Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection

(elasomeran/imelasomeran)

PLGB 53720/0004

Moderna Biotech Spain, S.L.

LAY SUMMARY

Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection

(elasomeran/imelasomeran)

This is a summary of the Public Assessment Report (PAR) for Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Spikevax bivalent Original/Omicron in this lay summary for ease of reading.

For practical information about using Spikevax bivalent Original/Omicron, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Spikevax bivalent Original/Omicron and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indication.

This application is a line extension of the existing product (original monovalent vaccine), Spikevax dispersion for injection (formerly known as COVID-19 Vaccine Moderna dispersion for injection).

Spikevax bivalent Original/Omicron is a vaccine used to prevent COVID-19 caused by SARS-CoV- 2. It is given as a booster injection to individuals aged 18 years and older.

As Spikevax bivalent Original/Omicron does not contain the virus, it cannot give a person COVID-19.

How does Spikevax bivalent Original/Omicron work?
Spikevax bivalent Original/Omicron stimulates the body's natural defences (immune system). The vaccine works by causing the body to produce protection (antibodies) against the virus that causes COVID-19.

The active substance in the vaccine is ribonucleic acid (RNA) encoding the SARS-CoV-2 Spike protein. The RNA is embedded in SM-102 lipid nanoparticles. Messenger ribonucleic acid (mRNA) carries instructions that cells in the body can use to make the spike protein that is also on the virus. The cells then make antibodies against the spike protein to help fight off the virus. This will help to protect a person against COVID-19.

Spikevax bivalent Original/Omicron contains two different types of messenger ribonucleic acid (mRNA), elasomeran and imelasomeran. Elasomeran encodes the spike protein of the original strain of the virus, whereas imelasomeran encodes the spike protein of the Omicron (BA.1 sub-variant) of the virus. The original Spikevax vaccine contains elasomeran only (monovalent vaccine).

How is Spikevax bivalent Original/Omicron used?
The pharmaceutical form of this medicine is a dispersion for injection and the route of administration is as an injection into a muscle in the upper arm.

Individuals 18 years of age and older
A booster dose will be given to the patient as a single 0.5 mL (50 microgram) injection. This should be at least 3 months after a second dose or a booster dose of a COVID-19 vaccine.

The doctor, pharmacist or nurse will inject the vaccine into a muscle (intramuscular injection) in the patient's upper arm.

For further information on how Spikevax bivalent Original/Omicron is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Spikevax bivalent Original/Omicron have been shown in studies?
Spikevax bivalent Original/Omicron has been studied in individuals who had received a primary series and booster dose of Spikevax (original) at least 3 months previously. One group of 437 participants received a second 50 micrograms booster dose of Spikevax bivalent Original/Omicron. Another group of 377 participants received a second 50 micrograms booster dose of Spikevax (original).

The results showed that a booster with the bivalent vaccine triggered a strong immune response against both the Omicron (BA.1 sub-variant) and the original strain. After one month, levels of antibody against Omicron (BA.1) were statistically superior for the bivalent vaccine compared to the original vaccine. Levels of antibody against the original strain were similar for both vaccines. In an exploratory analysis the bivalent vaccine was also found to generate a good antibody response against the Omicron sub-variants BA.4 and BA.5.

What are the possible side effects of Spikevax bivalent Original/Omicron?
The most common side effects with Spikevax bivalent Original/Omicron (which may affect more than 1 in 10 people) are swelling/tenderness of the underarm glands, headache, nausea, vomiting, muscle ache, joint aches, and stiffness, pain or swelling at the injection site, redness at the injection site, feeling very tired, chills and fever.

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Spikevax bivalent Original/Omicron approved?
It was concluded that Spikevax bivalent Original/Omicron injection should be effective as a booster injection in the prevention of COVID-19 caused by SARS-CoV- 2 in individuals aged 18 years and older. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Spikevax bivalent Original/Omicron has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Spikevax bivalent Original/Omicron?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Spikevax bivalent Original/Omicron. The RMP details the important risks of Spikevax bivalent Original/Omicron, how these risks can be minimised, any uncertainties about Spikevax bivalent Original/Omicron (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Spikevax bivalent Original/Omicron:

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

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Spikevax bivalent Original/Omicron are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Spikevax bivalent Original/Omicron product information, the Marketing Authorisation Holder (MAH) has committed to additional pharmacovigilance activities through the provision of effectiveness and safety data derived from pharmacovigilance and post-authorisation studies to further evaluate the long-term effectiveness and safety of Spikevax bivalent Original/Omicron.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Spikevax bivalent Original/Omicron

A Conditional Marketing Authorisation for Spikevax bivalent Original/Omicron was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 12 August 2022.

The full PAR for Spikevax bivalent Original/Omicron follows this summary.

This summary was last updated in October 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection (PLGB 53720/0004) could be approved.

The product is approved for the following indication:

- Spikevax bivalent Original/Omicron is indicated as a booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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

Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection is a bivalent vaccine containing equal amounts of elasomeran, an mRNA coding for the viral spike (S) protein of 2019-novel Coronavirus (embedded in SM-102 lipid nanoparticles) and imelasomeran, an mRNA coding for the Omicron (BA.1 sub-variant) viral spike (S) protein (embedded in SM-102 lipid nanoparticles).

Elasomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the full-length viral spike (S) protein of 2019-novel Coronavirus (SARS-CoV-2).

Imelasomeran is a single-stranded, 5'-capped mRNA, encoding the full-length variant of the SARS-CoV-2 spike (S) protein (Omicron variant B.1.1.529, also known as BA.1).

The mRNA encodes for the full-length, codon optimised SARS-CoV-2 spike (S) protein, that is composed of two subunits (S1 and S2) modified with 2 proline substitutions (K983P and V984P) within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a pre-fusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the RNA into cells for translation into viral protein. The delivered RNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. 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 neutralizing antibodies, which may contribute to protection against COVID-19.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as a full-dossier application. This application is a line extension to the Conditional Marketing Authorisation (CMA) of Spikevax (elasomeran) dispersion for injection, (PLGB 53720/0002; formerly known as COVID-19 Vaccine Moderna dispersion for injection), which was authorised in the Great Britain via a European Commission (EC) Decision Reliance Procedure on 31 March 2021. New non-clinical (four pharmacology studies, two pharmacokinetic studies and one general toxicity study) and clinical data (results from two parts of a pivotal immunogenicity and safety study) have been submitted to support this line extension. The general toxicity study was conducted in accordance with current Good Laboratory Practice (GLP). The immunogenicity and safety study was conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of the rolling review licensing route. The rolling review process is intended to streamline the development of novel medicines. As part of the process, the applicant submitted increments of the dossier for pre-assessment by the MHRA, rather than submitting a consolidated full dossier at the end of the product development process.

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy is required to enable the MHRA to conclude that the benefits are greater than the risks, and has been provided for Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection. The CMA for Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100601-PIP01-22-M01).

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, analysis, assembly and batch release of this product.

Batches of Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection are subject to Qualified Person (QP) certification and batch evaluation by an independent control laboratory before the vaccine is released into the UK.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 12 August 2022. Following consideration of the data that were submitted, the approval of the Conditional Marketing Authorisation was recommended.

A national Conditional Marketing Authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 12 August 2022.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a white to off white dispersion for injection presented in a multidose vial, which contains 5 doses of 0.5 mL each. Each dose contains 25 micrograms of elasomeran, a single-stranded, 5’-capped mRNA encoding the full-length original viral spike (S) protein of SARS-CoV-2 (embedded in SