aliquots, RT
2	modRNA BNT162b2 LNP	BNT162b2 V09	00715221-27-DS	00709594-0566-LNP	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C
3	modRNA Omi BA.4/BA.5_P2 LNP	Covid modRNA, pST4-mod_Vac_Omi_BA.4/BA.5_P2	00716042-0096-pVV00880	00717722-0004 F1	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C

Assay readout:

Evaluation and Sample Type	Time Points	Testing Facility
Pseudovirus neutralization test (pVNT) (sera)	49, 56, 77, 98	Pfizer
B and T cell analysis (spleen and LN)	77	Pfizer

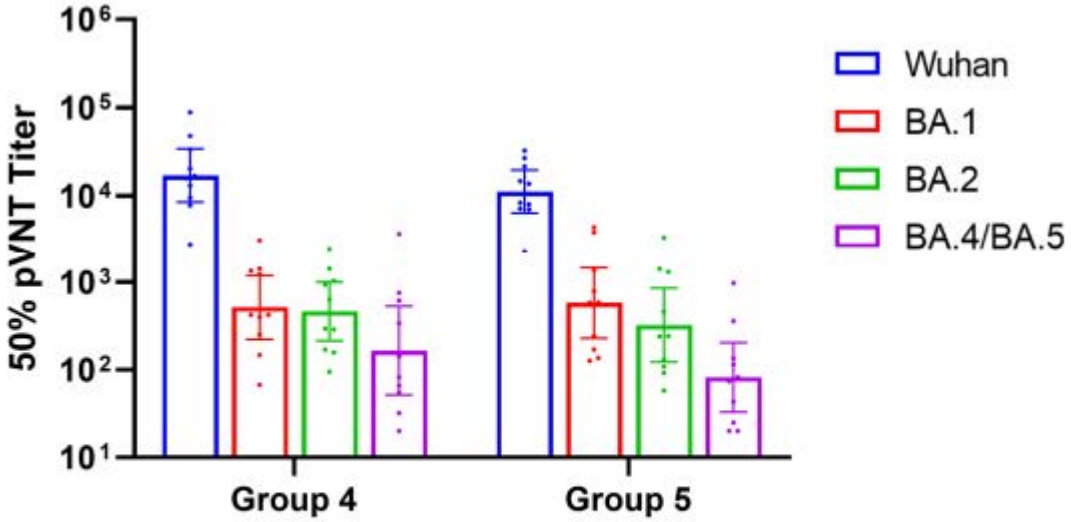
Pseudovirus stocks were generated in HEK-293T cells (ATCC, ref. #CRL-3216) using SARS-CoV-2 spike plasmid DNA and vesicular stomatitis virus (VSV; VSVΔG(G)-GFP virus: Kerafast, ref.# EH1019-PM) for use in the neutralization assays.

Results:

Immunogenicity

Initial immunization of a 2-dose primary series of BNT162b2 at a 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralizing antibody response against the Wuhan strain and substantially lower neutralizing titers against Omicron BA.1, BA.2, and BA.4/BA.5. Consistent with prior studies, BA.4/BA.5 titers were the lowest of the Omicron sublineages tested. Overall, the responses were similar across Group 4 (monovalent booster group) and Group 5 (bivalent booster group), with slightly lower Omicron BA.2 and BA.4/BA.5 titers observed in Group 5.

Figure 2. Functional Neutralizing Antibody Responses Elicited by Immunization of Naïve Mice With 2-Doses of BNT162b2 (Groups 4 and 5)

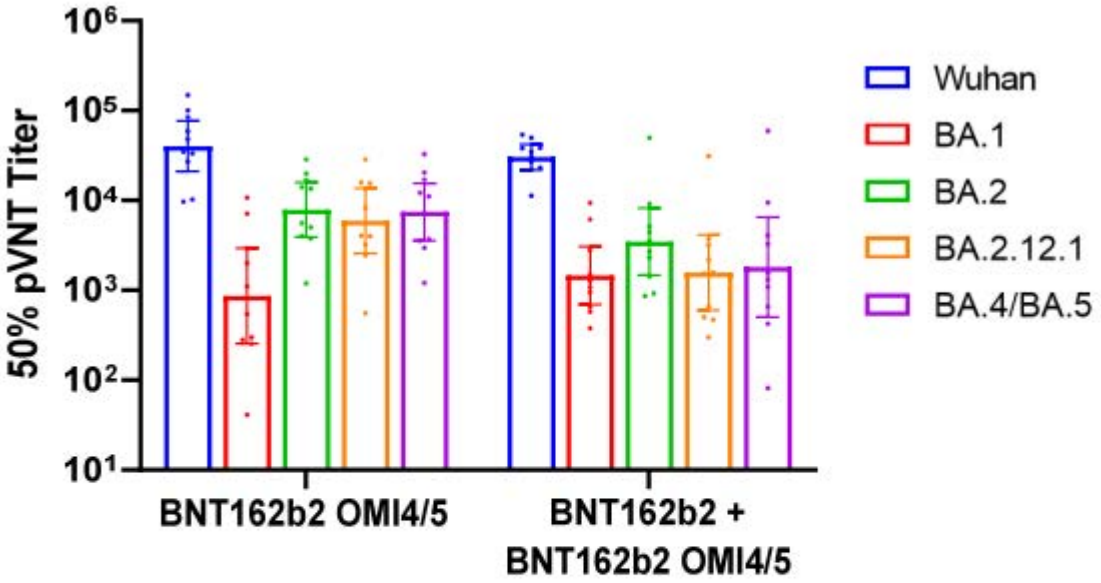


Two groups of 10 female Balb/c mice were immunized IM on Days 0 and 21 with 0.5 µg of BNT162b2. Neutralizing antibody responses against pseudovirus of Wuhan reference strain (blue) and Omicron BA.1 (red), BA.2 (orange), and BA.4/BA.5 (purple) variants of concern were measured by pseudovirus neutralization assay at 1 month post 2nd dose.

Two groups of 10 female Balb/c mice were immunized IM on Days 0 and 21 with 0.5 µg of BNT162b2. Neutralizing antibody responses against pseudovirus of Wuhan reference strain (blue) and Omicron BA.1 (red), BA.2 (orange), and BA.4/BA.5 (purple) variants of concern were measured by pseudovirus neutralization assay at 1 month post 2nd dose.

Intramuscular immunization of BNT162b2-experienced Balb/c mice with a 0.5 µg dose level of LNP-formulated BA.4/BA.5 variant-modified vaccines as a 3rd dose booster increased neutralizing antibody responses against the Wuhan reference strain and Omicron BA.1, BA.2, BA.2.12.1, and BA.4/BA.5. In the monovalent group, Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5 neutralizing titers increased by 2, 2, 17, and 45-fold, respectively, at 7 days post booster compared to 1 month post BNT162b2 Dose 2. In the bivalent group, Wuhan, Omicron BA.1, BA.2, and BA.4/BA.5 neutralizing titers increased by 3, 3, 11, and 22-fold, respectively, post booster compared to after BNT162b2 Dose 2. A balanced response against Omicron sublineages was achieved with both monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5) formulations. The monovalent BA.4/BA.5 formulation elicited slightly higher Omicron neutralizing titers compared to the bivalent BA.4/BA.5 formulation.

Figure 3. Neutralizing Antibodies Elicited by Immunization of BNT162b2-Experienced Mice With Omicron BA.4/BA.5 Variant-modified Monovalent and Bivalent modRNA Vaccines as a 3rd Dose Booster



Vaccine	Wuhan	Omicron			
		BA.1	BA.2	BA.2.12.1	BA.4/BA.5
BNT162b2 OMI4/5	40174	865	7884	5944	7454
BNT162b2+ BNT162b2 OMI4/5	30316	1459	3478	1573	1813

10 Balb/c mice per group were immunized IM on days 0 and 21 with 0.5 µg of BNT162b2; one month following dose 2, mice were boosted with an additional dose of either monovalent vaccine BNT162b2 BA.4/BA.5 (0.5 µg) or bivalent vaccine BNT162b2 + BNT162b2 BA.4/BA.5 (0.25 µg of each). Neutralizing antibody responses against the Wuhan reference strain (blue) and Omicron BA.1 (red), BA.2 (green), BA.2.12.1 (orange), and BA.4/BA.5 (purple) variants of concern were measured by pseudovirus neutralization assay at 1 week post 3rd dose.

REVIEWER'S COMMENTS:

In the current submission, the Sponsor provided a new murine study (VR-VTR-10976), where the monovalent or bivalent Omicron BA.4/BA.5 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2- experienced Balb/c mice. Sera were collected 1 month following a two dose primary series (vaccinations on Day 0 and Day 21) of the BNT162b2 prototype vaccine and 7 days after a 3rd dose of either a monovalent or bivalent BA.4/BA.5 variant-modified vaccine. Sera were tested with a non-validated SARS-CoV-2 pseudovirus neutralization assay. Initial immunization of a two dose primary series of BNT162b2 at 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralizing antibody response against the Wuhan strain and substantially lower neutralizing titers against Omicron BA.1, BA.2, and BA.4/BA.5.

A BA.4/BA.5 booster elicited higher BA.4/BA.5 neutralizing titers with a consistent response across Omicron sublineages, suggesting that a BA.4/BA.5-modified vaccine may be more effective overall against Omicron sublineages. The monovalent BA.4/BA.5 formulation induced higher responses to Omicron sublineages than the BA.4/BA.5 bivalent vaccine, however, these responses were better than those induced by the approved BNT162b2

vaccine. In addition, immunogenicity data in mice support that a BA.4/BA.5 bivalent vaccine may give a stronger immune response to BA.5 than the BA.1 bivalent vaccine.

4.4 Reviewer's Overall Conclusion on Non-Clinical Studies

Adding to the previously reviewed information the already characterized safety profile, these data further demonstrate that no new safety concerns are expected with the use of the bivalent mRNA-based platform.

5 CLINICAL STUDIES

6 COMMUNICATIONS WITH SPONSOR

7 PRODUCT MONOGRAPH

8 OTHER COMMUNICATIONS AND INFORMATION

9 NOC/C

10 PHARMACOVIGILANCE ACTIVITIES

11 BENEFIT-RISK ASSESSMENT

12 RECOMMENDATION

13 REFERENCES

14 APPENDIX

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Risk Management Plan Evaluation Report Provisional Approval Pathway

tozinameran/famtozinameran (Comirnaty Original /Omicron BA.4-5 COVID-19 Vaccine)

Submission No: PM-2022-05306-1-2

Sponsor: Pfizer Australia Pty Ltd

Round 1: 3 January 2023
Round 2: 23 January 2023

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TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type:	New biological entity
Sponsor:	Pfizer Australia Pty Ltd
Generic name:	tozinameran/ famtozinameran
Trade name:	Comirnaty Original/ Omicron BA.4-5 COVID-19 Vaccine
Dose form and strength:	Suspension for intramuscular injection; One vial (2.25 mL) contains 6 doses of 0.3 mL each One dose (0.3 mL) contains 15 µg of tozinameran and 15 µg of famtozinameran)
Drug class:	Active immunisation against COVID-19
Submission No; eSubmission ID:	PM-2022-05306-1-2; e006875 - (0000)
RMP file No:	E22-630788
TRIM reference:	D22-6245983
EU-RMP Version:	Round 1and 2 – version 9.0; date 4 November 2022; DLP Module SIII 16 May 2022 (C4591031 Substudy E), 11 March 2022 (C4591031 Substudy D – Cohort 2); Module SVII.3 Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 (Pfizer Clinical Database C4591031 Substudy E). 11 March 2022 (Pfizer Clinical Database C4591031 Substudy D – Cohort 2). 30 June 2022 (Pfizer safety Database)
ASA Version:	Round 1and 2 – version 0.7; date December 2022
Evaluator:	s22 [redacted] [Round 1 and 2]
Peer Reviewer:	s22 [redacted] [Round 1]
Date authorised:	3 January 2023 [Round 1] 23 January 2023 [Round 2/Post-ACV report]
RMP referral to ACV:	18 January 2023
Pharmacovigilance activities:	Routine Follow-up questionnaires Clinical Trial Post authorisation safety studies (PASS)
Risk minimisation Activities	Routine Risk minimisation measures implemented by the Australian Government
Black Triangle Scheme:	Yes, provisional registration
PSUR review issues:	Yes
IDMP referral:	Level 1 (Intensive Monitoring) - Provisionally registered new chemical / biological entity
RMP Compliance Tracker:	No

SUMMARY

- Pfizer Australia Pty Ltd has applied to register a new vaccine, tozinameran / famtozinameran (Comirnaty Original/ Omicron BA.4-5 COVID-19 Vaccine) through the Provisional Approval Pathway. This vaccine is proposed to be used as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The proposed dosing regimen involves 0.3 mL of the vaccine to be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series.
- Pfizer Australia Pty Ltd has submitted EU-RMP version 9.0 (dated 4 November 2022; DLP for Original/Omicron BA.4-5 Vaccine - Module SIII 16 May 2022 (C4591031 Substudy E), 11 March 2022 (C4591031 Substudy D – Cohort 2); Module SVII.3 Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 (Pfizer Clinical Database C4591031 Substudy E). 11 March 2022 (Pfizer Clinical Database C4591031 Substudy D – Cohort 2) and ASA version 0.7 (dated December 2022) in support of this application.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	Myocarditis and pericarditis	✓	✓*	✓	–
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	✓†	✓*	–	–
Missing information	Use in pregnancy and while breast feeding	✓	✓*≠	✓	–
	Use in immunocompromised patients	✓	✓*	✓	–
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	✓	✓*	✓	–
	Use in patients with autoimmune or inflammatory disorders	✓	✓*	–	–
	Interaction with other vaccines	✓	✓*	✓	–
	Long term safety data	✓	✓*	–	–

†Data Capture Aid (Adverse drug reaction follow-up forms)
≠Post-authorisation safety study
*Clinical trial

- The summary of safety concerns is acceptable. Advice from the clinical and nonclinical evaluators and, the ACV has been considered when arriving at this decision.
- The pharmacovigilance plan is acceptable from an RMP perspective. The acceptability of the clinical study plan will be assessed by the delegate.
- Only routine risk minimisation measures are proposed by the sponsor. There are risk minimisation measures implemented for COVID-19 vaccines by the Department of Health and Aged Care and State Governments for the COVID-19 vaccines supplied in Australia, including the Comirnaty vaccines. Introduction of Comirnaty Original/Omicron BA.4-5

vaccine is not expected to warrant additional risk minimisation measures as part of the RMP.

NEW AND OUTSTANDING RECOMMENDATIONS - ROUND 2

There are no outstanding RMP issues.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The COMIRNATY Original/Omicron BA.4-5] EU-Risk Management Plan (RMP) (version 9, dated 4 November 2023) with Australian Specific Annex (version 0.7 dated December 2022), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of 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. Each report must have been prepared within ninety calendar days of the data lock point for that report.

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

COMIRNATY Original/Omicron BA.4-5 is to be included in the Black Triangle Scheme. The PI and CMI for that COMIRNATY Original/Omicron BA.4-5 must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

Other advice to the Delegate

It is expected that the delegate will assess the clinical study plan and include relevant conditions of registration in the approval letter.

Issues for PSUR Review (for internal use only)

Screening of the MSSRs/ PSURs is recommended to determine whether further in-depth evaluation is required.

Rationale for IDMP Inclusion (for internal use only)

Provisionally registered COVID-19 vaccine.

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MAIN BODY

1. BACKGROUND

Pfizer Australia Pty Ltd has applied to register a new vaccine, tozinameran / famtozinameran (Comirnaty Original/ Omicron BA.4-5 COVID-19 Vaccine) through the Provisional Approval Pathway. This vaccine is proposed to be used as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The proposed dosing regimen involves 0.3 mL of the vaccine to be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series.

Pfizer Australia Pty Ltd has submitted EU-RMP version 9.0 (dated 4 November 2022; DLP[1] for Original/Omicron BA.4-5 Vaccine - Module SIII 16 May 2022 (C4591031 Substudy E), 11 March 2022 (C4591031 Substudy D – Cohort 2); Module SVII.3 Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 (Pfizer Clinical Database C4591031 Substudy E). 11 March 2022 (Pfizer Clinical Database C4591031 Substudy D – Cohort 2) and ASA version 0.7 (dated December 2022) in support of this application.

1.1. INDICATION

Section 4.1 (Therapeutic Indications) in the proposed Product Information (PI) document states:

> *COMIRNATY Original/Omicron BA.4-5 Vaccine has **provisional approval** for the indication below:*
> *As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*
>
> *The decision has been made on the basis of short term immunogenicity and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

1.2. BRIEF OVERVIEW OF FAMTOZINAMERAN

Famtozinameran, the new active ingredient in this vaccine, is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). Already approved tozinameran and riltozinameran encode the viral spike (S) protein of SARS-CoV-2 (Original) and the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1) respectively.

[1] See Appendix I for full list of DLPs

1.3. DOSAGE AND ADMINISTRATION

Comirnaty Original/Omicron BA.4-5 is indicated only for booster doses and does not require dilution. The dosage and administration instructions as per the proposed PI are as follows:

> *A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the completion of a COVID-19 vaccine primary series in individuals 12 years of age and older.*
>
> *COMIRNATY Original/Omicron BA.4-5 may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another COVID-19 vaccine.*
>
> *The decision when and for whom to implement a booster dose should be made based on available vaccine safety and immunogenicity data (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations*.

1.4. OVERSEAS REGULATORY STATUS

Comirnaty Original/Omicron BA.4-5 vaccine is approved to be used as a booster dose for individuals 12 years and older in the USA (EUA amendment), EU (Centralised procedure), Canada, and Singapore. Applications are under evaluation in Switzerland and New Zealand.

1.5. QUALITY OF THE SUBMISSION

The RMP and the ASA have been prepared in the recommended formats and are effective for evaluation.

2. SAFETY SPECIFICATION

2.1. NONCLINICAL ADVICE ON SAFETY SPECIFICATION

The Toxicology area of the Scientific Evaluation Branch (SEB) of the TGA is assessing the nonclinical section of the RMP. This evaluation will further inform the adequacy and completeness of the summary of the safety concerns as specified by the sponsor.

The sponsor should be aware that safety considerations may be raised by the nonclinical evaluator through the consolidated section 31 request and/or the nonclinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Round 2 update:
No concerns regarding the safety specification were raised by the nonclinical evaluator.[2]

2.2. CLINICAL ADVICE ON SAFETY SPECIFICATION

The Prescription Medicines Authorisation Branch (PMAB) of the TGA is assessing this section of the RMP. This evaluation will further inform the adequacy and completeness of the summary of the safety concerns as specified by the sponsor.

[2] Nonclinical evaluation report (Round 2) – TRIM Ref: D23-5014833

The sponsor should be aware that safety considerations may be raised by the clinical evaluator through the consolidated section 31 request and/or the clinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Round 2 update

No concerns regarding the safety specification were raised from clinical evaluation perspective[3].

2.3. PROPOSED SUMMARY OF SAFETY CONCERNS - ROUND 1

The sponsor has proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	Myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

The above summary of safety concerns is the same as the safety summary that was evaluated and deemed acceptable for Comirnaty Original and Comirnaty Original/Omicron BA.1 vaccines.

The PI states:

> *The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after the COMIRNATY booster (third dose). The most frequent adverse reactions in participants older than 12 years of age were injection site pain, fatigue, headache, myalgia, chills and arthralgia. No new adverse reactions were identified for COMIRNATY Original/Omicron BA.4-5.*

Subject to the evaluation of the nonclinical and clinical aspects of the SS (see Sections 2.1 & 2.2) and the ACV advice, this is considered acceptable from an RMP perspective.

[3] Clinical evaluation report (Round 1) – TRIM Ref: D23-5019795. Delegate's overview – TRIM Ref: D23-5052450

2.4. SUMMARY OF KEY CHANGES TO SAFETY SPECIFICATION - ROUND 2

There are no changes to the summary of safety concerns at Round 2. The nonclinical and clinical evaluators and, the ACV did not raise any concerns regarding the summary of safety concerns. The summary of safety concerns is considered acceptable.

3. PHARMACOVIGILANCE PLAN

3.1. PROPOSED PHARMACOVIGILANCE PLAN – ROUND 1

The sponsor has proposed routine pharmacovigilance for all safety concerns. Routine pharmacovigilance measures include implementation of the following Data Capture Aids (DCAs), which have been appended to the EU RMP:

- VAED Data Capture Aid
- Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) Data Capture Aid

The ASA states "*DCAs as per the EU-RMP will be implemented in Australia*".

The EU RMP states that the additional pharmacovigilance measures include 20 studies, of which 5 global, 5 in Europe only, 7 in US only, 2 in US and Canada and 1 in New Zealand/Australia. There are 9 interventional studies (C4591001, C4591007, C4591015, BNT162-01 Cohort 13, C4591024, C4591031, C4591044, C4591048 and 1 study for vaccine interactions), 3 Low-Interventional studies (C4591036, WI235284 and WI255886) and 8 non-interventional studies (7 safety and 1 effectiveness).
Table 73 of the EU RMP (page 156) contains a summary of the additional pharmacovigilance measures.

As Comirnaty Original/Omicron BA.4-5 COVID-19 vaccine is a new biological entity (Type A application), in addition to the routine submission of PSURs the sponsor should provide, expedited monthly safety summary reports (including safety data for patients in Australia) for the first 6 months **from the date of first supply in Australia**, and thereafter at intervals specified by the TGA.

Details of the clinical study plan as required for provisional registration has been included in the ASA. This plan has been provided in the TGA recommended format in a document separate to the ASA (e006875 (0000-) - Risk management plan).

3.2. ADEQUACY OF PROPOSED PHARMACOVIGILANCE PLAN

The currently proposed pharmacovigilance activities are the same as that has been evaluated and deemed acceptable for previous Comirnaty vaccines (Original and Original/Omicron BA.1). This pharmacovigilance plan continues to be acceptable from an RMP perspective. The delegate will assess the adequacy of the clinical study plan and determine the dates that the study reports require to be submitted to the TGA

4. RISK MINIMISATION PLAN

4.1. PLANNED RISK MINIMISATION ACTIVITIES - ROUND 1

Only routine risk minimisation measures are proposed in the RMP. There are risk minimisation measures implemented for COVID-19 vaccines by the Department of Health and Aged Care and State Governments. This approach has been deemed acceptable for currently approved COVID-19 vaccines (both monovalent and bivalent) in Australia. Implementation of only routine risk minimisation measures as part of RMP is considered acceptable.

4.1.1. Product labelling

4.1.1.1. Product Information

This vaccine contains a new biological entity, and as such meets the inclusion criteria for the Black Triangle Scheme. The following symbol and statement have been added to the top of the first page of the PI:

> ▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

As per TGA's requirement, the sponsor has included a statement in the PI explaining that the vaccine is a provisionally registered.

Section 2 of the PI contains the following sentence which requires 'riltozinameran' to be replaced with 'famtozinameran'.

> "One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran,…."

Round 2 update

The sponsor has made this amendment and provided an updated PI (D23-5014833).

4.1.1.2. Consumer medicine information

The precautions in the PI are satisfactorily incorporated into the CMI.

The following symbol and statement have been added to the top of the first page of the CMI, above the medicine name:

> ▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. You can report side effects to your doctor, or directly at www.tga.gov.au/reporting-problems.

As per TGA's requirement, the sponsor has included a statement in the CMI explaining that the vaccine is a provisionally registered.

4.1.2. Additional risk minimisation activities

Risk minimisation activities for COVID-19 vaccines that are supplied in Australia have been undertaken by the government's vaccination program. There are no additional risk minimisation measures implemented by the sponsor for the monovalent vaccine. The changes

proposed in this application are not expected to require additional risk minimisation measures as part of the RMP.

5. ROUND 2 EVALUATION

5.1. ACV ADVICE

ACV did not raise any concerns regarding the safety specification.

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

As a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.

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

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

5.2. RECONCILIATION OF ROUND 1 RECOMMENDATIONS

Recommendation 1: Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
RMP evaluator comment: The clinical or nonclinical evaluators did not raise any concerns regarding the safety specification.
Recommendation 2. The sponsor should provide a commitment to submit expedited monthly summary safety reports (including safety data for patients in Australia) for the first 6 months from the date of first supply of this vaccine in Australia, and thereafter at intervals specified by the TGA.
RMP evaluator comment: The requirement to provide monthly safety summaries will be imposed as a condition of registration.
Recommendation 3. Section 2 of the PI contains the following sentence which requires 'riltozinameran' to be replaced with 'famtozinameran'. "One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran,…."
RMP evaluator comment: The sponsor has made this amendment and provided an updated PI (D23-5014833).

APPENDIX 1 –DLPs FOR RMP VERSION 9.0

Age group	**Module SIII. Clinical Trial Exposure**	**Module SVII.3. Details of Important Risks**
12 years of age and older booster dose of a bivalent Omicron - (BA.1) modified vaccine (BNT162b2 + BNT162b2 OMI 30 μg)[a]	05 April 2022 (C4591031 Substudy E). 11 March 2022 (C4591031 Substudy D – Cohort 2).	05 April 2022 (Pfizer Clinical Database C4591031 Substudy E). 11 March 2022 (Pfizer Clinical Database C4591031 Substudy D – Cohort 2). 30 June 2022 (Pfizer safety Database)
6 months to <5 years (Primary series)	16 July 2021 (Phase 1) 29 April 2022 (Phase 2/3)	29 April 2022 (Pfizer Clinical Database - Study C4591007 Phase 2/3) 15 April 2022 (Pfizer Safety Database, non-CT dataset)
5 to <12 years of age (Primary series)	06 September 2021	06 September 2021 (Pfizer Clinical Database)
Booster (3rd) dose in 5 to <12 years of age	22 March 2022 (Phase 2/3)	22 March 2022 (Pfizer Clinical Database study C4591007) 31 August 2022 (Pfizer Safety Database, for non-CT dataset)
12-15 years of age, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database)	30 September 2021 (Pfizer Safety Database, for CT dataset)
Booster (3rd) dose in 12 -15 years of age	N/A	28 February 2022 (Pfizer Safety Database, both CT and non-CT datasets)
16 years and older, including severely immunocompromised (Primary series)	13 March 2021 (Pfizer Clinical Database) 23 October 2020 (BioNTech Clinical Database)	30 September 2021 (Pfizer Safety Database, for CT dataset)
Booster (3rd) dose in 16 years and older[b]	17 June 2021 (Pfizer Clinical Database)	17 June 2021 (Pfizer Clinical Database, study C4591001) 28 February 2022 (Pfizer Safety Database, for CT dataset)
Post-Authorisation Experience: 18 June 2022		

a. Detailed language is included in the proposed SmPC and in the Clinical Overview in support of Comirnaty Original/Omicron BA.1 and BA.4-5 (15/15) micrograms submissions

b. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

APPENDIX II – LIST OF ACRONYMS

AESI	Adverse Events of Special Interest
ACV	Advisory Committee on Vaccines
ASA	Australian Specific Annex
CMI	Consumer Medicine Information
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
PI	Product Information
PASS	Post-authorisation safety study
PMAB	Prescription Medicines Authorisation Branch
RMP	Risk Management Plan
SEB	Scientific Evaluation Branch
TGA	Therapeutic Goods Administration

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Nonclinical Evaluation Report

Tozinameran/famtozinameran

[COMIRNATY BIVALENT ORIGINAL/OMICRON BA.4-5]

Submission No: PM-2022-05306-1-2
Sponsor: Pfizer Australia Pty Ltd

December 2022 (Round 1)
January 2023 (Round 2)

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New vaccine

Sponsor: Pfizer Australia Pty Ltd

Generic name: **Tozinameran/famtozinameran**

Trade name: **COMIRNATY BIVALENT ORIGINAL/OMICRON BA.4-5 COVID-19 VACCINE**

Dose form and strength: Injection, Suspension; 15/15 µg in 0.3 mL

Drug class: mRNA encapsulated in LNP

Submission No: PM-2022-05306-1-2

Tox file No: E22-636157

TRIM reference: D22-6240013

Date authorised: 22 December 2022 (Round 1)
6 January 2023 (Round 2)

This report has been revised to incorporate additional data provided by the sponsor, and replaces the Nonclinical Evaluation Report issued at Round 1

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

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SUMMARY

- Pfizer Australia Pty Ltd has applied for provisional approval of a new bivalent COVID-19 vaccine containing tozinameran and famtozinameran (COMIRNATY ORIGINAL/OMICRON BA.4-5) in lipid nanoparticles (LNP). The Omicron BA.4-5 bivalent vaccine is indicated as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. The vaccine dose is 30 µg of mRNA/0.3 mL (15 µg of each mRNA) given intramuscularly (IM) at least 5 months after the completion of COVID-19 vaccine primary series.

- mRNA of the Omicron BA.4-5 variant is manufactured using the same processes as for the original monovalent vaccine (BNT162b2) followed by combining the Omicron BA.4-5 variant mRNA with BNT162b2 mRNA in equal amounts (15 µg each) prior to lipid nanoparticle formation.

- Module 4 comprised of a pharmacology study in mice comparing the immunogenicity of the Omicron BA.4-5 monovalent and the original/Omicron BA.4-5 bivalent vaccines against the Wuhan strain and Omicron BA.1, BA.2 and BA.4-5 and Delta either as part of the primary series of immunisation or as boosters following the primary series of immunisation with the original vaccine (*Study VR-VTR-10976*). To compare immune responses elicited by the original, Omicron BA.1 and Omicron BA.4/BA.5 variant-modified vaccine candidates, mouse sera from the study with the Omicron BA.1 bivalent vaccine (*Study VR-VTR-10944*; Submission PM-2022-03551-1-2) were also tested concurrently with 1 month post third dose sera from the new study in the same pseudovirus neutralisation assay runs. The following summary is based on the Health Canada evaluation report (Appendix 1) and the TGA evaluator's review of immunogenicity data 1 month after the 3rd (booster) dose.

- The original/Omicron BA.4-5 bivalent vaccine as a booster dose after two primary series of the original vaccine (BNT162b2) induced cross-variant neutralisation against the original Wuhan strain, Delta and Omicron lineages BA.1, BA.2, BA.2.12.1 and BA.4-5. Both the BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising antibody (NAb) titres against all Omicron sublineages tested (newer subvariants such as BQ.1.1 and XBB.1 not tested) than the original monovalent vaccine, and higher NAb titres against BA.4-5 than the original/BA.1 bivalent vaccine. Interestingly, NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine than the BA.4-5 monovalent vaccine (see comparison table below), possibly related to the lower BA.4-5 mRNA dose in the bivalent vaccine. However, the BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced similar B and T cell responses, with low cross-reactive B cell response to the Wuhan and Omicron BA.1 strains, but similar T cell response to the Wuhan and BA.4-5 strains.

Neutralising antibody (NAb) titres 1 month after a booster dose of monovalent or bivalent vaccine formulations following a primary series of immunisation with the original vaccine

Vaccines	Variants					
	Wuhan	Delta	BA.1	BA.2	BA2.12.1	BA.4-5
NAb Titre						
Original	70546	17911	1308	1378	973	603
BA.1 monovalent	21998	8454	7575	7030	404	1136
Original/B.1 bivalent	65839	28865	3366	16677	10385	15522
BA.4-5 monovalent	65839	28865	3366	16677	10385	15522
Original/BA.4-5 bivalent	34457	13291	3537	5391	4294	5446
NAb titre ratio						
BA.1 monovalent : Original	0.31	0.47	5.8	5.1	4.2	1.9
Original/BA.1 bivalent : BA.1 monovalent	3.0	2.3	1.0	1.4	1.1	1.1
BA.4-5 monovalent : Original	0.93	1.6	2.6	12	11	26
Original/BA.4-5 bivalent : Original	0.49	0.74	2.7	3.9	4.4	9.0
Original/BA.4-5 bivalent : BA.4-5 monovalent	0.52	0.46	1.1	0.32	0.41	0.35

- Overall, the Original/Omicron BA.4-5 bivalent vaccine as a booster dose induced broader NAb responses than the original monovalent vaccine. NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine (0.25 + 0.25 μg) than the BA.4-5 monovalent vaccine (0.5 μg); however, B and T cell responses were similar for the monovalent and bivalent vaccines.
- There were no protection studies for the Original/Omicron BA.4-5 bivalent vaccine. No toxicity studies on the bivalent vaccine were submitted. This is acceptable since the new mRNA (famtozinameran) uses the same backbone and manufacture platform as tozinameran and there are no changes to vaccine formulation except for the additional mRNA.

CONCLUSIONS AND RECOMMENDATION

- The original/Omicron BA.4-5 bivalent vaccine as a booster dose was immunogenic in mice and induced significantly higher neutralising antibodies against Omicron sublineages (newer sublineages such as BQ.1.1 and XBB.1 not tested) than the original monovalent vaccine. NAb titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine (0.25 + 0.25 μg) than the BA.4-5 monovalent vaccine (0.5 μg); however, B and T cell responses were similar for the monovalent and bivalent vaccines.
- There are no nonclinical objections to the provisional approval of the original/Omicron BA.4-5 bivalent vaccine.
- The proposed Product Information document accompanying the sponsor's letter of 15 December is acceptable from a nonclinical perspective.

APPENDIX 1 EVALUATION OF NONCLINICAL DATA

The following is based on the Health Canada evaluation (D22-6141024), plus 1 month post dose 3 data, which were not reviewed in the HC report. In addition, results of B and T cell responses provided in an updated report (VR-VTR-10976 (PRL-COVID-Ms-2022-06), Ver 4.0, dated 15 Dec 2022) are evaluated.

PRIMARY PHARMACODYNAMICS

VR-VTR-10976 (PRL-COVID-Ms-2022-06) - Study Report

The objective of this study is to evaluate the immunogenicity and breadth of coverage of BNT162b2 BA.4/BA.5 vaccines as either monovalent or bivalent (1:1 mixture of BNT162b2 and BNT162b2 BA.4/BA.5) formulations in both naïve and BNT162b2-experienced mice.

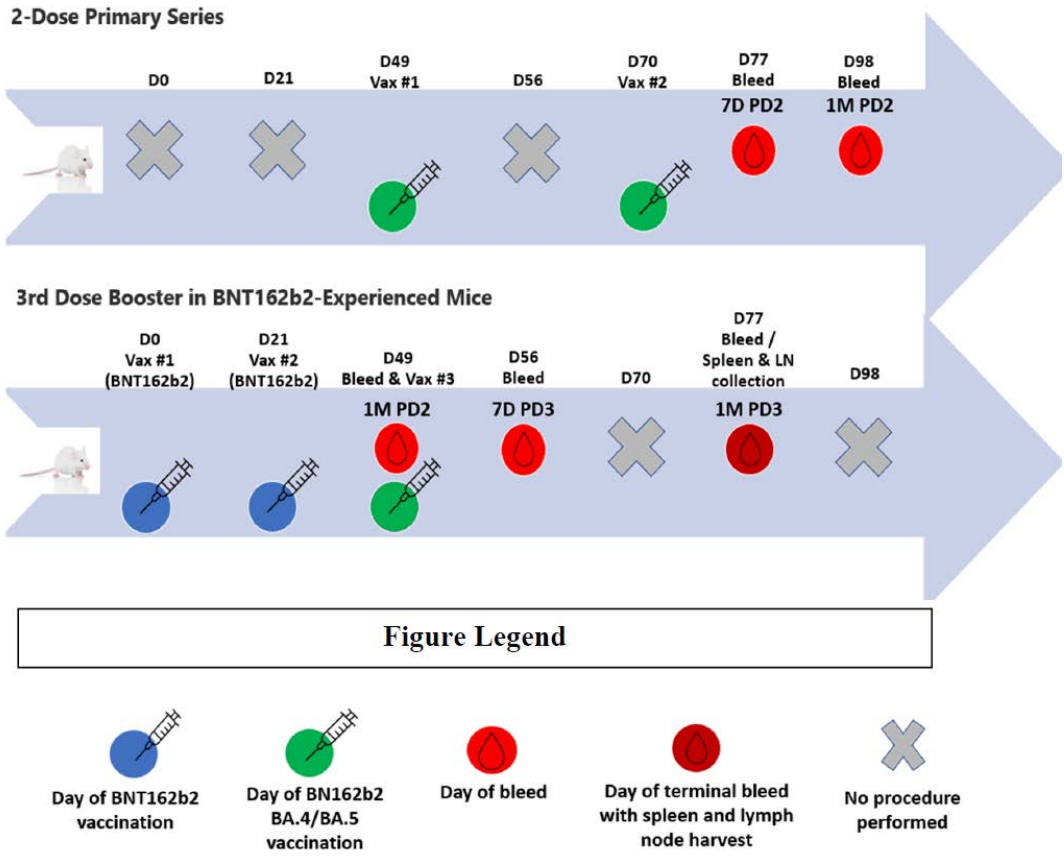
Rationale:

BNT162b2 encodes the full-length SARS-CoV-2 spike glycoprotein in a prefusion conformation and has been highly effective against COVID-19; however, as new SARS-CoV-2 variants of concern (VOCs) emerge, variant-modified vaccines may serve to optimally protect against current and future variants. The mutations of the Omicron BA.4/BA.5 variant were applied to BNT162b2 to generate an Omicron BA.4/BA.5 variant-modified vaccine (BNT162b2 BA.4/BA.5) that was evaluated in mice as both a monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5). formulation. The modRNAs are encapsulated into lipid nanoparticles (LNPs) to protect the modRNA from degradation and to enable delivery of the RNA into host cells after intramuscular (IM) injection.

Study Design:

To assess the impact of a variant-modified BNT162b2 BA.4/BA.5 vaccine on the immune response as a 3rd dose booster, BNT162b2-experienced mice received a booster with either a monovalent or bivalent BA.4/BA.5 vaccine one month after receiving the second dose of BNT162b2 (as part of the standard two-dose series given at Day 0 and Day 21). Sera was collected at multiple time points for evaluation of the neutralising antibody response against the reference strain and Omicron sublineages. Immunogenicity of a 2-dose primary series of the monovalent and bivalent BA.4/BA.5 vaccines was also evaluated in a cohort of naïve mice.

Figure 1. Study design timeline



***Study design*:**

	Group #	N	Vax (Day 0) (µg)	Vax (Day 21) (µg)	Vax (Day 49) (µg)	Vax (Day 70) (µg)	Vaccination (Day of Study)	Bleed (Day of Study)	Tissue harvest
Neg Control	1	5 / 5	X	X	Saline	Saline	49, 70	77 (7DPD2)[a] 98 (1MPD2)	Spleen and LN @ D77 (n=5)
Two dose primary series cohort	2	10	X	X	Omi BA.4/BA.5 P2 (0.5 µg)	Omi BA.4/BA.5 P2 (0.5 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	N/A
	3	10	X	X	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	49, 70	77 (7DPD2) 98 (1MPD2)	N/A
(BNT162b2 experienced) 3rd dose booster cohort	4	10	BNT162b2 (0.5)	BNT162b2 (0.5)	Omi BA.4/BA.5 P2 (0.5 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)
	5	10	BNT162b2 (0.5)	BNT162b2 (0.5)	BNT162b2 + Omi BA.4/BA.5 P2 (0.25 µg + 0.25 µg)	X	0, 21, 49	49 (1MPD2) 56 (7DPD3) 77 (1MPD3)[a]	Spleen and LN @ D77 (n=5)

a. Tissue harvest performed, spleens and lymph nodes collected.

***Study schedule*:**

Week	Day	Date	Procedure
0	0	25-May-2022	Vax #1 (Groups 4 and 5)
3	21	15-Jun-2022	Vax #2 (Groups 4 and 5)
7	49	13-Jul-2022	Vax #1 (Groups 1-3) Bleed (1MPD2) and Vax #3 (Groups 4 and 5)
8	56	20-Jul-2022	Bleed (7DPD3) (Groups 4 and 5)
10	70	03-Aug-2022	Vax #2 (Groups 1-3)
11	77	10-Aug-2022	Bleed (7DPD2) ® (Groups 1[a]-3)
			Terminal Bleed (Groups 1,[b] 4, 5) **Terminal bleed with Spleen and LN harvest (1MPD3) = (15 of the 25 terminally bled mice)**
14	98	31-Aug-2022	**Terminal Bleed (1MPD2) ® (Groups 1[c]-3)**

Test article:

Item #	Test articles	Description of Antigen	DS Lot #	DP Lot #	DP Matrix	Vials # / Storage
1	Saline	0.9% NaCl	N/A	B2106062	N/A	3 aliquots, RT
2	modRNA BNT162b2 LNP	BNT162b2 V09	00715221-27-DS	00709594-0566-LNP	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C
3	modRNA Omi BA.4/BA.5_P2 LNP	Covid modRNA, pST4-mod_Vac_Omi_BA.4/BA.5_P2	00716042-0096-pVV00880	00717722-0004 F1	10 mM Tris/300 mM Sucrose, pH 7.4	4 x 0.3 mL/vial, -80°C

Assay readout:

Evaluation and Sample Type	Time Points	Testing Facility
Pseudovirus neutralization test (pVNT) (sera)	49, 56, 77, 98	Pfizer
B and T cell analysis (spleen and LN)	77	Pfizer

Pseudovirus used in the neutralisation assay

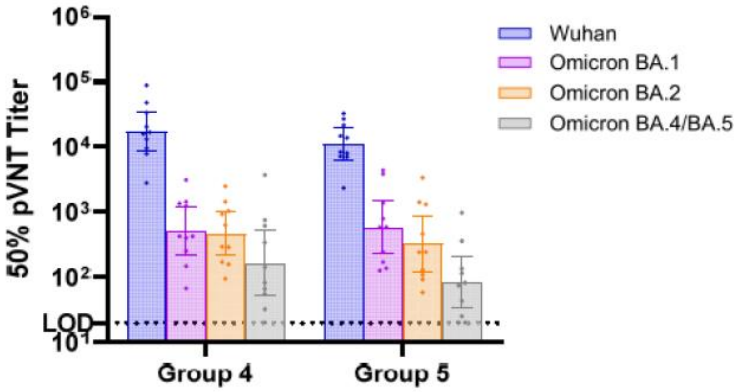
Pseudovirus stocks were generated in HEK-293T cells (ATCC, ref. #CRL-3216) using SARS-CoV-2 spike plasmid DNA and vesicular stomatitis virus (VSV; VSVΔG(G)-GFP virus: Kerafast, ref.# EH1019-PM) for use in the neutralisation assays.

Results:

Immunogenicity

Initial immunization of a 2-dose primary series of BNT162b2 at a 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralising antibody response against the Wuhan strain and substantially lower neutralising titers against Omicron BA.1, BA.2, and BA.4/BA.5 (Figure 2). Consistent with prior studies, BA.4/BA.5 titers were the lowest of the Omicron sublineages tested. Overall, the responses were similar across Group 4 (monovalent booster group) and Group 5 (bivalent booster group), with slightly lower Omicron BA.2 and BA.4/BA.5 titers observed in Group 5.

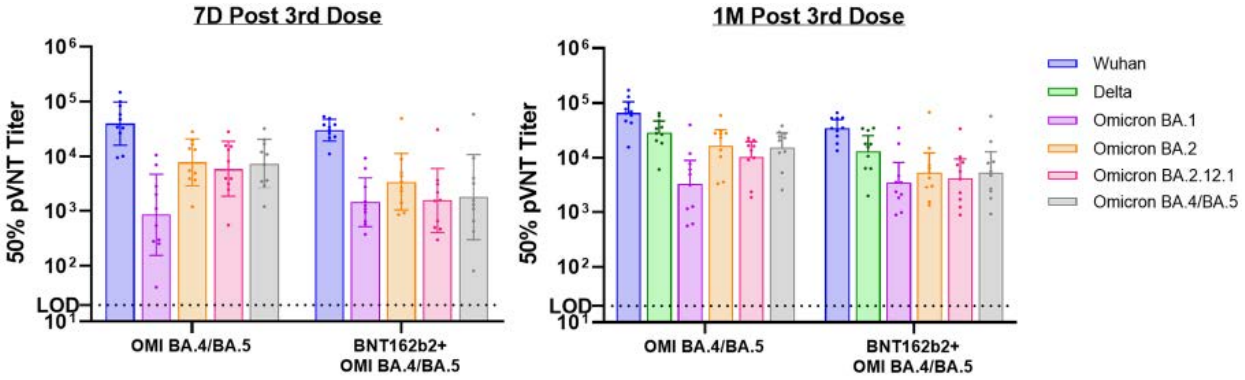
Figure 2. Functional neutralising antibody responses elicited by immunization of naïve mice with 2-doses of BNT162b2 (Groups 4 and 5)



Two groups of 10 female Balb/c mice were immunized IM on Days 0 and 21 with 0.5 µg of BNT162b2. Neutralising antibody responses against pseudovirus of Wuhan reference strain (blue) and Omicron BA.1 (red), BA.2 (orange), and BA.4/BA.5 (purple) variants of concern were measured by pseudovirus neutralisation assay at 1 month post 2nd dose.

Intramuscular immunization of BNT162b2-experienced Balb/c mice with a 0.5 µg dose level of LNP-formulated BA.4/BA.5 variant-modified vaccines as a 3rd dose booster increased neutralising antibody responses against the Wuhan reference strain and Omicron BA.1, BA.2, BA.2.12.1, and BA.4/BA.5 (Figure 3). In the monovalent group, Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5 neutralising titers increased by 2, 2, 17, and 45-fold, respectively, at 7 days post booster compared to 1 month post BNT162b2 Dose 2. A further increase in neutralising antibody responses was observed 1 month post third dose compared to 7 days post third dose. At 1 month post booster, the fold difference compared to 1 month post BNT162b2 Dose 2 increased to 4, 7, 36, and 94 for Wuhan, Omicron BA.1, BA.2 and BA.4/BA.5, respectively. In the bivalent group, Wuhan, Omicron BA.1, BA.2, and BA.4/BA.5 neutralising titers increased by 3, 3, 11, and 22-fold, respectively, 7 days post booster and 3, 6, 17, and 66-fold, respectively, 1 month post booster compared to after BNT162b2 Dose 2. A balanced response against Omicron sublineages was achieved with both monovalent (BNT162b2 BA.4/BA.5) and bivalent (BNT162b2 + BNT162b2 BA.4/BA.5) formulations. The monovalent BA.4/BA.5 formulation elicited slightly higher Omicron neutralising titers compared to the bivalent BA.4/BA.5 formulation.

Figure 3. Neutralising antibodies elicited by immunization of BNT162b2-experienced mice with Omicron BA.4/BA.5 variant-modified monovalent and bivalent modRNA vaccines as a 3rd dose booster



	7DPD3					1MPD3					
Vaccine	Wuhan	Omicron				Wuhan	Delta	Omicron			
		BA.1	BA.2	BA.2.12.1	BA.4/BA.5			BA.1	BA.2	BA.2.12.1	BA.4/BA.5
OMI BA.4/BA.5	40174	865	7884	5944	7454	65839	28865	3366	16677	10385	15522
BNT162b2+ OMI BA.4/BA.5	30316	1459	3478	1573	1813	34457	13291	3537	5391	4294	5446

10 Balb/c mice per group were immunized IM on days 0 and 21 with 0.5 µg of BNT162b2; one month following dose 2, mice were boosted with an additional dose of either monovalent vaccine BNT162b2 BA.4/BA.5 (0.5 µg) or bivalent vaccine BNT162b2 + BNT162b2 BA.4/BA.5 (0.25 µg of each). Neutralising antibody responses against the Wuhan reference strain (blue) and Omicron BA.1 (purple), BA.2 (orange), BA.2.12.1 (pink), and BA.4/BA.5 (grey) variants of concern were measured by pseudovirus neutralisation assay at 1 week post 3rd dose and at 1 month post 3rd dose with the addition of the Delta variant (green).

REVIEWER'S COMMENTS:

In the current submission, the Sponsor provided a new murine study (VR-VTR-10976), where the monovalent or bivalent Omicron BA.4/BA.5 variant-modified vaccines were tested as a two dose primary series in naïve Balb/c mice and as a 3rd dose booster in BNT162b2- experienced Balb/c mice. Sera were collected 1 month following a two dose primary series (vaccinations on Day 0 and Day 21) of the BNT162b2 prototype vaccine and 7 days after a 3rd dose of either a monovalent or bivalent BA.4/BA.5 variant-modified vaccine. Sera were tested with a non-validated SARS-CoV-2 pseudovirus neutralisation assay. Initial immunization of a two dose primary series of BNT162b2 at 0.5 µg dose level to establish the cohort of BNT162b2-experienced mice (Groups 4 and 5) showed a high neutralising antibody response against the Wuhan strain and substantially lower neutralising titers against Omicron BA.1, BA.2, and BA.4/BA.5.

A BA.4/BA.5 booster elicited higher BA.4/BA.5 neutralising titers with a consistent response across Omicron sublineages, suggesting that a BA.4/BA.5-modified vaccine may be more effective overall against Omicron sublineages. The monovalent BA.4/BA.5 formulation induced higher responses to Omicron sublineages than the BA.4/BA.5 bivalent vaccine, however, these responses were better than those induced by the approved BNT162b2 vaccine. In addition, immunogenicity data in mice support that a BA.4/BA.5 bivalent vaccine may give a stronger immune response to BA.5 than the BA.1 bivalent vaccine.

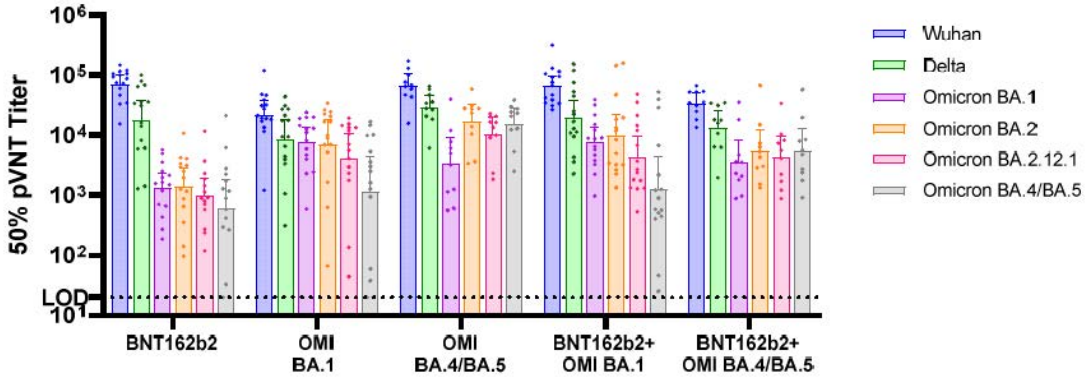
Reviewer's overall conclusion on non-clinical studies

Adding to the previously reviewed information of the already characterized safety profile, these data further demonstrate that no new safety concerns are expected with the use of the bivalent mRNA-based platform.

Additional data (not summarised in the HC evaluation report):

To compare immune responses elicited by Omicron BA.1 and Omicron BA.4/BA.5 variant-modified vaccine candidates, 1 month post third dose mouse sera from PRL-COVID-Ms-2022-01 study (VR-VTR-10944; Submission PM-2022-03551-1-2) were tested concurrently with 1 month post third dose sera from the present study (VR-VTR-10976, Ver 3) in the same pseudovirus neutralisation assay runs. Balb/c mice from both studies (2022-01 and 2022-06) were of a similar age range, were vaccinated and boosted following the same dosing interval, and at the same dose level.

Figure 4. Neutralising antibodies (1 month after the 3rd dose) elicited by immunisation of BNT162b2-experienced mice with Omicron BA.1 and BA.4/BA.5 variant-modified monovalent and bivalent modRNA vaccines as a 3rd Dose Booster



Vaccine	Wuhan	Delta	Omicron			
			BA.1	BA.2	BA.2.12.1	BA.4/BA.5
BNT162b2	70546	17911	1308	1378	973	603
OMI BA.1	21998	8454	7575	7030	4049	1136
OMI BA.4/5	65839	28865	3366	16677	10385	15522
BNT162b2 + OMI BA.1	65389	19206	7652	9855	4380	1294
BNT162b2 + OMI BA.4/BA.5	34457	13291	3537	5391	4294	5446

Balb/c mice were immunised IM on days 0 and 21 with 0.5 µg of BNT162b2; one month following dose 2, mice were boosted with an additional dose of either monovalent Omicron modified vaccine (0.5 µg) or bivalent vaccine (0.25 µg of each; 0.5 µg total) or BNT162b2 prototype vaccine. Omicron BA.1 variant-modified vaccines and BNT162b2 prototype were administered in PRL-COVID-Ms-2022-01 (15 mice per group) and BA.4/BA.5 variant-modified vaccines were administered in PRL-COVID-Ms-2022-06 (10 mice per group). All sera were tested concurrently in the same pseudovirus neutralisation assay runs. Neutralising antibody responses against the Wuhan reference strain (blue), Delta (green), Omicron BA.1 (purple), BA.2 (orange), BA.2.12.1 (pink), and BA.4/BA.5 (grey) variants were measured by pseudovirus neutralisation assay at 1 month post 3rd dose.

Comparison of neutralisation titres (titre ratios) induced by different vaccines

Vaccines	Variants					
	Wuhan	**Delta**	**BA.1**	**BA.2**	**BA2.12.1**	**BA.4-5**
BA.1 monovalent : Original	0.31	0.47	5.8	5.1	4.2	1.9
Original+BA.1 bivalent : BA.1 monovalent	3.0	2.3	1.0	1.4	1.1	1.1
BA.4-5 monovalent : Original	0.93	1.6	2.6	12	11	26
Original+BA.4-5 bivalent : Original	0.49	0.74	2.7	3.9	4.4	9.0
Original+BA.4-5 bivalent : BA.4-5 monovalent	0.52	0.46	1.1	0.32	0.41	0.35

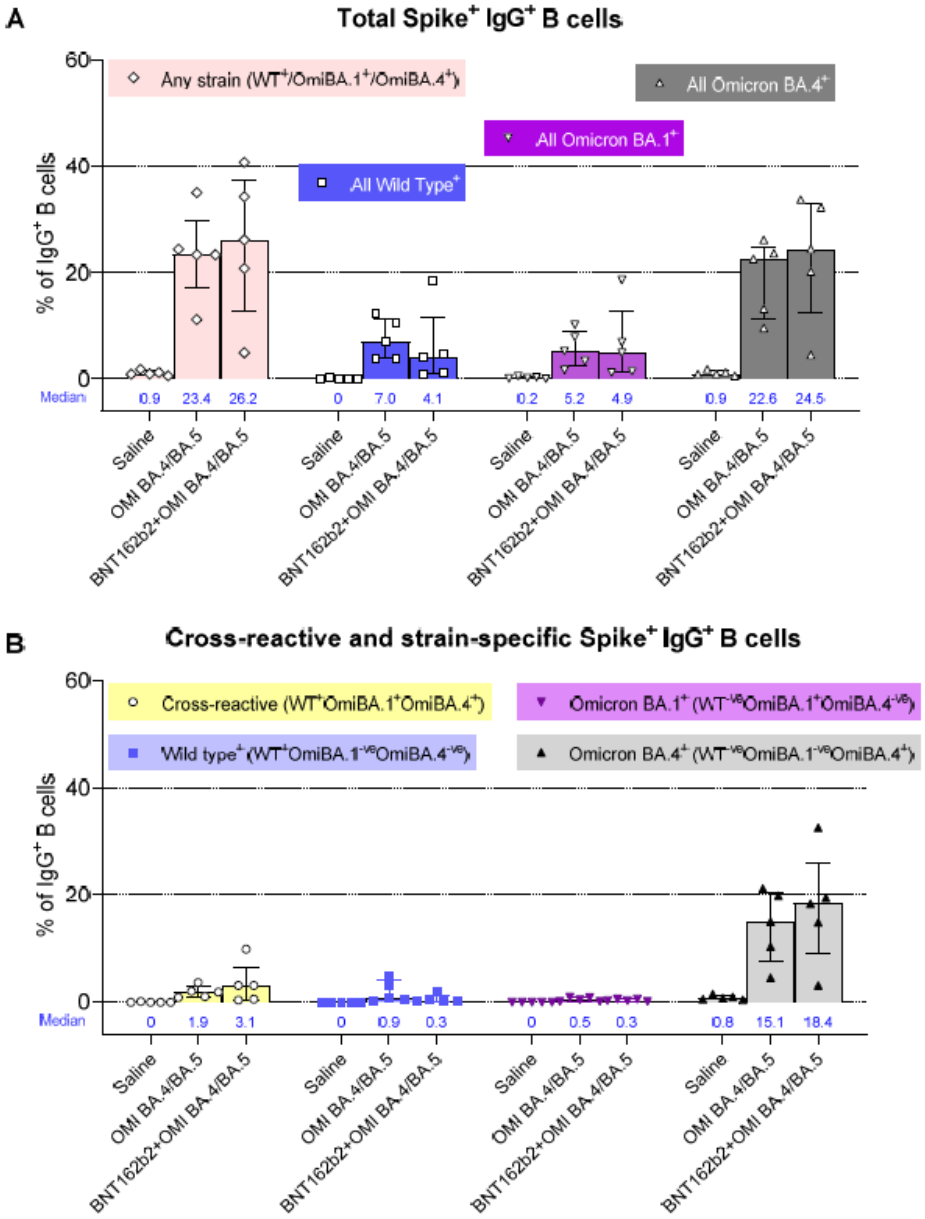
B cell response

Spike-specific IgG+ B cells in lymph nodes were determined by flow cytometry using fluorochrome-coupled spike trimer proteins.

In BNT162b2-experienced mice, both BA.4-5 monovalent and BNT162b2+BA.4-5 bivalent vaccines administered as a 3rd dose booster induced a high frequency of total spike-specific B cells (any strain), with the greatest proportion of the response accounted for by Omicron BA.4-antigen specific B cells (Fig. 5A). The booster dose induced low levels of cross reactive spike positive B cells that could bind all three strains, with slightly more cross-reactive B cells observed with the bivalent BNT162b2+BA.4-5 vaccine than with the BA.4-5 monovalent vaccine (Fig. 5B).

Conclusion: Both BA.4-5 monovalent and BNT162b2+BA.4-5 bivalent vaccines induced predominantly Omicron BA.4 strain-specific Spike+ B cells, with a low frequency of WT or Omicron BA.1 Spike+ B cells. The responses were not different between the monovalent and bivalent vaccines.

Figure 5. Spike-specific B cell response in lymph nodes following immunisation of BNT162b2-experienced mice with Omicron BA.4/BA.5 variant-modified monovalent and bivalent mRNA vaccines as a 3rd dose booster (n=5)



Each symbol represents an individual animal; bars depict median frequency with interquartile range.

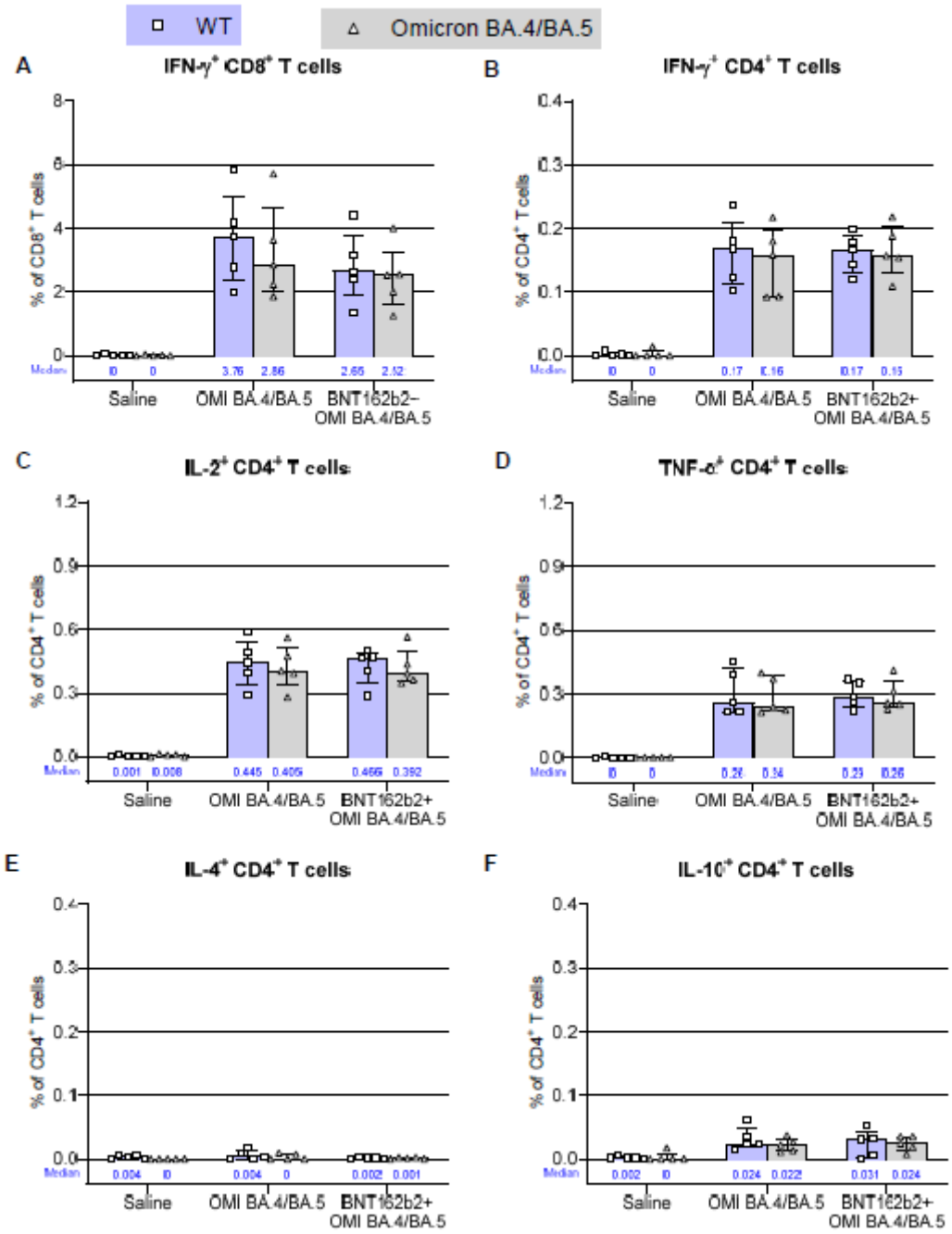
T cell response

Spike-specific T cells in spleen were determined by intracellular cytokine staining (ICS) and flow cytometry after stimulation with peptide pools (15aa, 11aa overlap) representing the spike protein sequence of WT or Omicron BA.4-5.

In BNT162b2-experienced mice, BA.4-5 monovalent or BNT162b2+BA.4-5 bivalent vaccines administered as a 3rd booster dose elicited similar frequencies of spike-specific T cells (Fig. 6). The frequency of IFN-γ-producing CD8+ T cells was higher than CD4+ T cells. The frequency of IL-2- and TNF-α-producing CD4+ T cells was slightly higher than the frequency of CD4+ T cells producing IFN-γ. Both vaccines induced low levels of IL-4 or IL-10-expressing CD4+ T cells, suggesting a Th1-biased T-cell response. The T-cell response to the peptide pool of WT and Omicron BA.4/BA.5 was

similar, suggesting that the variant-specific mutations have minimal impact on the polyclonal T-cell response.

Figure 6. Spike-specific T cell response in spleens following immunisation of BNT162b2-experienced mice with Omicron BA.4/BA.5 variant-modified monovalent and bivalent mRNA vaccines as a 3rd dose booster (n=5)



Each symbol represents an individual animal; bars depict median frequency with interquartile range.

TGA Evaluator's Comments:

- As expected, neutralising titres increased 1 month after the 3rd (booster) dose relative to 1 week after the 3rd dose for all vaccines.
- Both BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising titres to all Omicron sublineages tested than the original monovalent vaccine.

- Both the BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines induced higher neutralising antibody titres to BA.4-5 than the original/BA.1 bivalent vaccine.
- Neutralising titres against Omicron BA.2 and BA.4-5 sublineages (as well as the Wuhan strain and Delta variant) were lower for the Original/BA.4-5 bivalent vaccine than the BA.4-5 monovalent vaccine.
- The BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines as a 3rd booster dose induced similar total spike-specific IgG+ B cells, predominantly accounted for by Omicron BA.4-antigen specific B cells and with a low cross-reactive response to the Wuhan and Omicron BA.1 strains.
- The BA.4-5 monovalent and Original/BA.4-5 bivalent vaccines elicited similar, Th1-biased T cell responses. The T cell response to the peptide pool of WT and Omicron BA.4/BA.5 was similar, suggesting that polyclonal T-cell responses are not affected by variant-specific mutations.

Australian Government
Department of Health
Therapeutic Goods Administration

Nonclinical Evaluation Report

ChAdOx1-S COVID-19 Vaccine [COVID-19 VACCINE ASTRAZENECA®]

Submission No: PM-2020-06115-1-2
Sponsor: AstraZeneca AB

January 2021

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New vaccine
Sponsor: AstraZeneca AB
Generic name: **ChAdOx1-S COVID-19 Vaccine**

Trade name: **COVID-19 VACCINE ASTRAZENECA**
Dose form and strength: Multi-dose vial contains 5 x10^{11} VP (ChAdOx1-S) in 5 mL
Vaccine Type: Recombinant (replication-defective chimpanzee adenovirus vector expressing the SARS CoV-2 S surface glycoprotein)

Submission No: PM-2020-06115-1-2
Tox file No: E21-210182
TRIM reference: D20-3849280

Date authorised: 28 January 2021

This report has been revised to incorporate the sponsor's s.31 response and replaces the Nonclinical Evaluation Report issued at Round 1

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

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SUMMARY

- AstraZeneca Pty Ltd has applied for provisional registration of a new vaccine, ChAdOx1-S COVID-19 vaccine (also known as AZD1222). AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 Spike (S) surface glycoprotein for the prevention of COVID-19 in persons 18 years of age and older. The proposed dosing regimen is two doses of 5×10^{10} VP/0.5 mL, given 4-12 weeks apart intramuscularly (IM).

- The sponsor has generally conducted adequate pharmacology studies. As part of a rolling submission limited toxicity studies were provided (which included a GLP compliant repeat dose) with AZD1222. A bio-distribution study and a main developmental and reproductive toxicity (DART) study in mice are pending.

- AZD1222 was found to be immunogenic in nonclinical studies in mice, ferrets, rhesus macaques and pigs. AZD1222 induced both humoral and cellular immune responses in the animal models (T cell response was not assessed in ferrets). Antibodies neutralised virus strains isolated at the beginning of the pandemic as well as the D614G mutant (no data on activity against the new variants isolated in the UK and South Africa, which are believed to be more transmissible). However, antibodies generally declined after 2 weeks of the booster dose, raising long term immunity concerns.

- The vaccine provided some protection in ferrets and monkeys when challenged 4 weeks after the 1st or 2nd dose based on lower viral load (in both models), milder lesions (in ferrets) and lower computed tomography (CT) scores (in macaques). Prime – boost vaccine regimen did not add to better protection in these studies, although a booster dose enhanced antibody titres and T cell responses. There were no studies on protection of older animals from SARS-CoV-2 infection or duration of protection after immunisation. The animal studies were of short term; long term immunity was not assessed.

- Anti-ChAd vector antibodies were detected in monkeys immunised with AZD1222. Immunogenicity of AZD1222 might decrease with repeated vaccination due to induction of anti-vector antibodies.

- No effects of AZD1222 on cardiovascular and respiratory parameters were observed in mice following vaccination with 2.59×10^{10} VP (>500 times the clinical dose on a mg/kg basis) by the clinical route (IM). Specific observations for neurological effects in the repeat dose toxicity study in mice revealed no vaccine-related findings.

- A distribution study with AZD1222 is ongoing. In a study with a vaccine consisting of the same chimpanzee adenovirus vector, ChAdOx1 as AZD1222 but expressing a hepatitis B virus antigen, the highest vector virus RNA was detected at the injection site, followed by draining lymph node and spleen, with low distribution to other tissues, and there was no virus shedding in urine or faeces.

- The ChAdOx1 vector is expected to have negligible risks of integrating into the human genome or recombination with human adenoviruses.

- No systemic toxicity was observed in repeat dose toxicity studies where mice were injected 3 doses of AZD1222 by the IM route, 14 days apart. Treatment-related findings were limited to (reversible) acute inflammation at the injection sites. Dosing for this study was adequate, where each dose was 1000 times the human dose of VP/kg ($\sim 1.23 \times 10^{12}$ VP/kg body weight in mice *cf.* 1×10^{9} VP/kg in 50 kg humans). Use of a single species (mice) is consistent with the relevant guidelines and demonstration of good immunogenicity supports the use of this species as an appropriate animal model for the toxicity study.

- A reproductive toxicity study with AZD1222 is currently ongoing.

- AZD1222 was well tolerated locally in mice, where local reactions due to AZD1222 were minimal inflammation.

CONCLUSIONS AND RECOMMENDATION

- Primary pharmacology studies indicate the vaccine elicits both neutralising antibody and cellular immune responses to the spike (S) antigen in animal models.
- Antibodies generally declined quickly over 2 weeks after the booster dose of AZD1222. Long term immunity was not assessed in nonclinical studies.
- Immunogenicity of AZD1222 might decrease with repeated vaccination due to induction of anti-vector antibodies.
- New variants are continuously emerging and require testing to confirm effective immunity and protection by AZD1222.
- The ChAdOx1 vector is expected to have negligible risks of integrating into the human genome or recombination with human adenoviruses.
- Repeat dose toxicity studies with the proposed vaccine in mice raised no safety issues. Treatment-related findings were limited to (reversible) acute inflammation at the injection sites.
- A reproductive toxicity study is currently ongoing and therefore Pregnancy category B2 is considered acceptable. Without adequate assessment of effects on embryofetal development, this vaccine is not recommended for use in pregnant women.
- There are no nonclinical objections to the provisional registration of the vaccine, provided efficacy of the prime-boost regimen has been satisfactorily addressed by clinical studies.
- The proposed non-clinical statements in the draft Product Information are acceptable.
- The following post approval commitments are to be provided by the sponsor as outlined in the Table below:

Issue	Commitment	Estimated timeline
Distribution study	To provide the AZD1222 tissue distribution study (Study 514559) report	Audited draft report 30MAR21 Final report 13APR21
Reproductive toxicity	To provide the AZD1222 development and reproductive study (Study 490843) report	Audited summary 1FEB21 Audited draft report 15FEB21 Final report 8MAR21

ASSESSMENT

AstraZeneca Pty Ltd has applied for provisional registration of a new vaccine, ChAdOx1-S COVID-19 vaccine, also known as AZD1222 (Trade name: COVID-19 Vaccine AstraZeneca), under section 23AA of the Act. AZD1222 is indicated for the prevention of COVID-19 in persons 18 years of age and older. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 Spike (S) surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. The proposed dosing regimen is two doses of 5×10^{10} VP/ 0.5 mL, given 4-12 weeks apart intramuscularly (IM).

General comments

Module 4 comprised of nonclinical studies with clinical formulation. As a rolling submission, not all nonclinical data have been provided. The following data will be submitted later.

- AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse. Study Number 514556 (1169DM).
- A main developmental and reproductive toxicity (DART) study in mice.

Pharmacology

AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 Spike (S) surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus.

Primary pharmacology

Pharmacology studies were done in mice (BALB/c, CD-1), ferrets, rhesus macaques and pigs, and were only designed to address short term immunity (i.e. neutralising antibodies (NAbs), T cell responses and antibody response following immunisation and challenge) generally for up to 28 days or less. Immunogenicity data from a booster dose (particularly NAbs) varied significantly among species, which made it difficult to relate to the likely clinical impact without further investigation. Prime – boost vaccine regimen did not add to better protection in these studies. Subtyping of cellular immune cells (such as memory T cells) were not provided. A T_H1-biased immune response was observed in mouse, and pigs (note, it was not investigated in ferrets and were limited in both the NHP studies). No evidence of vaccine-elicited disease enhancement were observed in any of the protection studies. There were no studies on protection of older animals from SARS-CoV-2 infection or duration of protection after immunisation. The immunisation doses in all animal studies (6×10^9 – 5.12×10^{10} VP/animal) were less than or equal to the clinical dose (5×10^{10} VP/subject) based on dose per subject.

Immunogenicity

Mouse studies: In mice (CD-1 & BALB/c) in the first study, a single IM dose (6×10^9 VP/animal) induced IgG (higher levels of IgG2a compared to IgG1), neutralising antibodies, IFN-γ and increased S-specific CD4+ and CD8+ T cell populations. In the second study, an IM booster dose (6×10^9 VP/animal) in mice given 4 weeks after the prime dose did not statistically increase T-cell responses compared with the prime only vaccination, 3 weeks after the prime or booster vaccination, and anti-S antibodies were significantly increased after the booster dose in only BALB/c mice, but not in CD-1 mice. Both studies showed that the cellular responses were predominantly IFN-γ+ and TNF-α+ positive T cells, with negligible frequencies of IL-4+ and IL-10+ cells, which together with findings of higher levels of IgG2a compared to IgG1 (in the first study) are suggestive of a T_H1-biased immune response.

Ferret studies: Ferrets vaccinated with a single IM dose of AZD1222 (2.5 x 10^{10} VP/animal) induced NAbs, which were detectable from day 7 and titres increased up to day 28 (last sampling time before challenge). In this cohort, NAbs were enhanced upon exposure to SARS-CoV-2 virus challenge (28 days post immunisation) and remained at significantly high levels 28 days post challenge (DPC). In contrast, in IM prime-boost vaccine studies (28 days intervals, with the same dose), a significant increase in NAbs was detected 7 days after the boost before rapidly decreased after another 7 days. The levels continued decreasing and no subsequent increase was detected upon exposure to the challenge (on day 56) up to day 70 (last sampling point). The limited, transient benefit of the booster dose was confirmed in a second study in ferrets (6285) where a similar trend with increases in NAbs for only a week followed by rapid decline was observed. Furthermore, no subsequent increase was detected upon exposure to the challenge virus. Cellular immunity was not investigated in the ferret studies.

Monkey studies: In both NHP studies, a single dose only (Study 6284) or a single dose followed by a booster, 4 weeks apart (Doremalen et al., 2020) by IM injection of AZD1222 (2.5 x 10^{10} VP/animal) induced variable levels of NAbs in all vaccinated animals, suggesting the vaccine is immunogenic. In the booster animals, S-specific and NAbs were significantly increased compared to prime dose on day 14; however, this declined rapidly within 2 weeks. Interestingly, no statistically significant difference was observed in the T cell response including IFNγ+ T cells compared to controls 4 weeks post vaccination before virus challenge. In addition, the IFN-γ+ T cell response in the animals administered the booster was slightly lower than that in the prime only animals, with both vaccinated groups higher than the control group. Cellular immune response kinetics after vaccination was not determined.

Pig studies: A small number of pigs (*n*=3) received one (prime) or two doses (prime-boost, 28 days later) of AZD1222 (with 5.12 × 10^{10} VP/animal). Study results show a trend towards higher humoral (NAbs) and cellular responses (IFN –γ, CD4+, CD8+ T cell) in animals vaccinated with the prime-boost regimen. This was the only study where addition of a booster dose of the vaccine induced a sustained NAb response, at least for a short period of time measured in the study (14 days).

Protection against infection

AZD1222 provided some protection against SARS-CoV-2 challenge in ferrets and monkeys.

SARS-CoV-2 replicates in ferrets, but only causes mild clinical diseases and respiratory system pathology in this species (Muñoz-Fontela *et al*. 2020). Following challenge (3 x 10^4 $TCID_{50}$, SARS-CoV-2), no histological abnormalities developed in vaccinated and control animals in the first study. A decrease in virus shedding was detected by qRT-PCR from nasal wash, oral swab and rectal swab samples. However, in the second study (Study 6285), mild pulmonary lesions were observed in control animals, with a reduced severity in animals vaccinated with AZD1222 and a slightly increased severity (i.e. exacerbation) in animals vaccinated with formalin-inactivated SARS-CoV-2 (5 x 10^6 PFU) 7 DPC. Subsequent measurements revealed no significant differences 13-14 days post-challenge between the control and vaccinated groups. Vaccination with AZD1222 delayed lung pathology, whilst the opposite effect was observed with formalin-inactivated SARS CoV-2. There was little difference measured between prime only and prime – booster responses indicating little benefit of administration of a booster vaccination. Challenge doses were not comparable between the two ferrets studies as different units of virus dose were used (PFU or $TCID_{50}$), but the most likely difference in susceptibility could be due to a higher challenge dose used in the second study. The level of NAbs raised in response to vaccination appeared to correlate with reduced viral RNA in the upper respiratory tract with little difference in viral RNA between responses in prime only and prime boost groups.

SARS-CoV-2 replicates in rhesus macaques causing pathological features of viral pneumonia and variable induction of mild clinical disease (Muñoz-Fontela *et al*. 2020). Following challenge (5 x 10^6 PFU of SARS-CoV-2) in the single dose vaccination study, CT scan revealed a lower CT score at day 5

in vaccinated animals compared to controls and viral RNA was significantly lower on 7 DPC in BAL of the vaccinated animals compared to controls. Subsequent measurements revealed no significant differences 12-14 days post-challenge between the control and vaccinated groups. No clear distinction regarding adverse findings were reported in the lung in the provided histopathology data between controls and vaccinated animals at 13/14 DPC. In the prime – boost study clinical scores, viral loads in tissues, BAL gRNA and sgRNA levels were similar in both prime only and prime – boost animals but significantly lower than controls, suggesting both immunisation regimens provided protection and the booster dose did not add to better protection. An unexpected and unexplained finding of significantly higher viral RNA load in the intestinal tissues of prime–boost vaccinated animals compared to prime-only-vaccinated animals or control animals at 7 DPC requires further investigation. Serum IFN-γ levels (Th-1 cytokine) were upregulated in prime-only vaccinated animals, but not in prime-boost or unvaccinated control animals after virus challenge, and serum IL-10 levels (Th-2 cytokine) were upregulated in unvaccinated controls and one prime-only monkey but not in any prime-boost animals (other cytokines, including TNF, IL-2 and IL-4, were unaffected in any groups). Together, both these NHP studies show some protection in vaccinated animals 5-7 DPC with no evidence of vaccine-elicited disease enhancement.

Is the vaccine effective on all variant SARS-CoV-2 viruses?

During the course of the pandemic, mutations have arisen in the viral Spike (S) protein that has become dominant amongst viruses sequenced from patient samples. The sponsor has provided evidence showing that D614G mutation in the SARS-CoV-2 spike protein does not adversely affect virus neutralisation by Abs induced by AZD1222. However, other new variants are continuously emerging and require further testing to confirm effective immunity and protection against these new strains.

Prime/boost dose regimens

The observed lack of clear boosting of antibody or protection responses following a second immunisation in the mouse, ferret and monkey models requires further investigation. As discussed by the sponsor there are many possibilities for these observations including a high antigen causing dose blunting boost, clonal deletion by triggering apoptosis of high avidity T cells, inducing tolerance in targeted T cells or leading to terminal differentiation and exhaustion of T cells. It should be noted the dose regimen i.e. two doses at an interval of 4 to 12 weeks for clinical use have not been assessed in nonclinical studies (all studies in animal models were done with a dosing interval of 4 weeks).

Sterilizing Immunity

Sterilizing immunity, commonly seen with adenovirus vectors could also have played a role in the potential adenoviral removal after boost, hence limiting the effect of the booster. Vector antibodies were detected in the macaque pharmacology study (Doremalen et al., 2020) and are well known to be immune-dominant. Immunogenicity of AZD1222 might decrease with repeated vaccination due to induction of anti-vector antibodies.

Risk of ChAdOx1 integration into human genome and recombination with other adenoviruses.

The ChAdOx1 vaccine vector was derived from chimpanzee adenovirus isolate Y25 (CHAdY25), which is similar to the human adenovirus (HAdV) and have been grouped with HAdV species E (Dicks et al., 2012 & Lange et al., 2019). CHAdY25, was genetically modified and incapacitated for replication by deletion of the essential E1 genes and non-essential E3 genes. The E4 gene was modified to allow growth of the virus in T-REx-293 cells (that provide E1 region), during manufacturing of the vaccine. SARS-CoV-2 spike protein was inserted, to induce relevant antibodies. With these modifications, AZD1222 cannot replicate in the host cells. Vaccine quality will need to be assessed by the quality evaluator to ensure the vaccine has not gained replication competency during

manufacture. AdV are generally not considered to be capable of genetically integrating into the host genome but stay as episomal DNA in the nucleus of host cells until the cell is destroyed.

The likelihood of complementation and recombination of AZD1222 with other adenoviruses have been assessed as very low by the Office of the Gene Technology Regulator and recombination generally only occurs within the same adenovirus species (OGTR 2020). Naturally occurring homologues (wild-type ChAdV) are only known to circulate in chimpanzees. Adenovirus (AdV) infects epithelial cells of the respiratory, gastrointestinal, conjunctiva and urinary tract tissues (Lynch *et al.*, 2016). Administration of ChAdOx1 VP by the IM route is unlikely to encounter wild type AdV in epithelial cells as the VPs are expected to be largely confined to the IM injection site and distribution mainly to the draining lymph nodes and spleen.

The inserted gene encodes the full length SARS-COV-2 spike protein, and does not add virulence to the AdV vector. There is low homology between E1 flanking regions of the AZD1222 and HAdVs. Site directed recombination was used to insert the SARS-COV-2 spike into the E1 gene of AZD1222 making it stable and further decreasing the likelihood of recombination.

Safety pharmacology

No effects of AZD1222 on cardiovascular and respiratory parameters were observed in mice following vaccination with 2.59 x 10^{10} VP (>500 times the clinical dose on a mg/kg basis) by the clinical route (IM). With no CNS effects (based on a negative Irwin score) in mice in the repeat dose study with AZD1222, these safety pharmacology studies are sufficient and acceptable as per WHO guideline on nonclinical evaluation of vaccines (WHO 2005).

Pharmacokinetics

Distribution, persistence and shedding

A distribution study with AZD1222 (**Study 514559**) is ongoing.

A distribution and shedding study using ChAdOx1 vector with a hepatitis B virus (HBV) insert after 1 or 2 IM injections (on days 1 and 28) in mice showed distribution to all tissues tested in this study. The tissues tested were limited (i.e. brain, heart, draining inguinal lymph node, kidney, liver, lung, gonads, and spleen) and were all positive on day 2 by qRT-PCR. Levels on day 28 after the second dose were either below detection or low, indicating clearance in these tissues. The highest levels were noted at the site of administration (skeletal muscle) on day 2; however, data for day 28 were not available to determine how long it persisted at this site. No vaccine shedding was detected in faeces and urine (tested on days 2 and 7 post vaccination) and no vector DNA was detected in blood samples. Two other bio-distribution studies with a similar vector (ChAd63) were also submitted but both these studies were of limited use due to insensitive/invalidated vector detection methods or different route of vaccine administration (ear) to the clinical route (IM) of AZD1222. Clinical studies with the ChAd63 vector have also shown no shedding in urine but very low levels detected in skin swabs of the injection site following dosing by the IM route (Clinical Overview p13).

The study with AZD1222 (**Study 514559)** will provide information on the persistence of the vector at the injection site after a single IM injection of AZD1222 and will include bio-distribution in more tissues (i.e. bone marrow, adrenal and mammary glands, axillary and mesenteric lymph nodes, CNS and thymus) and at more time points (i.e. day 2, 3, 9 and 29 post vaccination). Given that the AZD1222 vaccine is made up of viruses that to not replicate, the vaccine is expected to be confined to the IM injection site and the draining lymph nodes, with low distribution to other tissues and no virus excretion is expected.

Repeat-dose toxicity

A 6 week, GLP compliant repeat-dose toxicity study was conducted in mice where 3 doses of AZD1222 (3.7x10^{10} VP/dose) were injected by the IM route 14 days apart followed by a 4 week

recovery period. The 3 doses administered to mice exceeded the intended number of injections (2) used in the proposed clinical regimen. Dosing for this study was adequate, where each dose was 1000 times the human dose of VP/kg (~1.23×10^{12} VP/kg body weight in mice *cf.* 1×10^{9} VP/kg in 50 kg humans). Use of a single species (mice) is consistent with the relevant guidelines and demonstration of good immunogenicity supports the use of this species as an appropriate animal model for the toxicity study. Vaccine testing in both sexes and group sizes (20/sex/treatment group, plus 5/sex/group for observation of recovery) were appropriate.

Treatment related findings were limited to acute inflammation in the injected area with minimal inflammation, cellular infiltration, oedema and haemorrhage. At the end of the 28-day recovery period, the inflammation changes showed total recovery. Other treatment related effects included increased body temperature and decreased albumin/globulin ratio (which did not completely recover). Overall, 3 IM injections of AZD1222 were locally and systemically well tolerated with treatment-related findings limited to transient acute inflammation at the injection site, which is a common reaction to vaccination. Similar findings were also observed with other ChAdOx1 vaccines (MERS, Chikungunya and influenza), plus draining lymph nodes enlargement and increased germinal centre.

Genotoxicity

No genotoxicity studies were conducted. This is in line with relevant guidelines.

Carcinogenicity

Carcinogenicity studies were not conducted. This is acceptable based on its duration of use, and applicable guidelines.

Reproductive toxicity

As AZD1222 is indicated for the active immunisation of individuals from the age of 18 years, this vaccine can be potentially administered to pregnant women and women with childbearing potential. A main fertility and embryofetal development study is ongoing and until the final report is made available, this vaccine is not recommended for use in pregnant women.

A preliminary GLP compliant, developmental and reproductive toxicity study in mice showed no test item related adverse effects on female fertility, fetal or pup survival, gross pathology in pups or in dams and fetal visceral or skeletal findings. The mice were dosed IM 2 x with 2.59×10^{10} VP AZD1222 (13 days) before the start of mating and once during gestation (GD6) for the embryofetal development group and GD6 and 15 for the littering group. Each dose was >500 times the clinical dose of AZD1222 based on VP/kg. This study was conducted with only a small number of female mice (n=15-16). AZD1222 induced an active immune response (antibody responses to S-glycoprotein) in all mice dams in the vaccine group. The exposure of fetuses (GD17.5) and pups (LD14) to vaccine-specific maternal antibodies was also demonstrated suggesting lactational transfer of anti-S glycoprotein antibodies.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2. Given animal reproductive studies have not been completed, this is considered appropriate.

Local tolerance

Local tolerance was assessed in the repeat dose toxicity study with AZD1222 and studies with ChAdOx1 MERS and Chikungunya vaccines. Local reactions were limited to minimal inflammation

(oedema, haemorrhage and mononuclear cell and mixed cell infiltration) at the injection site and in some animals extending to the sciatic nerve (no findings in nerve axons) and were reversible.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Key findings from nonclinical data are adequately identified in the Safety Specification (Part II, Module SII) of the Risk Management Plan (Version 1, of 21 December 2020).

PRODUCT INFORMATION

ROUND 1 EVALUATION — MILESTONE 3

The following comments refer to the draft Product Information document (Doc ID-004452129 v1).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The proposed text is acceptable:

> "It is unknown whether COVID-19 Vaccine AstraZeneca may impact fertility. No data are available."

Use in pregnancy

The sponsor proposes Pregnancy Category B2 and the following statement, which is acceptable:

> "There are a limited amount of data from the use of COVID-19 Vaccine AstraZeneca in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine associated risk.
>
> Animal reproductive toxicity studies have not been completed.
>
> As a precautionary measure, vaccination with COVID-19 Vaccine AstraZeneca is not recommended during pregnancy. Use of COVID-19 Vaccine AstraZeneca in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks."

Use in lactation

The following proposed text does not contain any nonclinical data and therefore requires the clinical evaluator to comment on acceptability.

> "There are no or limited data from the use of COVID-19 Vaccine AstraZeneca in lactating women. A risk to breastfed newborns/infants cannot be excluded.
>
> As a precautionary measure, it is preferable to avoid vaccination with COVID-19 Vaccine AstraZeneca when breastfeeding."

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Statements on the mechanism of action are supported by nonclinical data.

> "COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-COV-2. Following administration, the S glycoprotein of SARS-COV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses."

MAIN BODY OF REPORT

INTRODUCTION

BACKGROUND

AstraZeneca Pty Ltd has applied for provisional registration of a new biological entity, ChAdOx1-S also known as AZD1222 (Trade name: COVID-19 Vaccine AstraZeneca), under section 23AA of the Act. AZD1222 is indicated for the prevention of COVID-19 in persons 18 years of age and older. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 Spike (S) surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. The proposed dosing regimen is two doses of 5×10^{10} VP/0.5 mL per dose given 4 to 12 weeks apart intramuscularly (IM).

RELATED VACCINES

AZD1222 is a first adenovirus vector vaccine to be registered in Australia. There currently is no vaccines registered for COVID-19.

RECOMBINANT SARS-COV-2 SPIKE PROTEIN GENE

SARS-CoV-2 S (GenBank entry MN908947, amino acids 2-1273) was codon optimized to improve expression in human cells. DNA encoding the human tissue plasminogen activator (tPA) signal sequence was fused upstream of the S protein coding sequence. The tPA leader sequence enhances immunogenicity (Alharbi et al., 2017).

VIRAL VECTOR CONSTRUCT AND PRODUCT FORMULATION

AZD1222 (CAS No.: 2420395-83-9; other name: ChAdOx1 nCoV-19) is a recombinant, replication-deficient (E1 and E3 deleted) chimpanzee adenovirus that encodes the SARS-CoV-2 (nCoV-19) spike protein with a tissue plasminogen activator (tPA) leader sequence.

s47

s47

AZD1222 is formulated as indicated in Table 1.1. The quantity per vial represents label claim value of 5 mL. Each vial also includes a target overfill of 1.1 to 1.5 mL. The pH of the solution is 6.6. There are no novel excipients.

Table 0.1. Product formulation

Ingredient	Function
AZD1222	Active
L-Histidine	Buffer
L-Histidine hydrochloride monohydrate	Buffer
Sodium chloride	Tonicifier/stabilizer
Magnesium chloride hexahydrate	Stabilizer
Disodium edetate (dihydrate)	Stabilizer
Sucrose	Tonicifier/stabilizer
Ethanol (anhydrous)*	Stabilizer
Polysorbate 80	Surfactant/stabilizer
Water for Injection	Aqueous vehicle

s47

*** May be substituted with diluted ethanol manufactured from compendial ethanol**

OVERSEAS REGULATORY STATUS

A similar application has been made in the EU, UK, Canada, Switzerland and Singapore (all between September-October 2020). UK has granted authorisation approved via Regulation 174 for emergency supply (December 2020)

SCOPE OF NONCLINICAL DATA

Module 4 comprised of nonclinical studies with clinical formulations. As a rolling submission, not all nonclinical data have been provided. The following data will be submitted later.

- AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse. Study Number 514556 (1169DM)
- A main developmental and reproductive toxicity (DART) study in mice

PRIMARY PHARMACOLOGY

A summary of nonclinical pharmacology program is shown in the Table below.

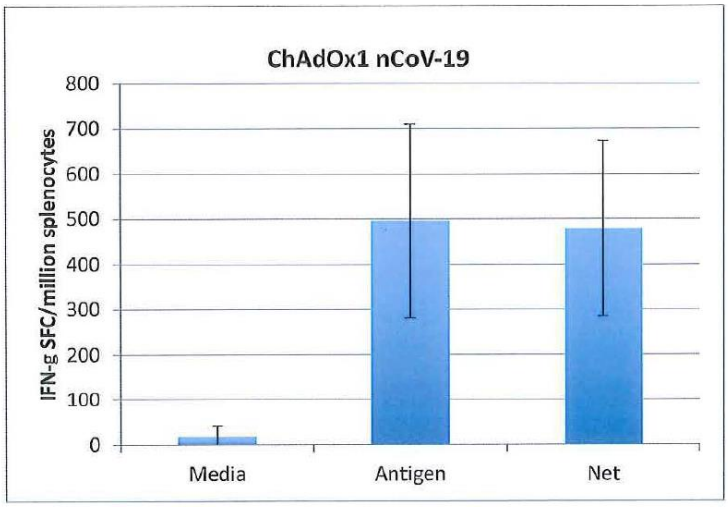
Summary of nonclinical pharmacological program

Study objective	Animal model and test material	Study
Murine immunopotency for different batches	Balb/C , Single dose **IM** $5x10^9$ VP, ChAdOx1 nCoV-19 (ADZ 1222), Jenner Institute Stock Number 3705 (either engineering run batch or ex PALL, CJ29, 5OL batch).	INT-ChAdOxl nCoV-19-POT-001 & INT-ChAdOx1 nCoV19-POT-004 (Internal report)
Murine Immunogenicity	Balb/C and CD-1 mice Single dose, IM 6 x 10^9 VP AZD1222	Van Doremalen et al. 2020
	Balb/C and CD-1 mice Day 0 and 28, IM 6 x 10^9 VP AZD1222	AR001111 & Graham et al. 2020
Non-human Primate Immunogenicity and protection	Rhesus macaque Day 0 and 28, IM 2.5 x 10^{10} VP AZD1222 or ChAdOx1 GFP	Van Doremalen et al. 2020
Non-human Primate Immunogenicity and protection	Rhesus macaques Single dose, IM 2.5 x 10^{10} vp AZD1222	6284
Ferret Immunogenicity and protection	Ferret Single dose, IM or IN 2.5 x 10^{10} vp AZD1222 or ChAdOx1 GFP	20-01125
	Ferret Day 0 and 28, IM 5.12 × 10^{10} vp AZD1222 or or ChAdOx1 GFP	6285
Porcine Immunogenicity	White-Landrace-Hampshire cross-bred pigs Day 0 and 28, IM 5.12 × 10^{10} vp AZD1222	AR001111 & Graham et al. 2020
Effect of D614G mutation on NAbs	Sera from n=6 ferrets from Study 20-01125, day 35 or 45 post-prime dose used to test 2 D614 variants and 1 G614 variants	20-01700

MURINE IMMUNOGENICITY

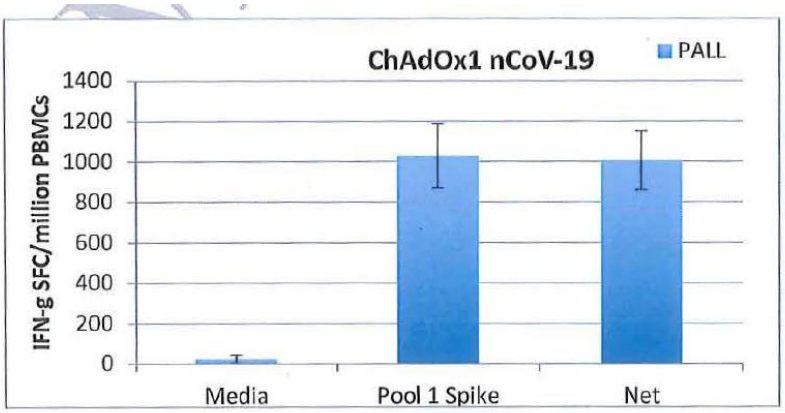
INT-ChAdOxl nCoV-19-POT-001 & INT -ChAdOx1 nCoV 19-POT -004 (Internal report)
Mice ♀ BALB/c, (n =5- 6)
Age: not specified
Route: **IM** with 1 single dose of $5x10^9$ VP, ChAdOx1 nCoV-19 (ADZ 1222), Jenner Institute Stock Number 3705 (either engineering run batch or ex PALL, CJ29, 5OL batch).
Immunity assessment: 12-13 days post vaccination the mice were sacrificed and the spleens harvested for a standard IFN-y ELISpot assay

- CBF GMP engineering batch of ChAdOxl nCoV-19, was immunogenic, with the number of spot forming cells per million splenocytes greater than 15, after background subtraction in the ELlSpot assay for 5 out of 5 mice (**Study INT-ChAdOxl nCoV-19-POT-001**, see Figure below).



Mean group data for CBF GMP engineering batch ChAdOx1 nCoV-19 (ADZ 1222)

- PALL produced ChAdOxl nCoV-19, at a dose of $5x10^9$ VP was immunogenic, with the number of spot forming cells per million splenocytes greater than 15, after background subtraction in the ELlSpot assay for 6 out 6 mice (**Study INT-ChAdOx1 nCoV-19-POT -004,** see Figure below).



Mean group data for PALL generated ChAdOx1 nCoV-19 (ADZ 1222)

Conclusion: both batches were equally immunogenic.

Doremalen et al., 2020
Mice BALB/c, (n = 5) and outbred CD-1 (n = 8)
Age: at least 6 weeks
Route: **IM** with 1 single dose of AZD1222 (6 x 10^9 VP) or ChAdOx1 GFP (control vaccine)
Immunity assessment: Humoral and cellular immune response (9-14 days after vaccination)

- Total IgG titres, were detected against spike protein subunits S1 and S2 in all vaccinated mice (Figure 1a), with higher levels of IgG2a compared to IgG1 (Figure 2).
- Virus-specific NAbs (cytopathic assay using SARS-CoV-2 virus and Vero E6 cells) were detected in all mice vaccinated with ChAdOx1 nCoV-19 (Figure 1b). Higher amounts were detected in CD-1 mice compared to BALB/c.
- Splenic T-cell response measured by IFN-γ ELISpot and intracellular cytokine staining (ICS), was detected against peptides spanning the full length of spike construct (Figure 1c).
- ↑ CD4+& CD8+ T cells were observed in both strains after immunization with increased expression levels of IFNγ and TNF and low expression of IL-4 and IL-10.

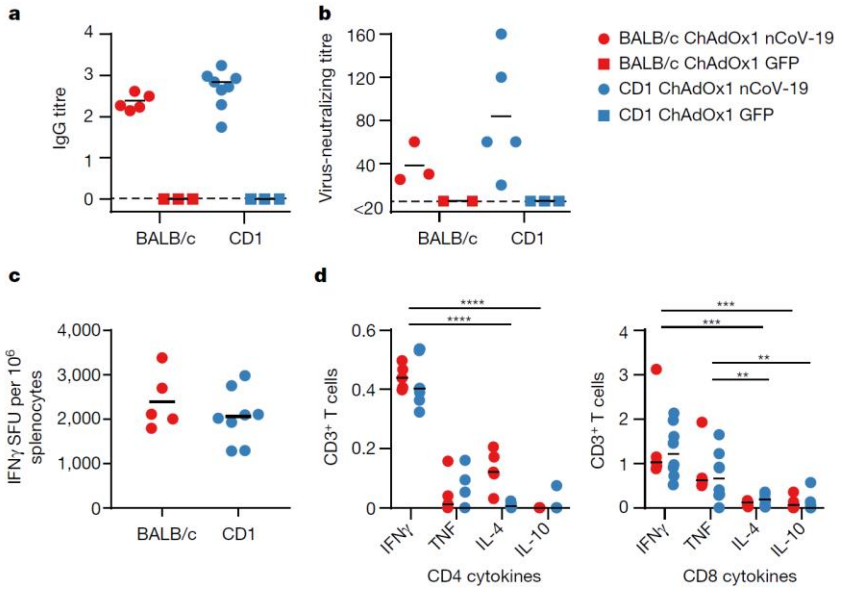


Figure 1. Humoral and cellular immune response to ChAdOx1 nCoV-19 vaccine in mice

a. End point titre of serum IgG detected against S protein on day 14. **b.** Virus neutralising titre in serum on day 9. **c.** Summed IFN-γ ELISpot responses in splenocytes towards peptides spanning the spike protein on day 14. Control mice had low (<100 SFU) or no detectable response. **d.** Summed frequency of spike-specific cytokine positive CD4+ or CD8+ T cells on day 14. SFU = spot-forming units.

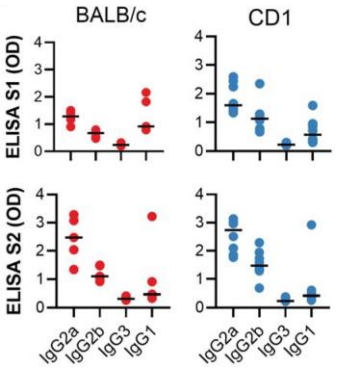
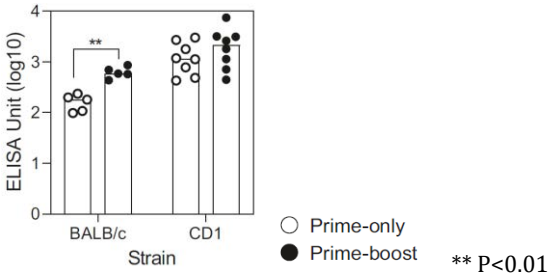


Figure 2. IgG subclass antibodies detected against S1 or S2 protein in sera of BALB/c or CD1 mice

Conclusion: A single dose of vaccine induced IgG (higher levels of IgG2a compared to IgG1), neutralising antibodies, increased S-specific CD4+ and CD8+ T cell populations in both species. Cellular responses were predominantly IFN-γ+ and TNF-α+ positive T cells, with negligible frequencies of IL-4+ and IL-10+ cells. Together these findings are suggestive of a TH1-biased immune response.

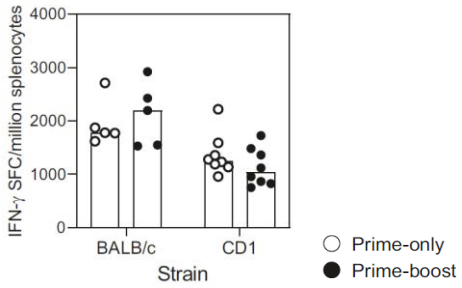
Report no. ar001111 & Graham et al. npj Vaccines. 2020;5:69. https://doi.org/10.1038/s41541-020-00221-3
Mice, inbred (BALB/c, *n* = 5/group) and outbred (CD1, *n*=8/group)
Age: 9-10 weeks
Immunisation: Day 0 (prime only) and 28 (prime and boost)
Route and dose: IM, 6 × 10^9 VP AZD1222
Assessment: Spleens & serum harvested on day 49.

- Antibodies were detectable by ELISA on Day 49 (see Figure below). Antibody titres increased after boost in BALB/c mice, but not in CD1 mice. Neutralisation antibodies were not determined.

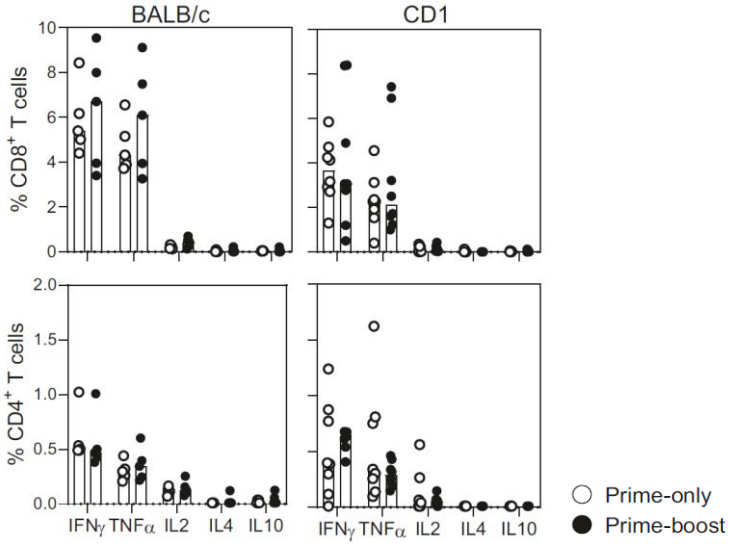


** P<0.01

- Analysis of SARS-CoV-2 S protein specific murine splenocyte responses by IFN-γ ELISpot assay showed no statistically significant difference between the prime only and prime-boost vaccination regimens, in either strain of mice (see figure below).



- Intracellular cytokine staining (ICS) of splenocytes (Figure below) showed that the cellular response was principally driven by CD8+ T cells.
- The predominant cytokine response of both CD8+ and CD4+ T cells was expression of IFN-γ and TNF-α, with negligible frequencies of IL-4+ and IL-10+ cells, suggesting a Th1 biased response.



Conclusion: IM booster dose did not statistically increase T-cell responses compared with the prime only vaccination, although anti-S antibodies were significantly increased after the booster dose in only BALB/c mice, but not in CD-1 mice. Cellular responses were predominantly IFN-γ+ and TNF-α+ positive T cells, with negligible frequencies of IL-4+ and IL-10+ cells, which is suggestive of a TH1-biased immune response.

FERRET IMMUNOGENICITY AND PROTECTION

Study: 20-01125
Ferrets ♀ (*n* = 4 /sex/group except 2/sex for the control groups)
Age: 4 months (Adults)
Body weight: 0.7-1.5 kg
Immunization: Day 0 only or Day 0 & 28,
Route/dose: IM or IN, with 2.5 x 10^{10} VP AZD1222, in 100 µl
Control: PBS, placebo
Challenge: IN, 3 x 10^4 ($TCID_{50}$) of SARS-CoV-2 (SARS-CoV/Australia/VIC01/2020)
NAb assay: SARS-CoV-2 (strain not specified) in cells (not specified).

Study design

Cohort	Test item & route	Day		Virus challenge	Study end
		0	28		
1	AZD1222 IM	Y	N	Day 28	Day 42
	AZD1222 IN	Y	N		
	PBS (control)	Y	N		
2	AZD1222 IM	Y	Y	Day 56	Day 70
	AZD1222 IN	Y	Y		
	PBS (control)	Y	Y		

Observations: Cohort 1 – days 31-39 & Cohort 2 – days 59-67
Sampling/Necropsy: Cohort 1 – days 42- 45, Cohort 2 – days 70-73.

Vaccine associated adverse events

- No injection site reactions or other observable treatment related clinical signs

Neutralising antibodies (NAb)

- Determined by virus neutralisation assay (VNT) with 100 $TCID_{50}$ of SARS-CoV-2 virus (cell line not stated)
- IM: Prime induced low, but detectable NAb, which was significantly increased by the booster dose, peaking 7 days after the booster and then rapidly declined by 5 fold 21 days after the booster. In the prime only group, NAb slightly increased after virus challenge, while the prime-booster animals showed no increase in NAb after challenge. Instead, NAb further decreased to pre-booster titres 2 weeks after challenge (6 weeks after the booster).
- IN: Prime did not induce detectable NAb prior to challenge and, following challenge only 75% of ferrets had measurable levels. Boost induced NAb in all ferrets detectable 7 days later, which were significantly lower than the titres of the IM group and then rapidly declined prior to challenge. NAb did not increase following challenge.

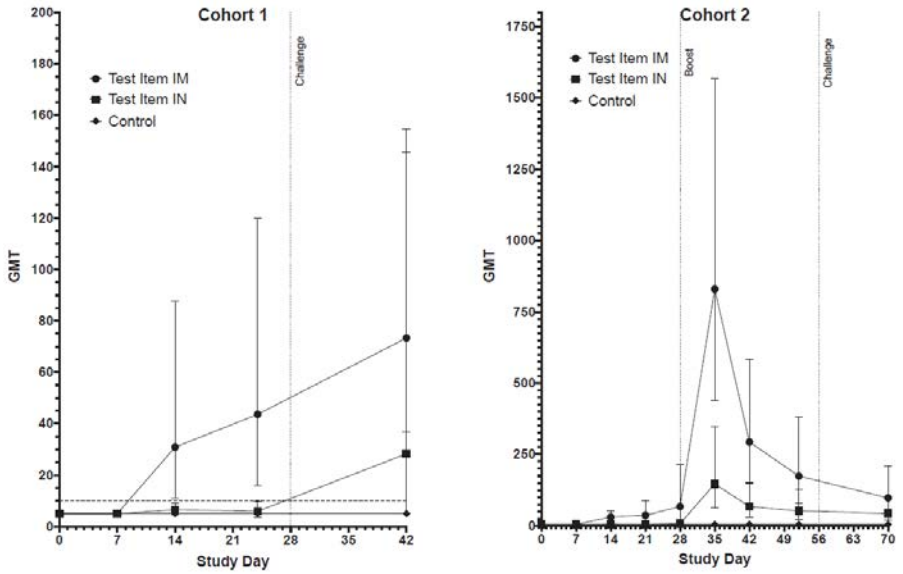


Figure 1. Virus neutralisation titres against SARS-CoV2

Clinical signs following challenge

- No vaccinated ferret showed clinical signs, with clinical scores (based on body temperature, sneezing, activity, etc.) of only 0 throughout the duration of the study

Virology

- A significant decrease in average virus shedding by qRT-PCR from nasal wash and oral swab was observed in all vaccinated groups (both IN and IM routes) post challenge day 3, 5 and 7 (nasal wash only), compared with the unvaccinated group (see figure below). Live virus numbers were not determined.

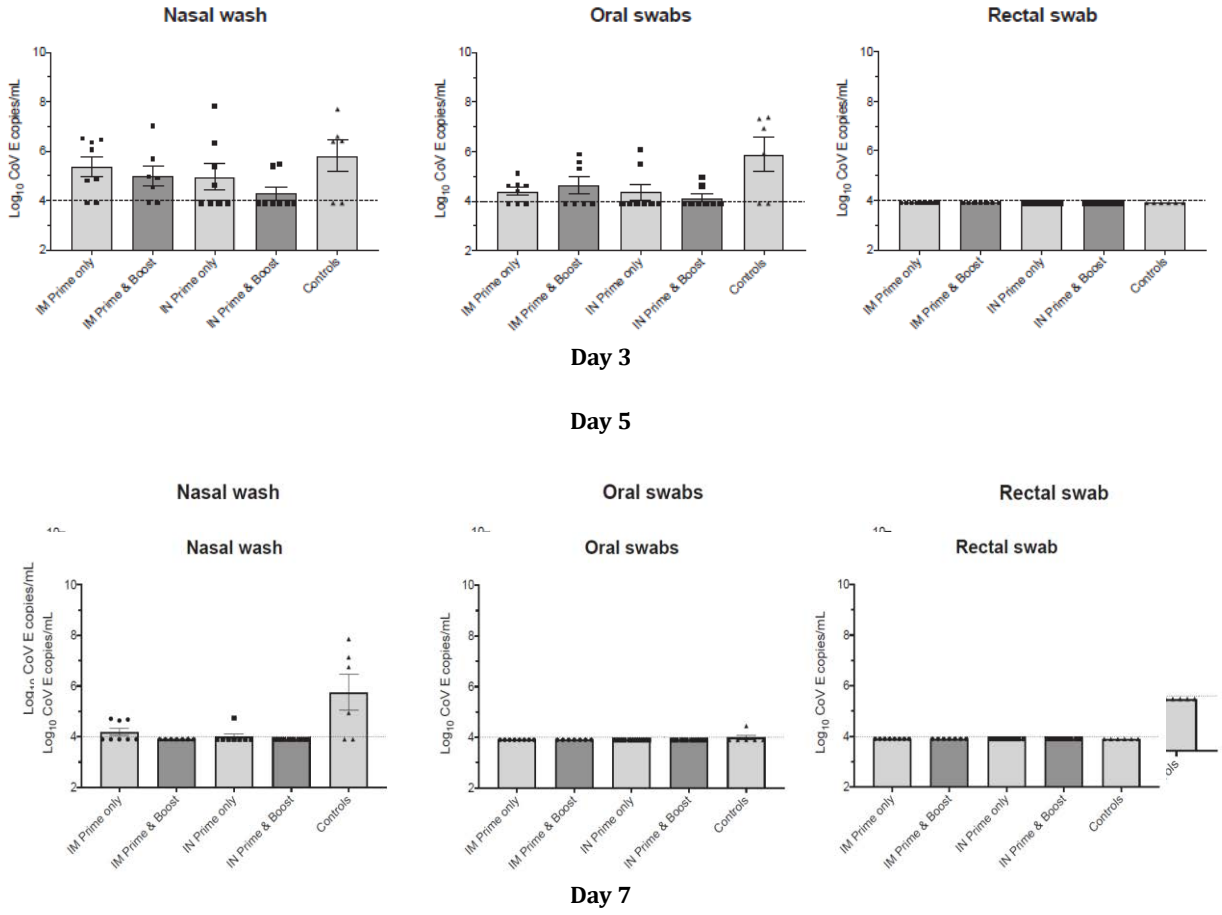


Figure 2. qRT-PCR testing of nasal washes and oral and rectal swabs on day 3, 5 and 7 post challenge

- No virus RNA was detected in tissues (lung, nasal turbinates, pharynx, trachea and retropharyngeal lymph node).
- Cellular immune response and histopathology of the respiratory system were not examined.

Conclusion: AZD1222 was immunogenic in ferrets and induced NAb. A booster dose significantly increased NAb titres, which rapidly declined (within 7 days). The vaccine was more immunogenic (when comparing NAb) by the IM route than by the IN route. However, vaccination by both routes reduced virus shedding. The IN route was slightly better in terms of protection (potentially due to local immunity that is not associated with NAb, which was not investigated).

Summary of prime and booster immunogenicity and protection studies in ferrets

Study: 6285
Ferrets ♀ (*n* = 2-6/group); body weight: ~ 1 kg
Immunization: Day 0 only or Day 0 & 28,
Route/dose: **IM**, with 2.5 x 10^{10} VP AZD1222 or ChAdOx1 GFP (vector control), 10 µg formalin-inactivated SARS CoV-2 in 1% alhydrogel
Control: PBS, placebo
Challenge: IN, 5 x 10^6 PFU of SARS-CoV-2 (Victoria/1/2020, Vero/hSLAM cell passage 3)
NAb assay
Sera were heat-inactivated (30 min, 56 °C), diluted and 60 PFU of SARS-CoV-2 (2019-nCoV/Victoria/1/2020) was added. After 1 h incubation at 37 °C and 5% CO_2, the virus:serum mixture was added to Vero E6 cells and incubated at 37 °C and 5% CO_2. At 4 DPI, cytopathogenic effects were assessed and plaque reduction neutralisation titres (PRNT) were recorded.

Experimental design

Group	Group size (n)	Vaccination day(s)	Challenge day	Cull days (days post infection)
1. ChAdOx1 nCoV-19 prime only	6	0	28	6 (n=2),13 (n=2),14 (n=1),-14 (n=1)*
2. ChAdOx1 nCoV-19 prime boost	6	0, 28	56	6 (n=2), 13 (n=2),14 (n=2)
3a. ChAdOx1 GFP prime only	4	0	28	6 (n=2), 13 (n=1),14 (n=1)
3b. ChAdOx1 GFP prime boost	4	0, 28	56	6 (n=2), 13 (n=1), 14 (n=1
4. Killed SARS CoV-2	6	14	28	7 (n=2), 15 (n=4)
5. Control	2	N/A	56	15 (n=2)

*** Animal 1-5 was euthanised on study day 14 on welfare grounds and was not challenged**

Clinical signs

- Two ferrets of the ChAdOx1 nCoV-19 prime group had sneezing on day 8 post-challenge (DPC). Sneezing was moderate (continuous for the 2-3 minutes of observation) in one ferret and minor (non-continuous). No further sneezing was observed. No sneezing was observed in other groups.
- Nasal discharge and slightly reduced activity were observed in one ferret of the ChAdOx1 nCoV-19 prime boost group on 3 DPC, with no clinical signs on all other days.

Body weight

- No significant difference in body weight gain between groups during the vaccination phase. During the challenge phase, there was a trend of decreased body weight gain between 8 and 13 DPC for the ChAdOx1 nCoV-19 prime and prime-boost groups, and there were differences in AUC to 13 DPC within the population (p=0.0264, one-way ANOVA), but pairwise comparison between groups did not reach significance (see figure below).
- Post-challenge body weight: ChAdOx1 nCoV-19 prime - 2/4 stable, 1/4 increased by 4.5% and 1/4 decreased by 9.2%; ChAdOx1 nCoV-19 prime-boost: stable for majority, 1/4 decreased by 4.8%.

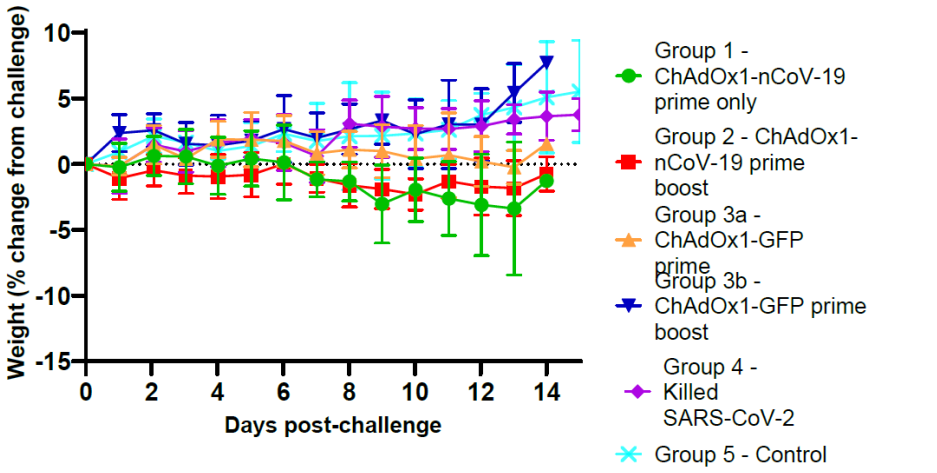


Figure 1. Weight % change post challenge phase

Body temperature

- No significant changes in body temperature in all groups during the vaccination and challenge phases.

Immunogenicity

PRNT - vaccination phase

- Prime-only vaccination induced NAbs, which increased upon exposure to the challenge. In prime-boost cases, an increase in NAbs was detected 7 days after the booster injection, and then markedly decreased after another 7 days (similar pattern to other ferret study 20-01125)
- Animals vaccinated with ChAdOx1-nCoV-19 had higher levels of NAbs compared to animals vaccinated with formalin-inactivated SARS CoV-2 on the day of challenge (see Figure below).

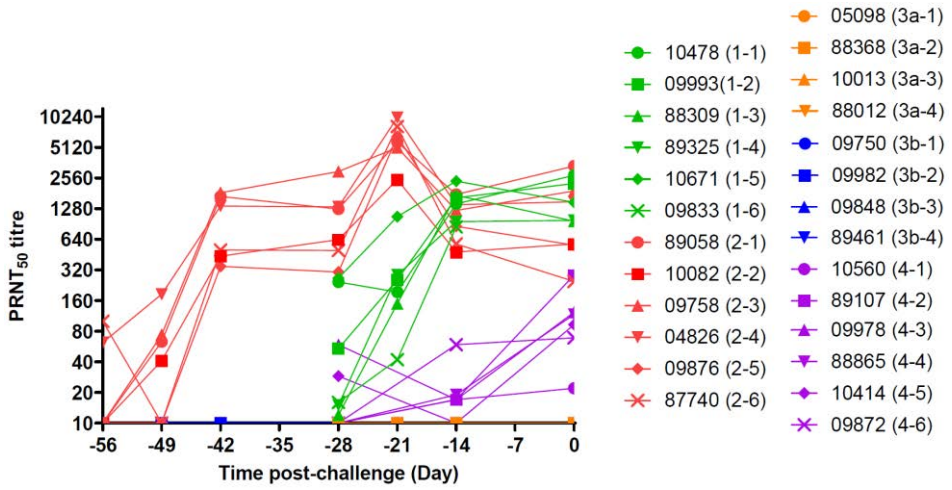


Figure 2.Normalised Plaque Reduction Neutralisation Titres in serum from animals in groups 1, 2, 3a, 3b and 4 during the vaccination phase

PRNT - Post challenge

- No significant increase in PRNT values in ChAdOx1 nCoV-19 prime only and ChAdOx1 nCoV-19 prime boost, similar pattern to ferret Study 20-01125 (see Figure below).
- Significant increases in PRNT value were observed in animals vaccinated with formalin-inactivated SARS CoV-2 with titres similar to the ChAdOx1 nCoV-19 groups

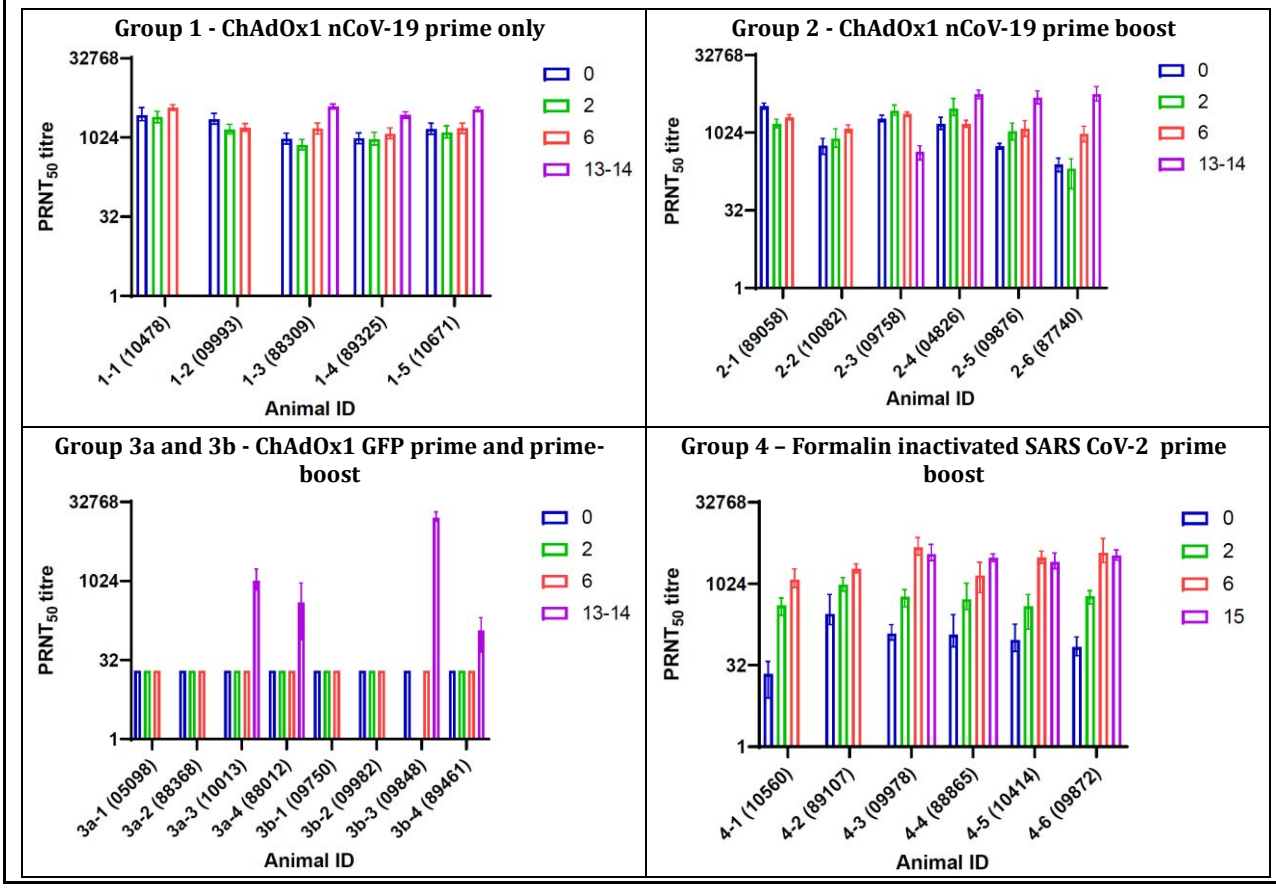


Figure 3. Post-Challenge Plaque Reduction Neutralisation Titres

Nasal wash white cell count after challenge

- Nasal wash white cell counts in the ChAdOx1 nCoV-19 prime group tended to be higher than counts in other groups, with a significant increase in cell count AUC 0-12 DPC (P=0.007, one-way ANOVA). By pairwise comparison of the AUC values, the ChAdOx1 nCoV-19 prime group had significantly higher cell counts than the ChAdOx1 nCoV-19 prime-boost group and GFP prime group.

WBC count after challenge

- White blood cell counts were highly variable; AUC 0-6 DPC was significantly lower in the ChAdOx1 nCoV-19 prime-boost group than in the ChAdOx1 nCoV-19 prime and killed SARS CoV-2 groups (see Figure below). Comparison on WBC on post-challenge days showed no significant difference between groups.

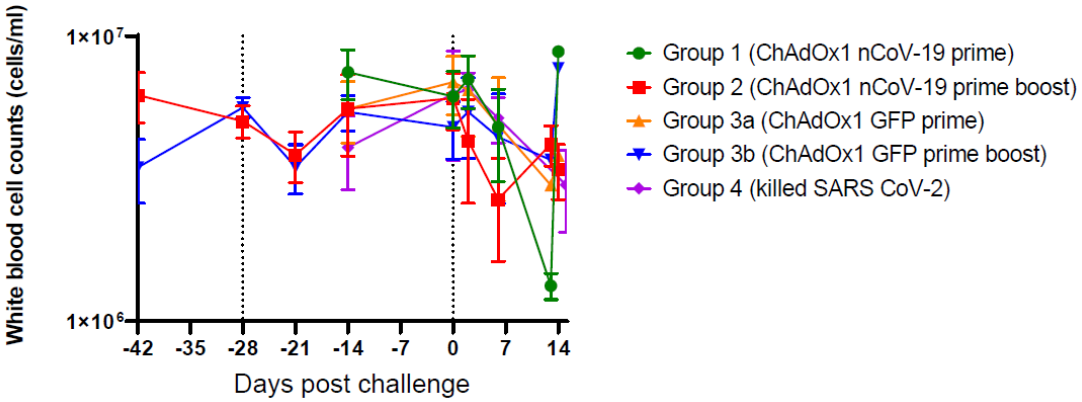
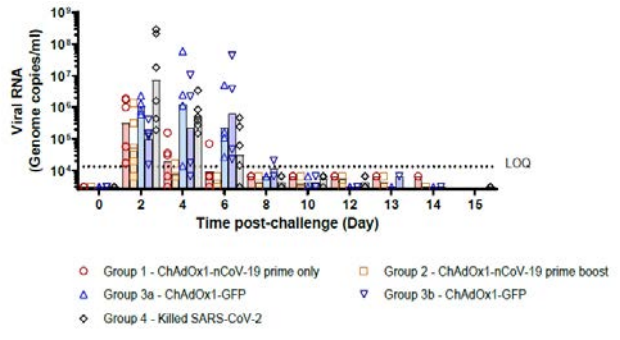
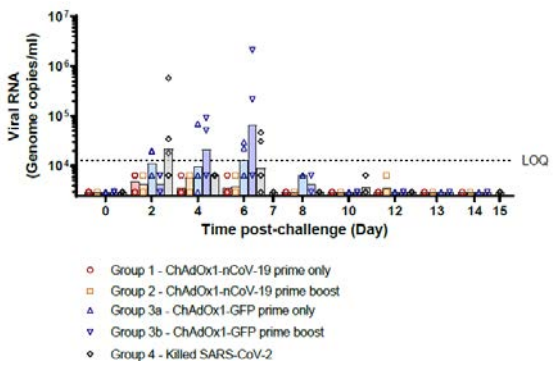


Figure 4. White blood cell counts

Virology

- Viral RNA in the upper respiratory tract (i.e nasal wash, throat swab, nasal cavity, tonsil) was reduced in ferrets vaccinated with AZD1222 compared to GFP control animals (See figures below).
- There was low viral virus RNA copies (below LOQ) in the lower airways (no significant difference observed in lungs, trachea, bronchoalveolar lavage), liver, spleen and kidney. Low numbers (> LoQ) were recovered in intestines (duodenum and colon) in the GFP control groups.
- In animals vaccinated with formalin-inactivated SARS CoV-2, viral RNA in the nasal and throat swabs peaked earlier, higher than in the GFP control animals on 2 DPC but similar to or lower than the GFP groups on later time points (including BAL, nasal cavity and tonsil).
- The level of neutralising antibodies raised in response to vaccination appear to correlate with reduced viral RNA in the upper respiratory tract
- There was little difference in viral RNA between responses in the ChAdOx1 nCoV-19 prime only and prime boost groups.

Geometric mean viral RNA in nasal washes of animals in all groups	Geometric mean viral RNA in throat swabs of animals in all groups
	
Geometric mean viral RNA in BAL of animals in all groups	Geometric mean viral RNA in nasal cavity of animals in all groups

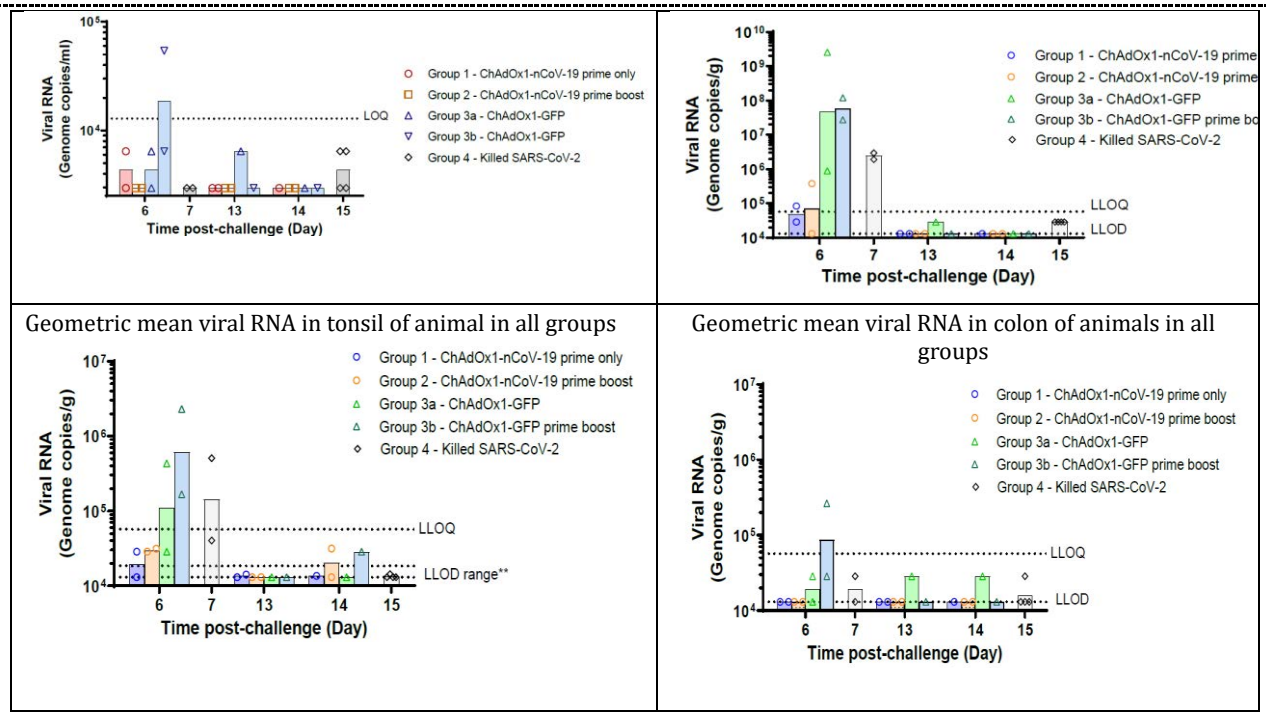


Figure 5. Geometric mean of Viral RNA copies

Lung pathology

- Mild pulmonary lesions were observed in the GFP control animals, with a reduced severity in animals vaccinated with ChAdOx1 nCoV-19 and a temporarily increased severity (i.e. exacerbation) in animals vaccinated with formalin-inactivated SARS-CoV-2 one week post-challenge. One week later, differences in lung pathology no longer existed between test and control groups with histopathology scores being minimum to mild (see summary of histopathological scores values (Table and Figure below)) .

Summary of histopathology findings after challenge

Group	Clinical signs challenge phase
Group 1 (ChAdOx1 nCoV-19 prime only)	• At 6DPC did not show any lesions in the lung, apart from minimal inflammatory cell foci within the parenchyma. • At 13-15DPC minimal scattered foci of inflammatory cell infiltration (low grade inflammation) and occasional bronchiolar infiltrates. • Average lesion score: 2 on 6 DPC, 4 on 13-14 DPC (total score of bronchial, bronchiolar, perivascular cuffing and alveoli of cranial and caudal lobes)
Group 2 (ChAdOx1 nCoV-19 prime boost)	• At 6DPC, animals from group 2 showed minimal scattered foci of inflammatory cell infiltration (low grade inflammation), and occasional bronchiolar infiltrates and perivascular cuffing. • At 13-14DPC, animals showed similar changes as observed at 6DPC with a varying degree of severity, always minimal to mild. • Average lesion score: 3 on 6 DPC, 4.5 on 13-14 DPC
Group 3a (ChAdOx1 GFP prime only)	• At 6DPC one animal in group 3a showed mild lesions and perivascular cuffing, whilst the other animals did not appear to show any different lung histopathology to control animals. The other animal was similar to Group 1 animals showing only occasional minimal bronchiolar infiltrates. • At 13-15DPC minimal to mild perivascular and peribronchiolar infiltrates together with a few scattered low grade inflammatory foci • Average lesion score: 5 on 6 DPC, 5 on 13-14 DPC
Group 3b (ChAdOx1 GFP prime boost)	• At 6DPC minimal to mild perivascular infiltrates together with few scattered low grade inflammatory foci. • At 13-14DPC, animals showed similar changes as observed at 6DPC with a varying degree of severity, always minimal to mild. • Average lesion score: 8 on 6 DPC, 7.5 on 13-14 DPC
Group 4 (formalin-inactivated SARS CoV-2)	• At 6 DPC mild to moderate bronchiolitis (infiltrates within the bronchioles and occasionally bronchi) and inflammatory foci within the parenchyma. Perivascular cuffing was observed frequently, with the infiltrates being mostly mononuclear cells

	(occasionally neutrophils and eosinophils were present). The cuffing was also affecting numerous airways. • At 14-15DPC variable degree of histopathological changes. 2 animals showed minimal inflammatory infiltrates, 1 animal showed mild bronchiolitis and 1 animal showed mild bronchiolitis and perivascular/peribronchiolar cuffing. • Average lesion score: 12 on 6 DPC, 5.5 on 13-14 DPC
Group 5 (control)	• No data

Other histopathological findings:
Inflammatory mononuclear infiltrates (mainly periportal) and/or of multifocal hepatitis of variable degree on 6-7 or 13-14 DPC in all the animals without difference between groups. Virus RNA positive staining was detected in a few scattered with alveolar walls in the lung, not related to the presence of lesions and no differences among groups on 6-7 DPC. Viral RNA was found in epithelial and or sustentacular cells within the olfactory and respiratory mucosa in only one animal of the GFP prime group on 6 DPC. No RNA positive cells were detected in lung or nasal cavity on 13-14 DPC and in duodenum or colon at any time point.

Conclusions:
A single dose of AZD1222 was immunogenic in ferrets and induced NAb. A booster dose increased NAbs, which declined to levels of the prime only group one week after the booster (similar to Study 20-01125). Animals vaccinated with ChAdOx1-nCoV-19 had higher levels of NAbs compared to animals vaccinated with formalin-inactivated SARS CoV-2. AZD1222 reduced viral RNA in the upper respiratory tract. Level of NAbs raised in response to vaccination correlate with reduced viral RNA in the upper respiratory tract. Animals vaccinated with formalin-inactivated SARS CoV-2, viral RNA in the upper respiratory tract on 2 DPC was higher than in all other groups, but similar to or lower than the GFP groups on later time points. Pathology finding were mainly in the lung and were minimal to mild in the GFP control animals, very slightly less in the vaccine groups, and slightly more severe lesions in the formalin-inactivated group on 6-7 DPC (similar among all groups on 13-14 DPC). There was no evidence of vaccine-elicited disease enhancement for AZD1222.

NHP IMMUNOGENICITY AND PROTECTION

Study 6284
Rhesus Macaques = (*n* = 3/sex); Age not provided
Immunization: Day 0
Route/dose: **IM** with 2.5 x 10^{10} VP AZD1222
Control: PBS
Challenge: intranasal (IN) & intratracheal (IT); 5 x 10^6 PFU of SARS-CoV-2 (SARS-CoV/Vero/hSLAM/Victoria/1/2020) administered 4 weeks post vaccination.
Experimental details

Group	Group size (n)	Sex (M/F)	Vaccination day	Challenge day	Cull days (days post challenge)
1. ChAdOx1 nCoV-19	6	3/3	0	27	7 (1/1), 13 (1/1), 14 (1/1)
2. Control	6	3/3	0	27	7 (1/1), 13 (1/1), 14(1/1)

Analysis: Serum neutralising antibody titres, antigen-specific T cell responses measured by ELISpot. Nasal washes, throat and rectal swabs were collected on alternate days following challenge and blood was taken at 3 and 7 days post-challenge **(DPC)**. Flow cytometry-based methods to assess immune cell profiles. In-life Computed Tomography (CT) scans were performed at 5 and 12 days post-challenge to assess the presence of COVID disease features. PCR - viral RNA in nasal washes, swabs, BAL fluid and selected tissues at necropsy. Viral RNA in the lung was also measured by RNAscope and pulmonary lesions were identified by histopathology.
NAb assay: SARS-CoV-2 (strain not specified) in Vero E6 cells.

Note: SARS-CoV-2 replicates in rhesus macaques causing pathological features of viral pneumonia and variable induction of mild clinical disease[1].
Clinical data vaccination phase :
Animals scored healthy and happy
Clinical Observations - Post challenge
2 had diarrhoea (6-9 DPC) and 1 animal had laboured breathing (12 DPC) on the day of CT scanning (N.B. no breathing issues were reported at the time of scanning). She was still scored as active despite the laboured breathing and was scored as healthy at all other times.
Body weight during vaccination and challenge phase
- No significant weight changes during vaccination phase in vaccinated or control animals.
- < 5% weight changes in vaccinated animals during challenge phase cf. >5% in some control animals.

Body temperature during vaccination and challenge phase

- Body temperature unchanged among vaccinated animals and controls during vaccination phase
- In the challenge phase, body temperature was significantly higher in animals in the control group compared to the vaccinated animals when both comparing AUC to 7DPC for all animals and AUC to 12DPC for the 4 animals per group euthanised at the end of the study (p=0.0288 and p=0.0366 respectively, unpaired t test), see Figure below.

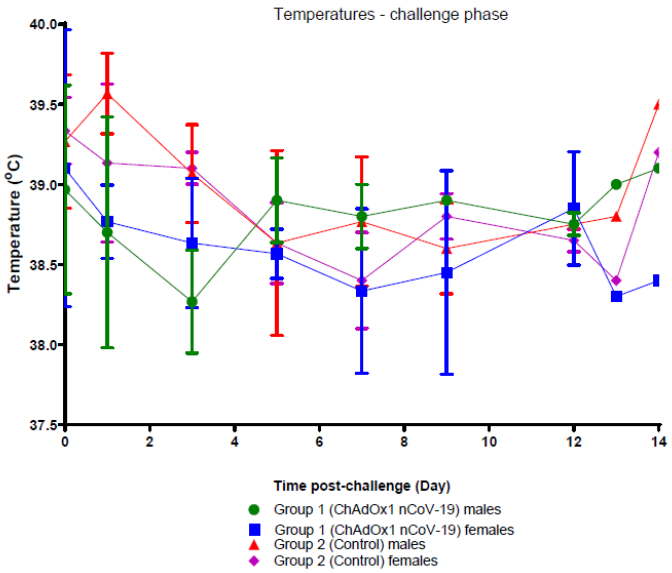


Figure 1. Mean temperatures of males and females in vaccinated and control groups during the challenge phase

Lymph node scores during vaccination and challenge phase (by clinical examination)

- Axillary LN scores in vaccinated animals tended to decrease over the vaccination phase and inguinal LN scores were relatively consistent throughout the vaccination phase (with fluctuations due to subjective measurement as per the sponsor). Both LNs fluctuated in controls with no clear pattern.
- During the challenge phase, all vaccinated animals showed decreased axillary LN and inguinal scores immediately following vaccination to 1DPC then increased to 1-3DPC. A similar trend was seen with axillary LNs in controls but no consistent pattern could be established with inguinal LN in control animals. There was no significant difference between groups.

Haemoglobin findings

- Haemoglobin remained relatively consistent throughout the vaccination phase in vaccinated animals. Following challenge, there was an initial decrease that continued to decrease in 4/6 vaccinated animals and increased in 2/6 animals (3-7 DPC). Levels decreased in all control animals. There was no significant difference between groups.

Neutralising antibodies pre and post challenge

- Neutralising antibody levels increased in response to vaccination, from baseline to day 14 and from day 14 to day 27 pre-challenge (see Figure below). High variability among animals

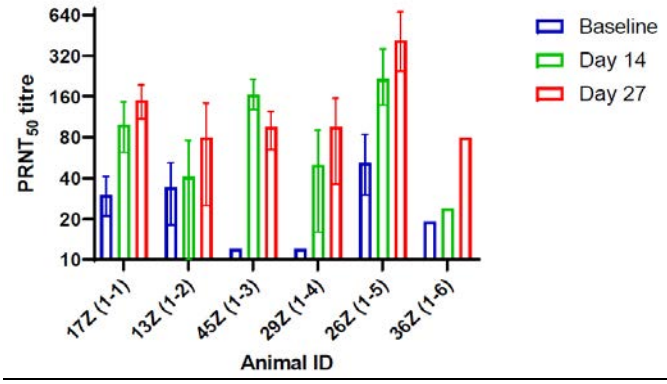


Figure 2. Plaque reduction neutralisation titres of serum from vaccinated animals pre-challenge

- All vaccinated animals had increased NAb between 3-7DPC, which further increased titre at 2 weeks post challenge (see Figures below). Control animals also developed NAb after challenge.

Plaque reduction NAb titres of serum from animals following challenge with SARS-CoV2

Vaccinated animals	Not vaccinated animals

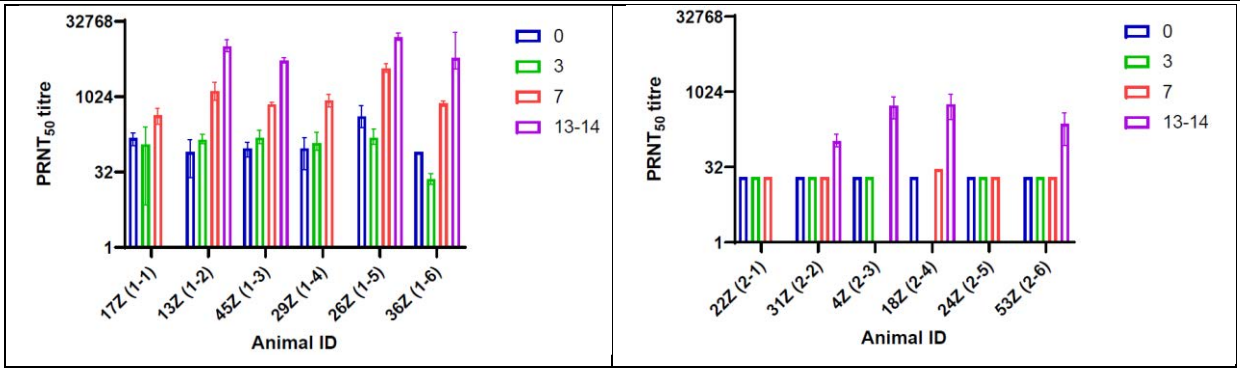


Figure 3. Plaque reduction NAb titres of serum from animals following challenge with SARS-CoV2

Immune cells

Nasal wash and white blood cell counts

- No significant differences were observed in nasal wash white cell counts and WBC counts between vaccinated groups and controls, during vaccination and challenge phase using a NucleoCounter. However, results using flow cytometry showed a significant reduction in WBC counts in controls between 0 and 7DPC, whilst WBC count in the vaccinated animals remained consistent (note flow cytometry results are in cells/µl whilst NucleoCounter reports in cells/mL) (see flow cytometry blood cell count Figure below). The flow cytometry results generally correlated with the NucleoCounter results for WBC, but the statistically significant difference between 0 and 7DPC by flow cytometry but not by NucleoCounter was not explained.
- Neutrophils displayed a reduction in both vaccinated and control groups; significant reduction for the control group between 0 and 3DPC, but it was less evident in vaccinated animals.
- Ratio of neutrophils to lymphocytes reduced in both groups (significant for the control group between 0 and 3DPC) and returned to baseline by 14DPC.
- No significant difference between the two groups for WBC, neutrophils and neutrophil:lymphocyte ratio.

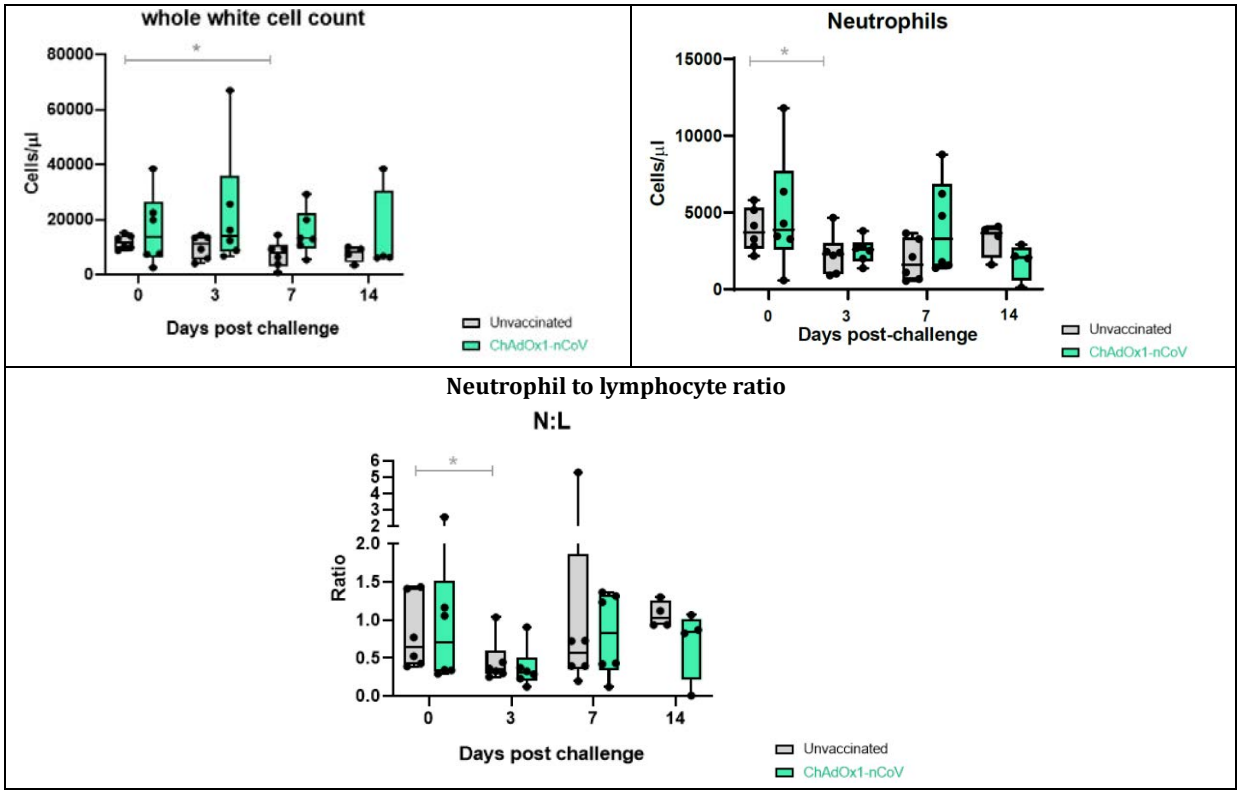


Figure 4. Whole blood immunophenotyping by flow cytometry during challenge phase

Monocytes

- Activated/non-classical (CD16+) monocyte numbers increased in vaccinated animals 3DPC, compared to the baseline level for vaccinated animals and the levels at 3DPC in the control animals. Levels returned to baseline by 7DPC.
- A significant increase in monocyte to lymphocyte ratio was observed in vaccinated animals from 0-3DPC, which remained elevated to 7DPC. Monocyte to lymphocyte ratio returned to baseline level by 14DPC.

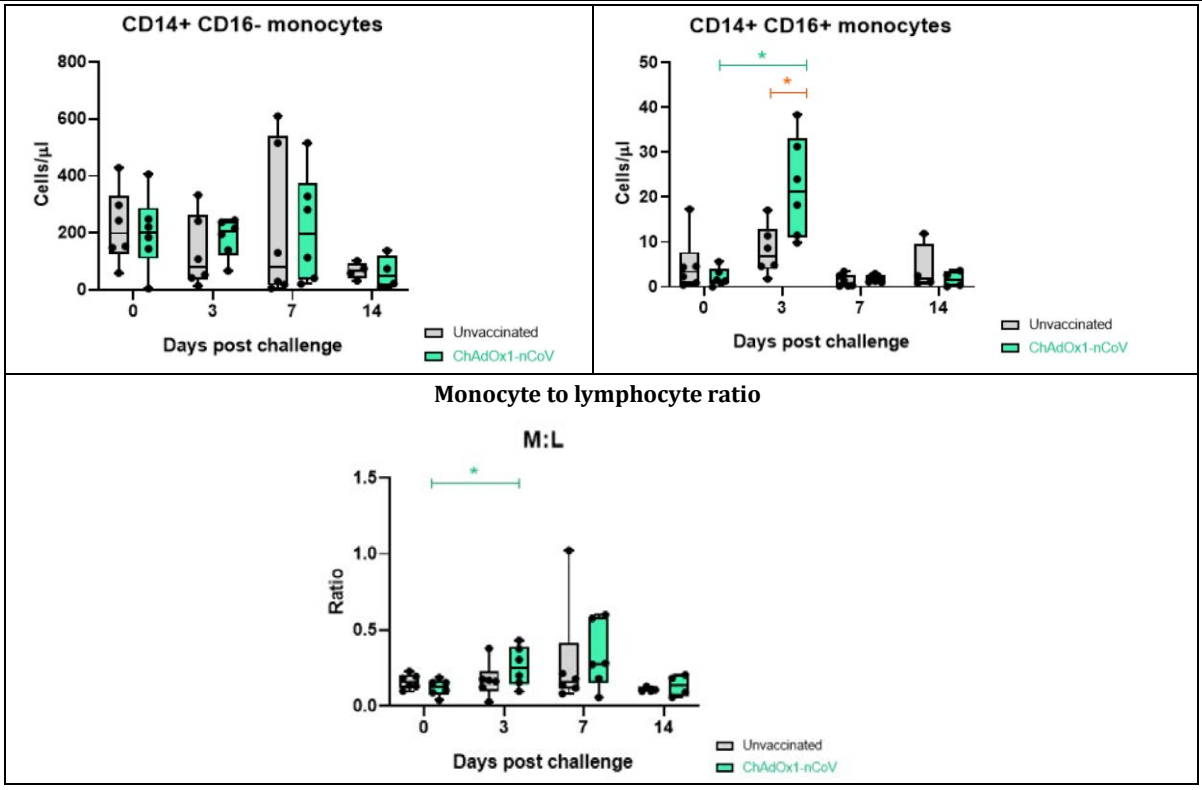


Figure 5. Monocytes during challenge phase

Cell populations on day of challenge by IDEXX haematology analyser

- There was a trend for vaccinated animals to have a lower monocyte, eosinophil and basophil counts, but these differences did not reach statistical significance.
- Similar to the flow cytomethy results (above), monocyte to lymphocyte ratio in the vaccinated animals was slightly lower than in the control animals but there was little difference in neutrophil to lymphocyte ratio.

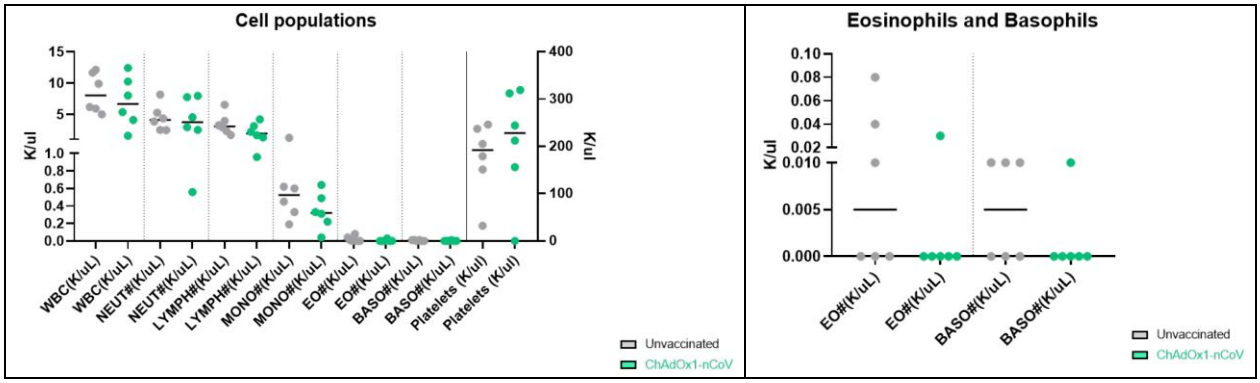


Figure 6. Cell populations on day of challenge

CD4+ and CD8+ T cells

- CD4+ helper T cells and CD8+ cytotoxic T cells significantly decreased from 0-7DPC in control animals, but there was a non-significant trend for decreased T cells throughout the whole challenge phase. Reduction in T cells was less apparent in the vaccinated animals.

  At 3DPC there was a significantly higher number of activated (HLA-DR+) helper T cells in the vaccinated group compared to the control group.

  The baseline (pre-challenge) level of activated (HLA-DR+) cytotoxic T cells was significantly lower in the vaccinated animals compared to the control animals, however there was a significant increase in this cell population in the vaccinated group from 0-3DPC, whilst in the control animals activated cytotoxic T cell levels tended to decrease throughout the challenge phase of the study.
- Presence of both helper and cytotoxic T cells expressing the co-inhibitory marker PD-1 significantly increased in both groups from 0-3DPC, after which expression reduced for the remainder of the study. There was no difference between groups.

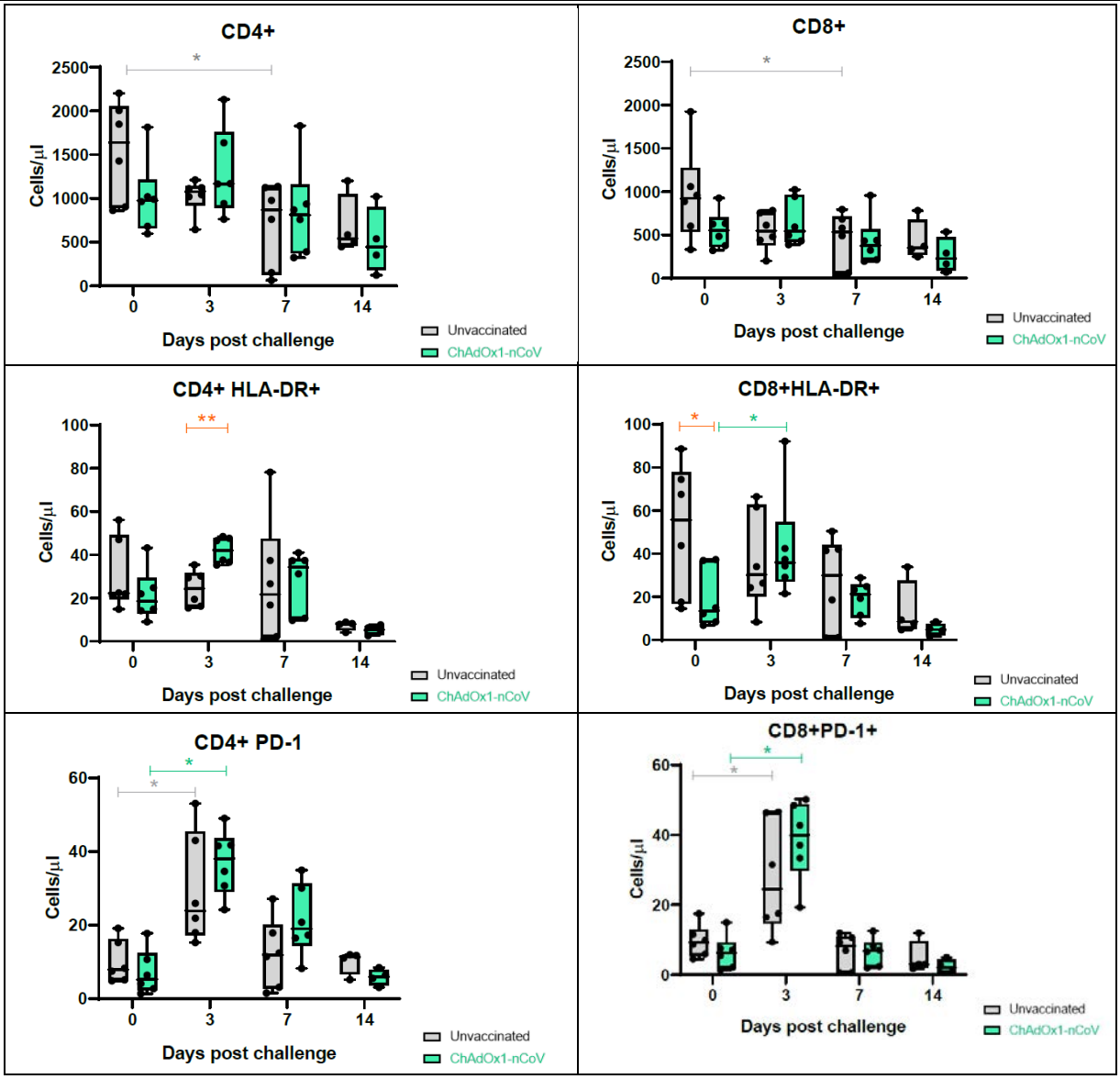
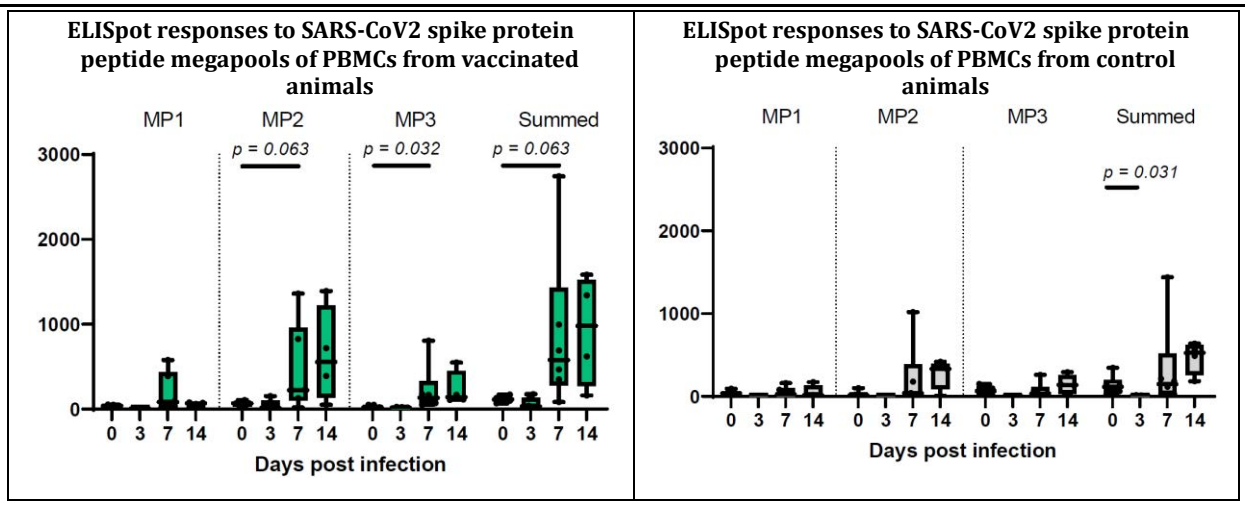


Figure 7. T cells during challenge phase

ELISpot

- PBMCs from vaccinated and unvaccinated animals after challenge were stimulated with pools of peptides (PP) spanning the SARS-CoV2 spike protein (10 peptide pools, comprising of 15mer peptides, overlapping by 11 amino acids; the pools were combined to form 3 megapools: MP1 = PP1,2,3; MP2 = PP4,5,6; MP3 = PP7,8,9,10) and IFN-γ release measured by ELISpot (responses are shown in Figures below).
- Results with MP stimulation are shown below. The responses at 3DPC to MP2 and the summed peptide response were significantly different between groups (p=0.0022). The difference in the response to MP3 between groups at both 3 and 7 DPC almost reached statistical significance (Mann Whitney test, p=0.06). The difference between groups on the day of challenge was not significantly different.



Lung abnormalities

CT radiology 16 days prior to challenge and at 5 and 12 DPC

- No abnormalities before challenge
- Abnormal scans were reported across all groups. Lung abnormalities (unilateral & bilateral disease, ground glass opacity (GGO), crazy paving, peripheral consolidation and presence of nodules) were more severe in ♂ compared to ♀. Day 5 - 2/6 had abnormalities in vaccinated animals (2♂ unilateral & bilateral disease, 2♂ GGO, 1♂ nodule) and 4/6 had abnormalities in controls (2♂ & 2♀ bilateral disease, 2♂ & 2♀ GGO, 1 ♂ crazy paving, 2 ♂ & 2 ♀ peripheral consolidation & 1 ♂ nodule). Day 12 – no difference between vaccinated and control.
- Distribution of COVID-induced pulmonary abnormalities were only slightly restricted in vaccinated macaques at day 5 (1 ♂ upper and middle lobe disease, 2 ♂ lower lobe disease, 2 ♂ with peripheral disease) compared to unvaccinated macaques at day 5 (1 ♂ upper lobe disease, 2 ♂ & 1 ♀ middle lobe disease, 2 ♂ & 2 ♀ lower lobe disease, 2 ♂ random distribution, 2 ♀ peripheral distribution). Day 12 – no difference between vaccinated and control.
- There was a trend for total, pattern and distribution scores reduced in vaccinated animals compared to controls at day 5. Outcomes appeared to be equivalent by day 12 (see figure below).
- Between days 5 and 12, total CT score increased in 3/4 vaccinated animals and remained zero in the final animal. Over the same period of time the total CT score decreased in 3/4 in control animals and increased marginally from 0 to 2 in the final animal. Any differences do not reach statistical significance (see figure below).

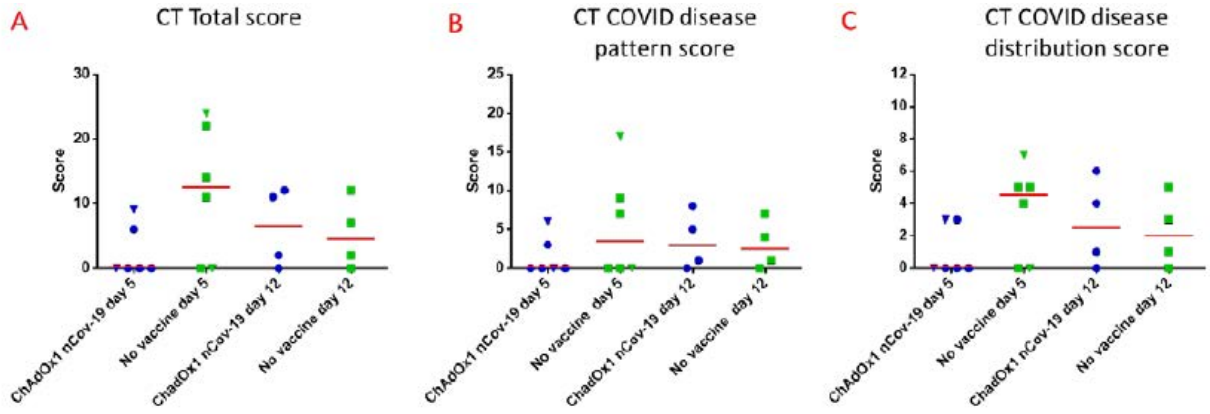


Figure 8. Total, pattern and distribution scores on days 5 and 12 in both groups

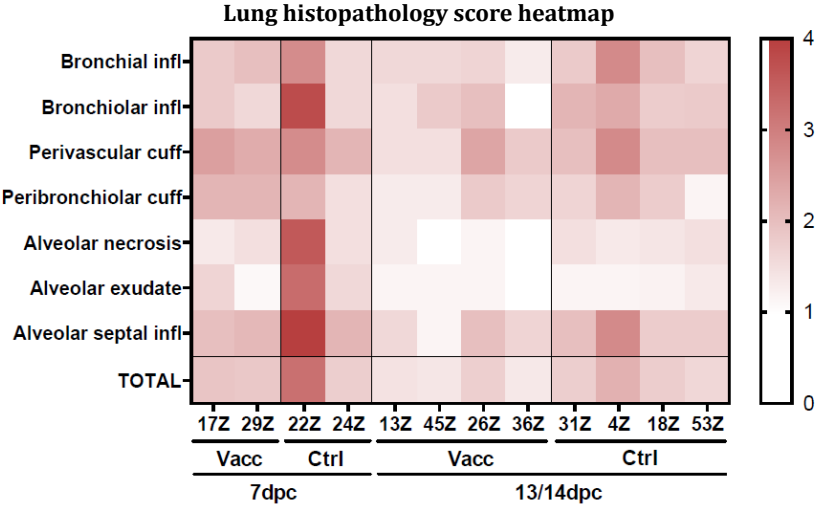
Reference line represents median. Day 5 scores in animals euthanised on day 7 are denoted by upside down triangles

- 67% of the CT scores above 5 were in ♂ subjects at day 5, with 75% of high CT scores on day 12 being from ♂.
- There was a trend, especially in vaccinated animals, for disease score to be worse in males compared to females.

Histopathology:

- Significant histopathology changes were only observed in the lungs.
- Lesions consistent with infection of SARS-CoV-2 were observed in both groups.
- Bronchial & bronchiolar inflammation, perivascular & peribronchiolar cuffing, alveolar necrosis, exudate and septal inflammation were observed in both vaccinated and control groups. However severity was to lesser extend in vaccinated animals compared to control (see heat map below).

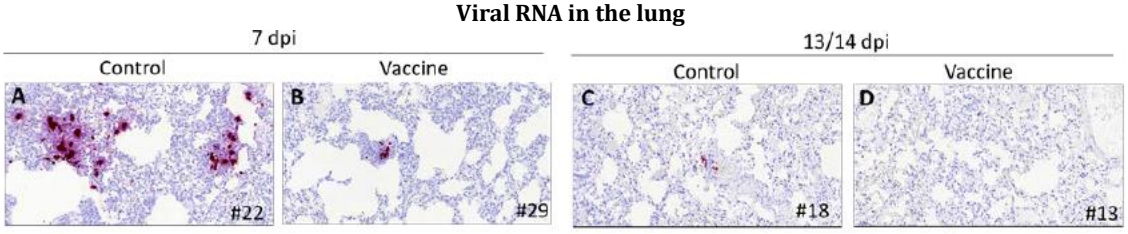
Lung histopathology score heatmap



Presence of viral RNA in lung sections

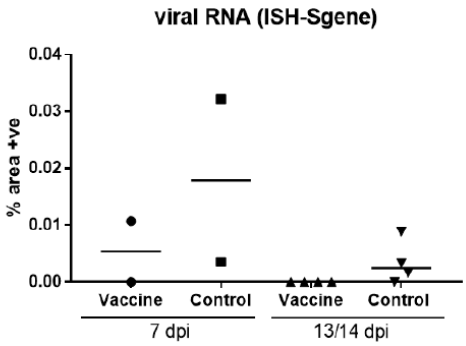
- Viral RNA was detected in 1/2 vaccinated animals at 7 dpi and none at 13/14 dpi in sections of formalin-fixed lung tissue examined by RNAscope (see Figure below)

Viral RNA in the lung



- No viral RNA was detectable in extrapulmonary tissues by *in situ hybridisation* (ISH). The results of viral RNA image analysis in lung sections are summarised in the Figure below.
- In control animals, viral RNA was present in quantities that correlated with the severity of lesions. It was detected in both animals at 7DPI and 3 out of 4 animals at 13/14DPI.
- Vaccinated animals showed reduced pathology at 7DPI and 13/14 DPI and presence of viral RNA was only detected in 1 animal at 7DPI and none at 13/14 DPI.

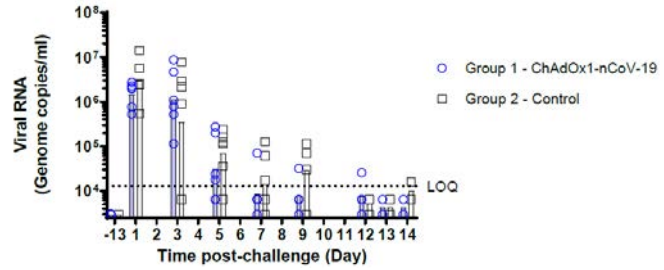
Area of viral RNA in the lung



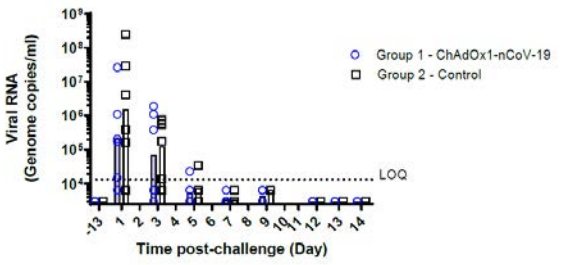
Viral load in vaccinated animals compared to controls

- No evidence for reduced viral RNA in vaccinated macaque nasal washes and throat swabs (see figures below) when compared to controls.
- There was reduction in viral RNA in the BAL fluid, lungs and upper trachea in vaccinated animals when compared to controls (see Figures below).
- No viral RNA was detected in liver, spleen, duodenum and kidney in control or vaccinated animals.
- Moderate virus level was detected in the colon of 1 out of 2 vaccinated animals at 7DPC. The level of RNA was higher than the control (LoQ). No other animals (test and control) had detectable RNA.

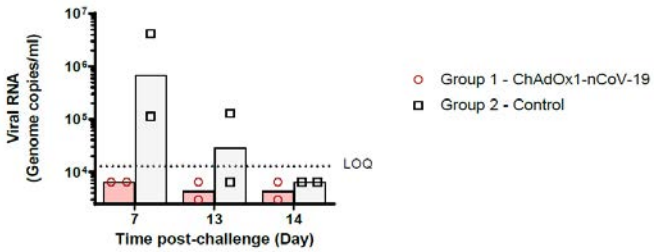
Nasal Wash



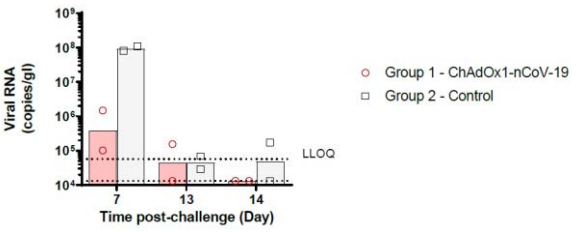
Throat swab



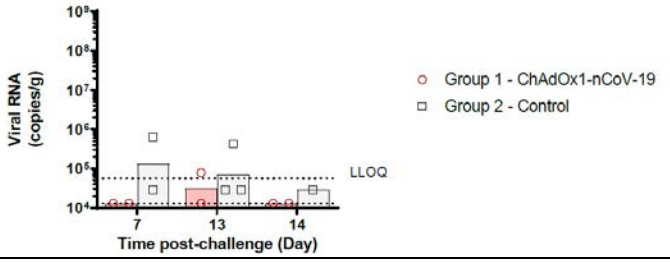
Bronchoalveolar lavage



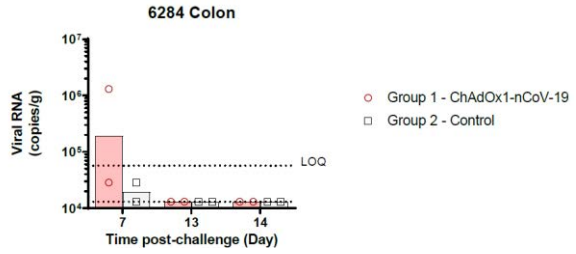
Lung



Upper trachea



Colon



Conclusions:

Generally no difference in antigen-specific T cells from controls (note number of activated CD8+ T cells was significantly lower in vaccinated animals compared to controls) on the day of challenge, but NAbs at higher levels in vaccinated animals suggests vaccine is immunogenic. While a single dose vaccination did not prevent illness in the vaccinated animals, abnormalities were less and tended to be milder than those observed in controls, thus the vaccine provided some protection. Virus was reduced in lungs and BAL fluid of vaccinated animals however little evidence of reduction in viral RNA in nasal washes or throat swabs. There was no evidence of vaccine-elicited disease enhancement for AZD1222. Cellular immune response kinetics during vaccination phase and demonstration of long term immunity/protection was not investigated in this study.

Study Details:
Doremalen et al., 2020
Rhesus macaques (17 male, 1 female; 2-4 years old)
Prime vaccination with 2.5 x 10^{10} VP AZD1222 (*n*=6) or ChAdOx1 GFP (*n* = 5) on day 0 via IM route.
Prime Boost vaccination with 2.5 x 10^{10} VP AZD1222 (*n*=6) or ChAdOx1 GFP (*n* = 1) at 4 weeks after 1st dose via IM route.
Challenge: 28 days post vaccination with 2.6 × 10^6 $TCID_{50}$ virus (strain nCoV-WA1-2020 (MN985325.1))
Challenge Route: IN (0.5 mL per nostril); IT (4 mL); oral (1 mL) and ocular (0.25 mL per eye) of 4 × 10^5 $TCID_{50}$ /mL in sterile DMEM
Animals were examined on 1, 3, 5, and 7 DPC and were euthanized at 7 DPC.
NAb assay: SARS-CoV-2 (strain not specified) in Vero E6 cells

Results

Adverse effects of vaccine

- No adverse events were observed after vaccination.

Immune response

- Spike-specific Abs were present as early as 14 days after vaccination and were significantly increased after the booster dose. Endpoint IgG titres of 400–6,400 (prime) and 400–19,200 (prime–boost) were measured on the day of challenge (Figure 2b)
- Virus-specific NAbs were also significantly increased after booster dose (day 14 after booster) and detectable in all vaccinated animals before challenge (5–40 (prime) and 10–160 (prime–boost)) (Figure 2c). However, the levels decreased before challenge (28 days after booster dose).

  SARS-CoV-2 spike-specific T cell responses were detected on the day of challenge by IFNγ ELISpot assay after the stimulation of PBMCs with a peptide library that spanned the full length of the spike protein. No statistically significant difference in the magnitude of the response was found between the prime–boost and prime-only group (Mann–Whitney U-test, P = 0.3723), (Figure 2d).

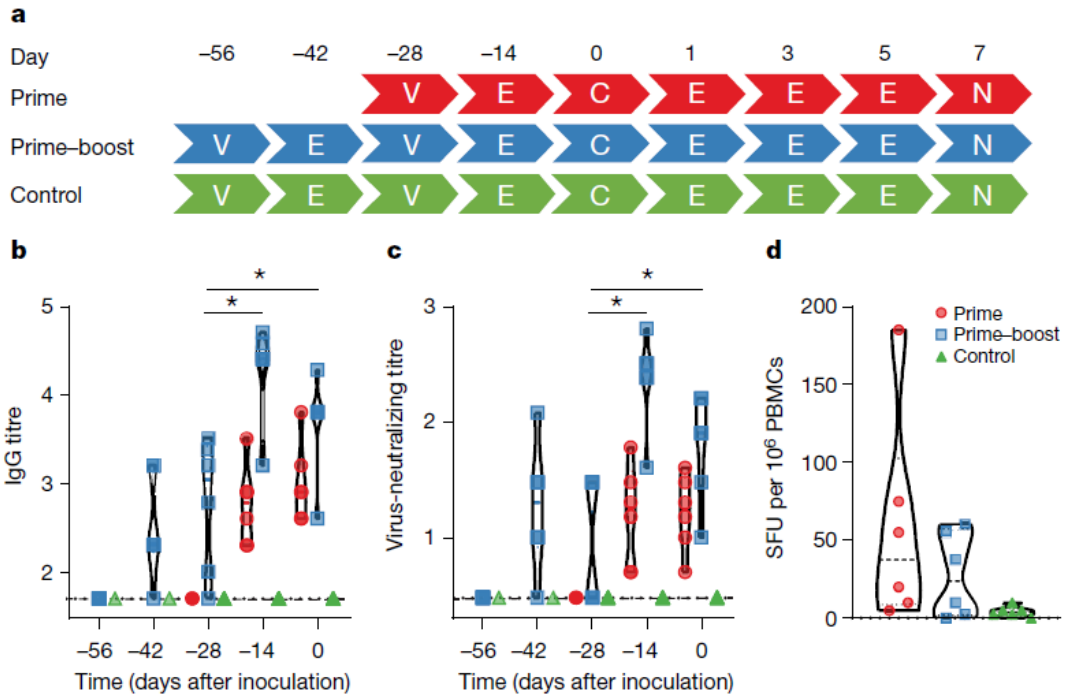
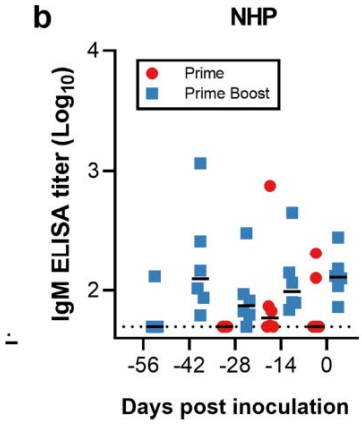


Figure 2. Humoral and cellular immune responses to ChAdOx1 nCoV-19 vaccination in rhesus macaques
a, Study schedule for NHPs. **C,** examination and challenge**; E,** examination**; N,** examination and necropsy**; V,** vaccination**.** **b,** Endpoint IgG titre in serum against trimeric spike protein. log_{10}-transformed IgG endpoint titrations are shown, which were obtained by ELISA. **c,** log_{10}-transformed virus-neutralizing titres in the serum. **d**, Summed IFNγ ELISpot responses in peripheral blood mononuclear cells collected on the day of challenge to peptides that span the full length of the spike protein. Red circles, prime-only vaccine; blue squares, prime–boost vaccine; green triangles, controls. The dotted line shows the limit of detection. *P = 0.0313. Statistical significance was determined using two-tailed signed-rank Wilcoxon tests.

- IgM antibodies were present in the serum after vaccination on the day of the challenge in six out of six prime–boost and two out of six prime-only animals (Extended Data Fig. 2b).

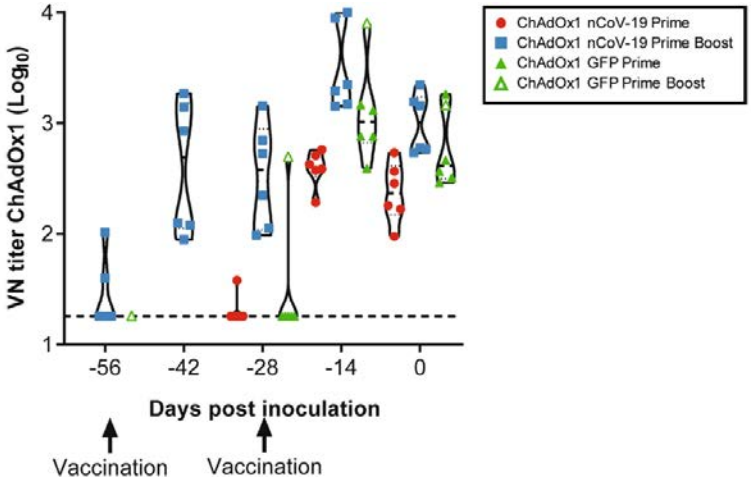
Extended Data Figure 2. Spike-specific serum IgM



Extended Data Figure 2. Spike-specific serum IgM

b, Spike-specific serum IgM in NHPs after prime–boost or prime-only vaccination. n = 6 animals per group examined in 2 independent experiments

- Vaccination with ChAdOx1 nCoV-19 resulted in the induction of NAbs against the vaccine vector itself within 28 days of vaccination (Extended Data Figure 3).
- An increase in the SARS-CoV-2 virus-NAb titre was not significantly correlated with the ChAdOx1 virus-neutralizing titre (two-tailed Pearson correlation, $r^2 = 0.6493$ P = 0.0529)



Extended Data Figure 3 | ChAdOx1 neutralizing antibodies in serum of vaccinated NHPs.

The control NHP treated with the prime–boost regimen is shown as an open triangle. VN, virus neutralizing. *n* = 6 animals per group examined in 2 independent experiments

Clinical signs post challenge

- After challenge in both the upper and lower respiratory tracts of rhesus macaques, the average clinical score of control animals was higher compared with ChAdOx1 nCoV-19-vaccinated animals. This was significantly different on 4–7 DPI (Figure 3a).

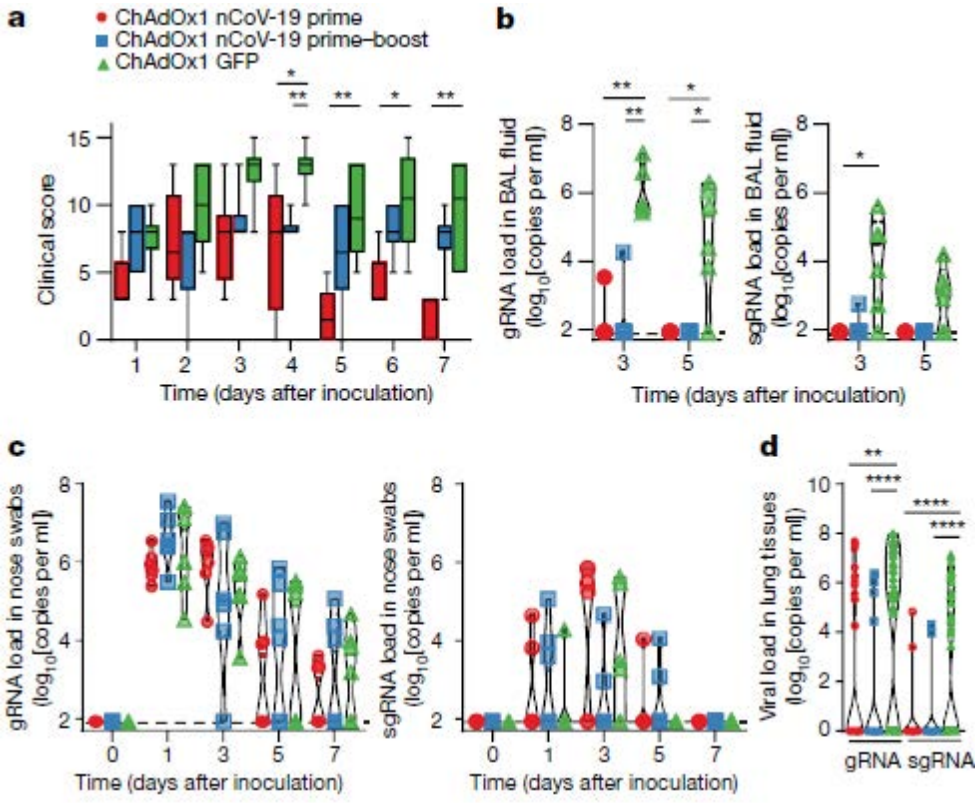


Figure 3 | Clinical signs and viral load in rhesus macaques inoculated with SARS-CoV-2 after vaccination with ChAdOx1 nCoV-19.

a, Clinical score in NHPs. Boxes show the 25th to 75th percentiles, the centre line is the median and whiskers range from the 5th to 95th percentiles. *n* = 6 animals per group were analysed in two independent experiments. P values for the indicated comparisons were as follows: P = 0.0238 (prime and control, 4 DPI.); P = 0.0043 (prime–boost and control, 4 DPI); P = 0.0043 (prime and control, 5 DPI); P = 0.0152 (prime and control, 6 DPI); P = 0.0022 (prime and control, 7 d.p.i.). **b, c,** Viral load in BAL fluid (b) (*P = 0.0152; **P = 0.0022) and nose swabs **(c) obtained from rhesus macaques. d,** Viral load in lung tissue. n = 6 lung lobes of six animals per group analysed in two independent experiments. **P = 0.0011; ****P < 0.0001. The dotted line indicates the limit of detection. Statistical significance was determined using two-tailed Mann–Whitney U-tests.

Viral Load in respiratory tract post challenge

- In BAL fluid obtained from control animals, viral genomic RNA (gRNA) and subgenomic RNA (sgRNA), the latter of which is indicative of virus replication, were detected on all days.
- Viral gRNA and sgRNA were detected in only two vaccinated animals on 3 DPI, and the viral load was significantly lower (Figure 3b).
- Viral gRNA was detected in nose swabs from all animals and no difference was found on any day between vaccinated and control animals.
- Viral sgRNA was detected in a minority of samples, with no difference between groups (Figure 3c).
- Infectious virus could only be detected at 1 and 3 DPI in prime-only vaccinated and control animals, and 1 DPI in prime–boost vaccinated animals (Extended Data Table 1) from nasal swabs.

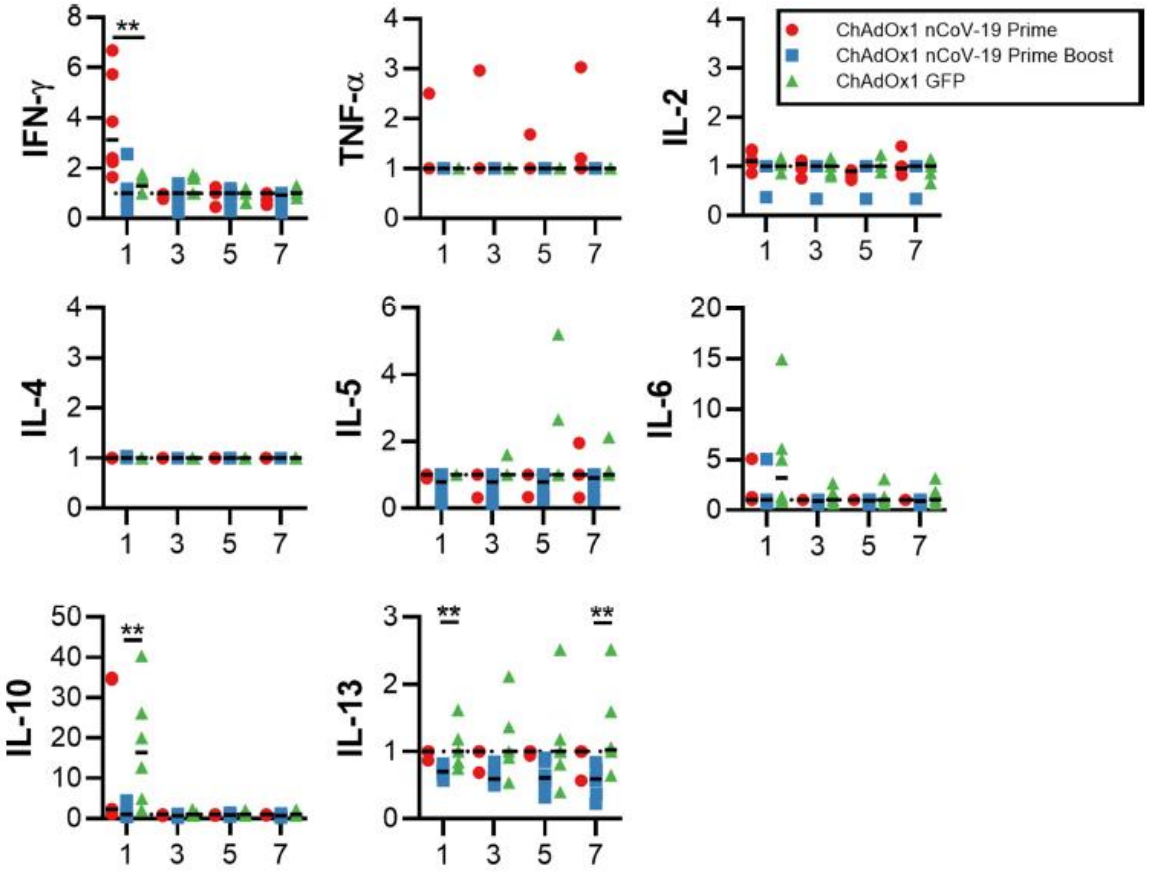
Extended Data Table 1 | Virus isolation from nasal swabs

	ChAdOx1 nCoV-19 Prime	ChAdOx1 nCoV-19 Prime-boost	ChAdOx1 GFP
1 DPI	4/6	2/6	4/6
3 DPI	2/6	0/6	1/6
5 DPI	0/6	0/6	0/6
7 DPI	0/6	0/6	0/6

Virus was isolated from nasal swabs of rhesus macaques after challenge with SARS-CoV-2.

Cytokine Response

- After prime-boost vaccination, the levels of TH1 (IFNγ and IL-2) or type-2 T helper cell (TH2) (IL-4, IL-5 or IL-13) cytokines in the serum of NHPs were low and no evidence of a dominant TH2 response was detected (Extended Data Fig. 4).
- Significant upregulation in IFNγ at 1 DPI in ChAdOx1 nCoV-19 prime-only-vaccinated animals, but not in prime–boost-vaccinated or control animals.
- IL-10 and IL-13 were significantly upregulated in control animals compared with prime–boost-vaccinated animals on 1 and 7 DPI (IL-13 only), but not compared with prime-only-vaccinated animals.
- No significant differences were observed between ChAdOx1 nCoV-19-treated and control animals for TNF, IL-2, IL-4, IL-5 and IL-6 (Extended Data Fig. 4)

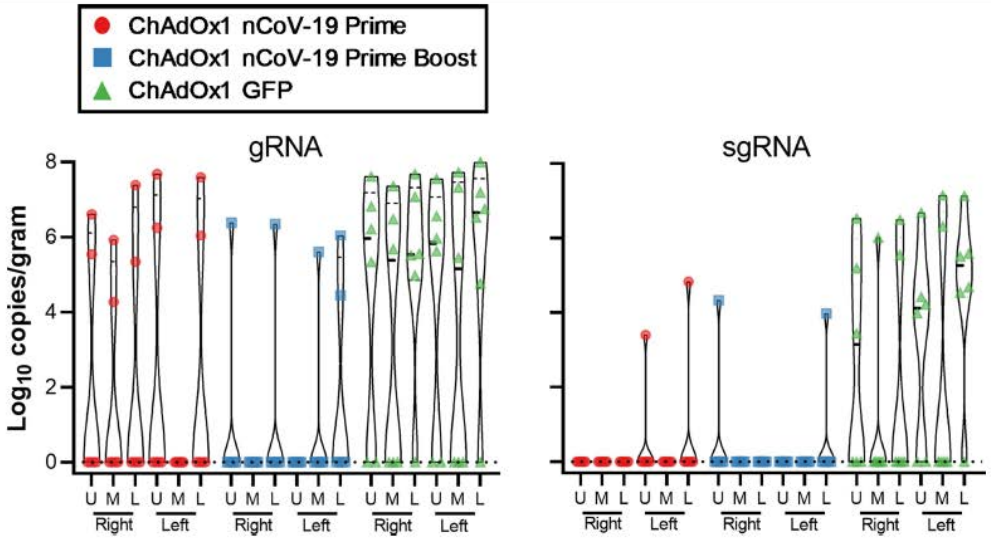


Extended Data Figure 4. Serum cytokines in rhesus macaques challenged with SARS-CoV-2.
Fold increase in cytokines in serum compared to pre-challenge values. **P < 0.01. The lines indicate the median. Statistical significance was determined by two-tailed Mann–Whitney U-test. P values for the different cytokines were: IFNγ, P = 0.0087; IL-10, P = 0.0043; IL-13, P = 0.0043 (left) and P = 0.0065 (right). *n* = 6 animals per group examined in 2 independent experiments.

Pulmonary pathology and viral load

- None of the vaccinated monkeys developed pulmonary pathology after inoculation with SARS-CoV-2. All lungs were histologically normal and no evidence of viral pneumonia nor immune-enhanced inflammatory disease was observed.
- No SARS-CoV-2 antigen was detected by immunohistochemistry in the lungs of any of the vaccinated animals.
- Three out of six control animals developed some degree of viral interstitial pneumonia. Lesions were widely separated and characterized by thickening of alveolar septae by small amounts of oedema fluid and few macrophages and lymphocytes. Alveoli contained small numbers of pulmonary macrophages and, rarely, oedema. Type-II pneumocyte hyperplasia was observed. Multifocal, perivascular infiltrates of small numbers of lymphocytes that formed perivascular cuffs were observed. Immunohistochemistry analysis showed the presence of viral antigen in type-I and II pneumocytes, as well as in alveolar macrophages, in five out of six control animals.
- No lesions or immunohistochemistry-positive cells in nasal mucosa in any of the animals.
- The viral gRNA load was high in the lung tissues of all control animals and viral sgRNA was detected in five out of six control animals (Figure 3d).
- In the prime-only-vaccinated group, the viral gRNA load was significantly lower in lung tissues and below the limit of detection in two out of six vaccinated animals; viral sgRNA was detected only in the lung tissue of one animal (Figure 3d and Extended Data Figure 5).

- In the prime–boost-vaccinated group, viral gRNA was detected in two out of six animals; one animal was weakly positive in one lung lobe and one animal, which mounted a limited response to vaccination, was positive in four lung lobes.
- Viral sgRNA could only be detected in lung tissue from the animal with a lower immune response (Figure 3d and Extended Data Figure 5).
- No infectious virus was detected in any lung tissue.

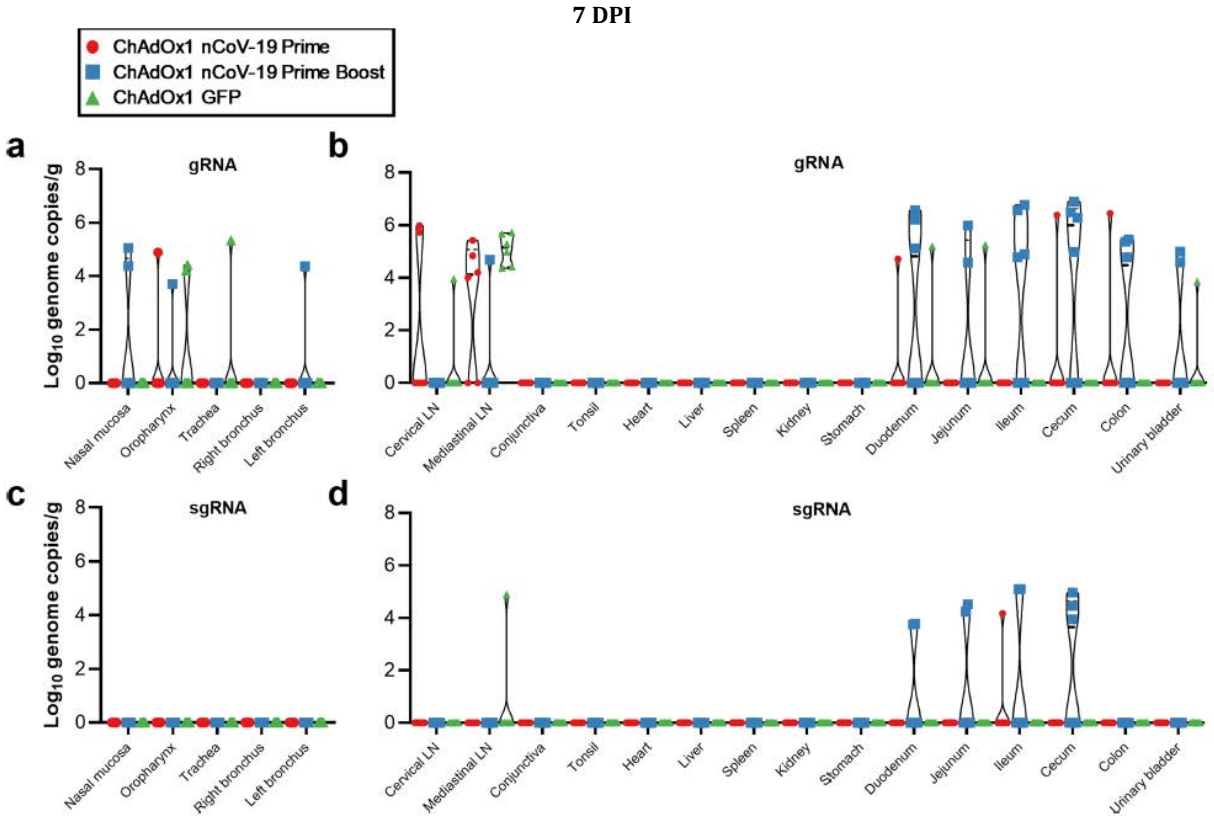


Viral gRNA (left) and sgRNA (right) in lung tissues.

Extended Data Figure 5. Viral load in lung tissue of rhesus macaques challenged with SARS-CoV-2 at 7 DPI

Extrapulmonary pathology and viral load

- No lesions were observed in gastrointestinal tissues of any animals.
- SARS-CoV-2 antigen could be detected in lymphocytes and macrophages in the lamina propria of the intestinal tract of all control animals. This was also observed in six out of six prime-only-vaccinated animals and three out of six prime–boost-vaccinated animals.
- There were no histological differences between lymphoid tissues of vaccinated or control animals.
- Viral gRNA could be detected in extrarespiratory tissues but was predominantly low in all animals and not associated with the detection of sgRNA.
- The viral gRNA load in intestinal tissues of prime–boost-vaccinated animals was higher than the levels measured in control and prime-only-vaccinated animals and was associated with the detection of sgRNA.
- No infection of intestinal tissue was observed by immunohistochemistry, no infectious virus was detected in intestinal tissue (Extended Data Figure 6).



Extended Data Figure 6. Viral load in tissues of rhesus macaques challenged with SARS-CoV-2 at 7 DPI. a, Viral gRNA in respiratory tissues excluding lung tissue. **b,** Viral gRNA in non-respiratory tissues. **c,** Viral sgRNA in respiratory tissues excluding lung tissue. **d,** Viral sgRNA in non-respiratory tissues.

Conclusion:

Prime-boost showed a higher response to IgG (IgG subtypes not provided) and NAb than a single dose but increase in titres only lasted for 14 days. ELISpot responses were at least 3-fold higher in prime only animals compared to prime-boost animals but was reported to be not statistically significant. Prime-boost vaccination before challenge had limited benefit in improving clinical scores up to 7 DPC compared to single dose vaccination. BAL gRNA and sgRNA levels reported were similar between prime-only and prime-boost vaccinated animals compared to high levels seen in controls, so no relevant benefit could be concluded between prime and prime-boost animals in this set of data. In lung tissues there appeared to be a decrease in RNA (both gRNA and sgRNA) compared to controls, however due to high degree of variability among animals these findings are not conclusive. An unexplained increase in viral RNA was observed in the gastrointestinal tract at 7DPC generally in prime-boost immunised animals but not prime only or controls and requires further investigation. Cytokine measurements following challenge revealed IFN-γ levels in prime-only animals on 1DPC, but not in prime-boost animals at the same timepoint. Vaccine related cytokine measurement pre-challenge was not determined. Overall the vaccine provided some protection in vaccinated animals compared to controls. Deficiencies included absence of cellular immune response during vaccination phase and long-term immunity/protection studies.

PORCINE IMMUNOGENICITY

Report no. AR001111, & Graham et al. Vaccines. 2020;5:69 https://doi.org/10.1038/s41541-020-00221-3

Female Large White-Landrace-Hampshire cross-bred pigs (n=3/ group)
Age: 8-10 weeks
Immunisation: Day 0 (prime only) and 28 (prime and boost)
Route and dose: IM, 5.12×10^{10} vp AZD1222

- Antibodies were detectable by ELISA on Day 14, and were significantly boosted by the second immunisation (see table below)

Antibodies by ELISA

DPV	Ab (FL-spike ELISA)						Ab (RBD ELISA)					
	Prime			Prime boost			Prime			Prime boost		
0	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
7	<10	<10	<10	<10	<10	<10	<10	<10	14	<10	<10	<10
14	<10	88	20	55	249	60	12	166	95	40	236	61
21	131	246	215	145	384	110	106	289	296	133	367	113
28	56	377	270	180	526	194	110	430	328	177	556	151
35	156	521	356	7203	8870	6025	142	399	322	4793	8311	4402
42	124	461	347	4566	10376	5226	138	457	333	3253	9362	4560

DPV: days post vaccination; FL-spike: soluble ectodomain of the SARS-CoV-2 spike protein; RBD: SARS-CoV-2 spike protein receptor binding domain

- Neutralising antibodies were induced in 4/6 pigs after a single immunisation and were boosted by a second immunisation (see Table below).

DPV	SARS-CoV-2 ND_{50} (virus neutralisation assay)[a]						SARS-CoV-2 pps IC_{50} (pseudovirus neutralisation assay)[b]					
	Prime			Prime Boost			Prime			Prime Boost		
0	<10	<10	<10	<10	<10	<10	<20	<20	<20	<20	<20	<20
14	17	34	160	34	40	<10	<20	<20	40	40	160	<20
28	<10	40	95	40	67	<10	<20	<20	40	40	40	<20
42	<10	160	80	4305	12177	1522	40	160	40	640	2560	640

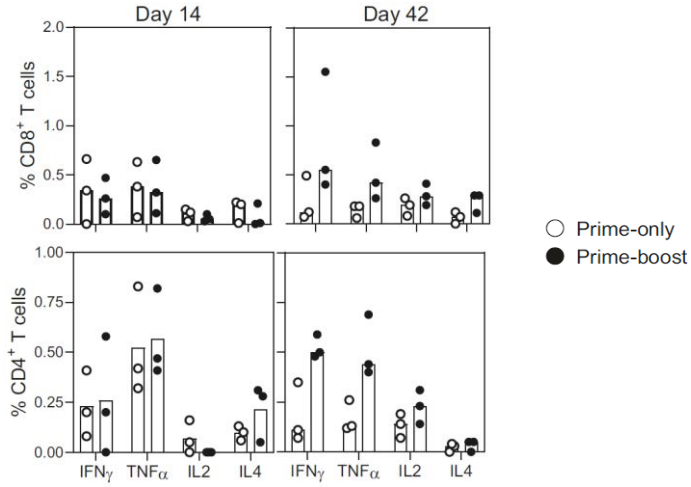
SARS-CoV-2 pps: pseudotyped SARS-CoV-2; a, SARS-CoV-2 isolate England-2 stock propagated in Vero E6 cells; b, Lentiviral-based SARS-CoV-2 pseudoviruses

- All pigs mounted an IFN-γ response on 14, 28 and 42 days post immunisation. Responses of the prime/boost group were statistically significantly greater 42 days post immunisation compared to earlier time points and the prime only group ($p < 0.05$) (see Table below). Cells were stimulated by three pools of synthetic peptides representing residues 1-331 (Pool 1), 332-748 (Pool 2) and 749-1273 (Pool 3).

IFN-γ ELISpot analysis of PBMC

DPV	IFN-γ SFC/million PBMC					
	Prime			Prime Boost		
0	0	5	0	4.0	10	19.0
14	252.7	164.7	592	876.0	101.0	370.7
28	37.3	162.7	107.3	186.7	124.0	149.3
42	54.0	136.7	78.0	628.7	492.0	917.3

- Both CD4+ and CD8+ T cell responses (by ICS analysis) were induced. There are no day 0 baseline data. The Th1 response (expression of IFN-γ and TNF-α) of both CD8+ and CD4+ T cells was higher than the Th2 response (IL-4).



SARS-CoV-2 –specific T cell responses from ChAdOx1 nCoV-19 prime-only and prime-boost vaccination regimens in pigs. Each data represents an individual pig with bars denoting the median response per group/time point.

Conclusions: Study results show a trend towards higher humoral (NAbs) and cellular responses (IFN–γ, CD4+, CD8+ T cells) in animals vaccinated with the prime-boost regimen. Addition of a booster dose of the vaccine significantly enhanced the immune response, at least for a short period of time measured in the study (14 days). The T cell findings suggest a Th-1 biased immune response.

AZD1222 ANTIBODIES AGAINST THE D614G MUTANT

Study details

Serum samples: (*n*=6) derived from Study No. 20-01125 – day 35 or 42 post prime dose

Microneutralisation assays: D614 variants :hCoV-19/Australia/VIC01/2020 –**VIC01**; hCoV- 19/Australia/SA01/2020 – **SA01** and a G614 variant isolate (hCoV-19/Australia/VIC31/2020 – **VIC31**) in Vero E6 cells.

Amino acid difference compared to Wuhan-Hu-1: SA01 contained no amino acid differences in the S protein, VIC01 contained an S247R mutation, while VIC31 contained only the D614G mutation

Results

- NAb titers were statistically greater in the animals that had received AZD1222 via IM (overall median titre 320) compared to those who received dose via the IN route (overall median titre 160) when combined for the three viral isolates (see Figure below).

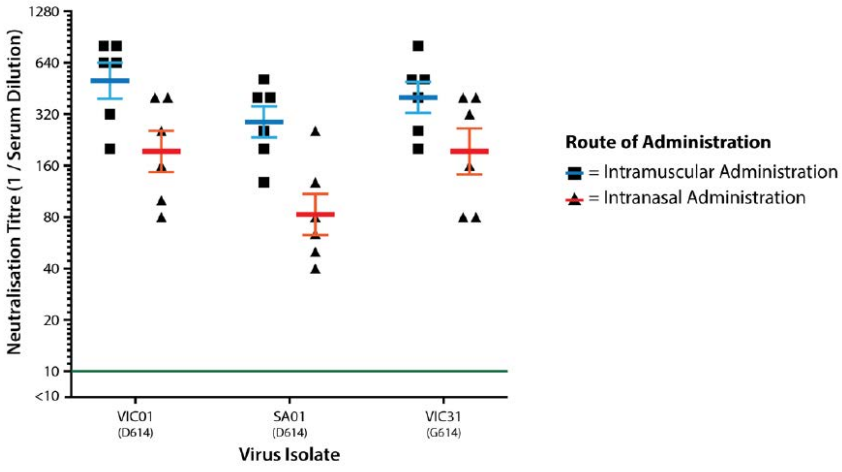


Figure 1: Mean NAb titres (calculated from Log_2-values) to 3 circulating Australian SARS-CoV-2 isolates. Bold horizontal lines represent overall mean titre of the vaccination route/isolate combination with uncertainty bars representing SEM. Square and triangle marks represent mean titres of the triplicate titres for each serum sample/isolate combination.

- Overall median neutralisation titres against the virus isolates (combining IM and IN) resulted in titres of 320 against both VIC01 and VIC31, whilst a titre of 160 against SA01.

Conclusions: No significant effects of the D614G mutation in the SARS-CoV-2 Spike protein on relative neutralisation of D614 and G614 variants with serum samples collected from ferrets that had received prime-boost administrations of AZD1222.

SAFETY PHARMACOLOGY

No effects of AZD1222 on cardiovascular (for at least 4 h) and respiratory parameters (for at least 24 h) were observed in conscious male mice following vaccination (see Table 3.1 below).

3.1 CARDIOVASCULAR AND RESPIRATORY EFFECTS

Study details	Experimental details	Parameters measured	Results
In vivo			
Study no. 617078 Charles River Laboratories, Tranent, UK 4 Nov 2020 GLP	**Mice** (ICR; conscious) 2.59 x 10^{10} VP IM AZD1222 (10 mL/kg) Vehicle: A438 Buffer Reference: 1.2 mg/10 mL Salbutamol n = 8 ♂ The same group dosed with vehicle on day 1 and test article (or reference item) on day 4	**Cardiovascular** Blood pressure, heart rate, body temperature by telemetry up to 24 h post dose. **Respiratory** Respiratory parameters using whole body plethysmographs; duration of 4 h.	**Cardiovascular parameters** • No changes in arterial blood pressure, heart rate, body temperature **Respiratory Parameters** • No vaccine-related changes in respiratory rate, tidal volume, minute volume, peak inspiratory and peak expiratory flows, inspiration or expiration. Statistically significant differences were noted for all the above parameters when comparing average of all time points including the pre-dose value. However, the respiratory recording profiles (i.e. changes relative to pre-dosing values) were similar between the control and AZS1222 groups. • Positive control validated the test system

PHARMACOKINETICS

DISTRIBUTION & SHEDDING

Distribution and shedding

A distribution study with AZD1222 is ongoing. A distribution and shedding study of an HBV vaccine developed using the same chimpanzee adenoviral vector (ChAdOx1) used in developing AZD1222 is summarised in Table 4.1.1. Distribution studies with similar replication incompetent vectored vaccines (AdCh63) used in clinical trials of malaria vaccines (AdCh63 ME-TRAP and AdCh63 MSP-1) in mice were also provided and are summarised below in Table 4.1.2.

Distribution and shedding study of ChAdOx1-HBV

Study no.: 0841MV38.001 (GLP compliant)

Vaccine: ChAdOx1-HBV (MVA-HBV was not discussed)
Species: Balb/C mice
Dose/route: IM as outlined in Table. Group 2 was only administered a single dose, Group 3 & 4 were administered 2 doses 28 days apart and group 1 (control) were administered saline prior to day 1

Group	# of animals/sex	ChAdOx-1 HBV (VP/dose)	Day 1	Day 28	Euthanised
1	2 ♂/2 ♀	0	-	-	Day 29
2	5 ♂/5 ♀	2.4×10^{10}	ChAdOx1-HBV administered by IM route	-	Day 1
3	4♂/5 ♀			ChAdOx1-HBV administered by IM route	Day 29
4	6♂/5♀				Day 56

Tissue collection: Group 2 - 24 h after dosing on Day 1, Groups 1 and 3 - 24 h after the second (boost) dosing on day 28 & Group 4 on Day 56, 28 days after the second (boost) dose.
Biodistribution samples: whole blood, injection site (skeletal muscle), brain, heart, draining inguinal lymph node, kidney, liver, lung, gonads, and spleen.
Shedding: urine, faeces (up to day 35)
Bioanalytical: qPCR - QuantStudio 7 Flex Real-Time PCR System detecting ChAdOx1 – backbone.
The detection limit was Ct value <40 (~30 DNA copy numbers). The precision of each standard level was as follows: the %CV of the calculated DNA copy number for the remaining wells of each standard level was ≤ 15%, except for the LOQ and 10X LOQ, which was ≤ 35% and r^2 was ≥0.96.

Results:
Distribution: ChAdOx1-HBV was not present in whole blood samples at any time-point. Distribution to all tissues was noted on day 2 and day 29 and this included brain, heart, kidney, liver, lung, lymph node, skeletal muscle, spleen, testes and ovaries. The highest levels (copies/mg sample) were noted in skeletal muscle at the injection site, with the copy number noted on day 2 (1 day after the first administration) ranging from 3×10^5 to 10×10^6 copies/µg sample. Due to experimental error, comparison of copy number in skeletal muscle on Day 29 and Day 56 was not determined. On day 56 only low levels were noted in 1 sample (of 7) for brain, heart and liver, 1 of 3 for ovary, 1 of 4 for testes and 4 of 7 in lymph node samples at this timepoint (see Table below). Note whole blood was negative at all time points.

Mean copy numbers/µg sample in positive tissues

Tissue	Day 1	Day 29	Day 56
Brain	454 (6/10 pos)	2.8E+3 (4/8 pos)	107 (1/7 pos)
Heart	366 (3/10 pos)	9.8E+3 (1/8 pos)	50 (1/7 pos)
Kidney	219 (3/10 pos)	47 (1/8 pos)	0 (0/7pos)
Liver	378 (8/10 pos)	106 (3/8 pos)	126 (1/7 pos)
Lung	229 (8/10 pos)	66 (2/8 pos)	0 (0/7 pos)
Draining Lymph Node	2.8E+4 (8/10 pos)	1.14E+6 (7/8 pos)	1.3E+3 (4/7 pos)
Ovary	125 (1/5 pos)	181 (3/5 pos)	498 (1/3 pos)
Skeletal Muscle	9.75E+6 (10/10 pos)	Experimental error	
Spleen	1.43 E+3 (9/10 pos)	9.09E+6 (4/8 pos)	0(0/7 pos)
Testis	130 (2/5 pos)	0 (0/3 pos)	34 (1/4 pos)

Shedding: Faecal (41 samples) and urine (39 samples) showed no shedding in these matrices at the time points sampled.

Distribution studies with AdCh63 in mice

<table>
<tr><th>Study details</th><th>Major Findings</th></tr>
<tr><td>Study: UNO0014/RMPBioDIST-001
Vaccine: AdCh63 MSP-1 and MVA MSP-1 (chimpanzee adenovirus 63-vectored malaria vaccine and modified vaccinia Ankara–vectored malaria vaccine targeting MSP-1)
Species: Balb/C mice
Dose/route: 1 × 10^{10} VP, AdCh63 MSP-1 and 1.037x10^{8}pfu, MVA MSP-1/ IM (hindlimb)
Harvest: days 0, 1 and 8
Tissue/organs investigated: injection site, draining lymph nodes (DLNs), liver, spleen, gonads (either ovaries or testes and epididymis).
Virus detection: tissues homogenised, 3 freeze-thaw cycles, centrifuged, infected permissive cells. Permissive cells (no details provided) were exposed to the clarified samples for 4 days, virus harvested inoculated to cell monolayer and subsequently immunostained using either anti-vaccinia antibody (for MVA) or anti-hexon antibody (for AdCh63).
GLP</td><td><u>AdCh63 MSP-1</u>
<table><tr><th></th><th colspan="3">Percentage positive</th></tr><tr><th></th><th>Immediate 1/sex</th><th>24 h 3/sex</th><th>Day 8 3/sex</th></tr><tr><td>Injection site</td><td>100%</td><td>0%</td><td>0%</td></tr><tr><td>DLN</td><td></td><td>0%</td><td>0%</td></tr><tr><td>Spleen, Gonads & liver</td><td></td><td>0%</td><td>0%</td></tr></table>
<u>MVA MSP-1</u>
<table><tr><th></th><th colspan="3">Percentage positive</th></tr><tr><th></th><th>Immediate 1/sex</th><th>24 h 3/sex</th><th>Day 8 3/sex</th></tr><tr><td>Injection site</td><td>100%</td><td>100%</td><td>100%</td></tr><tr><td>DLN</td><td></td><td>66.6%</td><td>0%</td></tr><tr><td>Spleen, Gonads & liver</td><td></td><td>0%</td><td>0%</td></tr></table>
Comment: Detection system not sensitive. Need more sensitive method such as PCR</td></tr>
<tr><td>Study: UNO0009/MAB-001
Vaccine: AdCh63ME-TRAP
Species: Balb/C mice
Dose/route: 3.3 x 10^{9} VP/ 15 µl/ear
Terminated: Day 8
Tissue/organs investigated: ovaries, testes and epididymis (pooled), cervical lymph nodes, ovary, liver and spleen
Virus detection: grinding mouse tissue samples and inoculating HEK293 cells, 5 days incubation followed by Real Time-PCR to detect viral growth (no optimisation of PCR/or cycle threshold (CT) data provided).
GLP</td><td>• No infectious AdCh63 ME-TRAP virus particles were detected in any internal organ (reproductive organs, spleen, liver, cervical lymph nodes).
• One week after intradermal injection the AdCh63 ME-TRAP was only detected at the injection site (dermis on the rear aspect of each pinna).
• There was no evidence of replication of the virus or presence of a disseminated infection

Comment: Ear not a relevant route. Only a summary report.</td></tr>
</table>

SINGLE-DOSE TOXICITY

No single dose toxicity studies have been performed with AZD1222.

REPEAT-DOSE TOXICITY

A repeat dose GLP study with AZD1222 and two toxicology studies with the same replication incompetent chimpanzee adenoviral vectored vaccines were provided . A human adenovirus vector AdCh63 vector (Study UNO0013) was also provided, but has not been reviewed, as this study is not considered relevant.

Table 0.1. Overview of repeat-dose toxicity studies

Species & strain	Study	Vaccine	Recovery	Route	Dose (VP); frequency		Date	GLP
Mouse (Balb/C)	513351	AZD1222	28 days	IM	3.7×10^{10}	Days 1, 22 and 43	30/12/20	Yes
Mouse (Balb/C)	QS18DL	ChAdOx1 MERS & ChAdOx1 Chik	13 days	IM	1×10^{10}	Days 1 &15	1/12/18	Yes
Mouse (Balb/C)	XMM0003	ChAdOX1 NP+M1 (Day 1)	13 days	IM	1×10^{10} VP + 1.5×10^{7} pfu	Days 1 and 15	26/02/14	Yes

6-week study with AZD1222

Study 513351 (1156PM) **Laboratory**: Charles River Laboratories Edinburgh Ltd, UK **Date**: 30 December 2020 (Dosing initiated: 8 Sep 2020) **GLP**: yes (OECD, FDA) **Lot No**.: MS00684-92;	**Mice** (Balb/c; 7–8 weeks old) **Age:** 7-8 weeks **Body weight**: mean ~35 g (♂), ~25 g (♀) **Dose**: 3.7×10^{10} VP/dose (in 0.07 mL with 0.035 mL in thigh of each hindlimb) **Route and frequency:** 3 injections IM (on Days 1, 22 and 43) + 28 day recovery period **Test article:** AZD1222 **Vehicle**: AZD1222 vehicle (10 mM histidine, 7.5% [v/w] sucrose, 35 mM NaCl, 1 mM MgCl, 0.1% [v/w] Polysorbate-80, 0.1 mM EDTA and 0.5% [v/w] ethanol, pH 6.6) **Group size***:* 20/sex main study (necropsy on day 45) + 20/sex recovery (necropsy on day 74) + *n*=5/sex immunogenicity (Abs against S-glycoprotein)

Major findings

Mortality: No test related mortality

Clinical signs: No test related effect

Dermal scoring: No clinical observations of erythema/oedema at injection site

Body weight gain: No test related effect

Body temperature: ↑ in ♂ on Day 1 & statistically significant ↑ Day 22, 4 h postdose (mean of 38.25°C c.f. 36.98°C controls)

Irwin observations: no effects on body temperature, pupil size or Irwin observations, when assessed in ♂ on day 8 & 29

Haematology: ↓ monocytes ♂ (0.43x) & ♀ (0.39x; statistically significant) on Day 45

Serum chemistry:

AZD1222- related plasma chemistry

Dose	0		3.7×10^{10}	
Day 45 (n=10)				
Globulin#	17.90	15.26	1.19***	1.22**
Albumin#	31.29	34.85	0.94*	0.90**
Day 74 (recovery period)				
Globulin#	-	12.95	-	1.19*

 # concentration in g/L for the control groups and fold **change** for the treated **group**s relative to the respective control group; * p < 0.05; ** p < 0.01; *** p < 0.001.

Organ weights (bodyweight-relative): statistically significant ↑ in spleen weight by 1.3x ♂ & 1.6x ♀ and normal end of recovery

Gross pathology: no AZD1222 related findings

Histopathology:

Sex	♂		♀	
Viral Particle (VP)/dose	0	3.7×10^{10}	0	3.7×10^{10}
Number of animals	10	10	10	10
Administration site 1 (*n* =10)				
Inflammation, subcutaneous tissue; myofiber, minimal	2	10	1	10
Mononuclear cell	2	6	0	3
Mixed cell	0	4	1	7
Oedema, subcutaneous, minimal	8	9	7	5
Haemorrhage, subcutaneous, minimal	0	0	0	1
Administration site 2 (*n* =10)				
Inflammation, subcutaneous tissue; myofiber, minimal	4	10	1	9
Mononuclear cell	4	6	0	1
Mixed cell	0	4	1	8
Oedema, subcutaneous, minimal	9	9	10	4
Haemorrhage, subcutaneous, minimal	2	2	0	2
Congestion, subcutaneous, minimal	1	0	0	0
Sciatic Nerve (*n*=10)				
Inflammation, perineurial, minimal	0	9	2	9
Mononuclear cell	0	5	0	1
Mixed cell	0	4	2	8

Inflammatory cells at the sciatic nerve were epineurial/perineurial and did not extend into the endoneurium. No findings were present in the underlying axons. Inflammation of at the sciatic nerve resulted from an extension of inflammation from the adjacent injection site.

Recovery animal: no histopathology findings considered related to the administration of AZD1222

Immunogenicity results:

Mean immunogenicity Response: S-specific Antibody Concentration (AU/mL)

	♂	♀
Day 22	372.405	816.330
Day 43	993.835	1636.206
Day 74 (recovery period)	1240.280	2477.321

All samples collected from **animals during the pretreatment phase prior to immunisation were below the limit of quantification (BLQ) for the assay (0.250 AU/mL) and considered seronegative. The S antibody was measured by an ECL immunoassay using SULFO-TAG labelled goat anti-mouse antibody and plates coated with recombinant SARS-CoV-2 trimeric spike protein.**

NOAEL: not determined

2-week study with ChAdOx1 MERS and ChAdOx1 Chik

Study: QS18DL **Laboratory:** Envigo CRS Limited, UK **Date:** 1 December 2018 (First dose: Jun 2017) **GLP:** Yes **Lot No.:** Not provided	**Strain:** Balb/C **Age:** ~8 weeks old **Test article:** ChAdOx1 MERS or ChAdOx1 Chik vaccine **Route and frequency:** 2 injections IM on day 1 and 15 **Dose:** 1×10^{10} VP **Vehicle:** PBS **Group size:** 10/sex **Duration:** 4 weeks (blood collection and necropsy on day 28)

Mortality: no deaths

Clinical signs: no treatment related clinical signs

Local tolerance: no local reactions

Body weight gain: ↓ body weight gain in (~ 0.8 -0.9 x control) in both groups

Food consumption: no significant treatment-related effects in both groups

Ophthalmology: not done

Haematology: ChAdOx1 Chik - ↑ WBC all (1.1x & 1.8x control), ↑ lymphocyte all (eosinophil and monocyte counts- 1.1x and 1.8x control), neutrophil and large unstained cell counts ♀ (1.6-2.5x control)

ChAdOx1 MERS: ↑ WBC ♂ &♀ (1.4x- 1.3x control) , ↑ lymphocyte, eosinophil and monocyte counts ♂ & ♀ (between 1.2x and 1.6x control) , and ↑ neutrophil ♀ (1.3x control), ↑ platelet count ♂&♀ (1.1x control)

Serum chemistry: ChAdOx1 Chik - ↑ glucose (♂ 1.2x control; ♀ 1.3x control);

ChAdOx1 MERS - ↓ Triglyceride (♂ 0.56x control; ♀ 0.64x control), phosphorus (♀ 1.2x control).

Organ weights (bodyweight relative):

- ChAdOx1 Chik - ↑ spleen ♀ (1.1x control) & ↓ liver ♂ (0.95x control)
- MERS - ↑ spleen ♀ (1.1x control) & ↓ liver (0.92x - 0.90x control)

Gross Pathology: Finding in the right lumbar lymph node in mice ChAdOx1 Chik

Group/Gender	1 ♂	2 ♂	3 ♂	1 ♀	2♀	3 ♀
Enlarged	0	1	1	0	4	7
Number of mice examined	6	10	10	6	10	10

- Enlargement was observed in 1 ♂ & the majority of ♀ given ChAdOx1 MERS

Histopathology:

- Right lumbar lymph node : ↑ germinal centre; ↑ cellularity paracortex in both treated groups
- Spleen: ↑ germinal centre in both treated groups
- Intramuscular injection site: ↑ inflammatory cell infiltrate (lymphocytic/mononuclear cells) in muscle and interstitial tissue of both treated groups

Serology: no data

NOAEL: not established

2-week study with ChAdOX1 influenza

Study: XMM0003 **Laboratory:** Huntingdon Life Sciences, UK **Date:** 26 February 2014, (First dose: Sep 2011) **GLP:** Yes **Batch No.:** 01 09 07	**Strain:** Balb/C **Age:** ~8 weeks old **Test article:** ChAdOx1 NP+M1 & MVA NP+M1 (modified vaccinia Ankara–vectored vaccine expressing nucleoprotein and matrix protein 1) **Route and frequency:** 2 injections IM on day 1 and 15 **Dose:** 1×10^{10} VP (ChAdOx1 NP+M1) on day 1, followed by 1.5×10^{7} pfu (MVA NP+M1) on day 15 **Vehicle:** PBS **Group size:** 10/sex **Duration:** 4 weeks (blood collection and necropsy on day 28)

Mortality: no deaths
Clinical signs: no treatment related clinical signs
Local tolerance: Increased myofibre degeneration and inflammation
Body weight gain: no treatment related effects
Food consumption: no treatment-related effects
Ophthalmology: not done
Haematology: Day 28 ↑ neutrophil, lymphocyte, eosinophil, monocyte and large unstained cell count ♀ (1.5X and 2X control), ↑ lymphocyte count ♂ (1.4X control), ↑ WBC (1.8X ♀ & 1.2X ♂).
Serum Chemistry: ↑ total protein all (1.04X), ↑ glucose ♀ (1.26X), ↑ potassium (1.11X ♂ & , 1.18X ♀), ↓ sodium ♀ (0.98X control)
Organ weights (bodyweight relative):
- ↓ liver ♀ (0.93X control)

Gross Pathology: Lymph nodes

Group/sex	♂ control	♂ test	♂ control	♀ test
Right popliteal enlarged	0	1	1	9
Lumbar enlarged	0	0	0	10
Number of mice examined	5	10	5	10

Histopathology:
- Right popliteal & lumbar lymph node: ↑ germinal centre development 10/10 ♀
- Mesenteric LN: germinal centre development & cellularity, generalised 1/5 ♀
- Spleen : ↑ extramedullary haematopoiesis was seen in treated ♀

Serology: no data
NOAEL: not established (only one dose tested)

REPRODUCTIVE AND DEVELOPMENTAL STUDIES

Table 0.1. Overview of reproductive toxicity studies

Species & strain	Study type		Dose (VP)	Frequency	Study	GLP
Mouse	Embryofetal development	(pilot)	2.5×10^{10}	2x (13 week days prior to pairing for mating) and GD6 or GD6 & GD15	490838	Yes
		(main)	**Study on-going. To be provided post provisional approval.**			

IM administration in all studies

PRELIMINARY FERTILITY AND EARLY EMBRYONIC DEVELOPMENT

<table>
<tr><th>Study details</th><th>Major findings</th></tr>
<tr><td>Study 490838 (1151RM)
Charles River Laboratories Edinburgh Ltd, UK
12 November 2020
GLP

Mice (CD-1); n = 15-16 ♀/dose
Treatment: EFT phase 2 doses on day 1 (13 days prior to pairing for mating) & GD6; Littering phase 2 doses on GD6 and GD15
Sacrificed: gestation day 17 or lactation day 14
Dose: 2.59 x 10^{10} VP, IM
Vehicle: A438 Buffer</td><td>
Fertility and littering phase
Maternal mortalities: no treatment related effect
Maternal body weight gain: no treatment related effect
Food consumption: no treatment related effect
Maternal clinical signs: no treatment related effect
Mating: no treatment related effect
Oestrus cycling: no treatment related effect
Fertility: no treatment related effect
Litter size, pup mortality and sex ratio: no treatment related effects
Litter and pup weights: no treatment related effects
Dam and litter observations during lactation: no treatment related effects
Gross pathology: no treatment related effects on dam or pups
Embryofetal development Phase
Maternal performance: no treatment related effect
Gravid uterine weight and corrected body weight: no treatment related effect
Ovarian, uterine examinations and litter observations: no treatment related effects
Fetal data
Body weight: no treatment related effect
External, visceral and skeletal findings: no treatment related effect
Immunogenicity: see Table below. Seropositivity of fetuses and pups was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively.
Immunogenicity response
<table>
<tr><td rowspan="2">Antibody Concentration (AU/mL)</td><td colspan="3">EFD Phase Dams</td><td>Fetal[C]</td></tr>
<tr><td>Day 14</td><td>GD 7[A]</td><td>GD 17.5</td><td>GD 17.5</td></tr>
<tr><td>Mean</td><td>354.883</td><td>788.115</td><td>184.065</td><td>91.011</td></tr>
<tr><td></td><td colspan="3">Littering Phase Dams</td><td>Pups[D]</td></tr>
<tr><td></td><td>GD 7</td><td>GD 15[B]</td><td>LD 14</td><td>LD 14</td></tr>
<tr><td>Mean</td><td>NA (BLQ)</td><td>55.751</td><td>155.144</td><td>266.213</td></tr>
</table>
BLQ = Below Limit of Quantification (0.250 AU/mL); All control animals were BLQ; A = samples were taken on day after booster immunisation on GD 6; B = samples were taken on day of booster immunisation before IM injection of vaccine; C = Result obtained from pooled fetal sample/litter; D = Result obtained from pooled sample collected from pups/litter
NOAEL (female fertility): not determined only one dose tested.
Conclusion: There were no test item-related effects seen for dams in-life including at the injection site, for female reproduction, fetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no test item-related fetal visceral or skeletal findings.
</td></tr>
</table>

LOCAL TOLERANCE

The local effects observed in the toxicity study with the ChAdOx vector vaccines (see repeat dose studies) are considered non adverse and are generally related to the inflammatory reaction to the vaccine. No dedicated local tolerance studies was provided for AZD1222

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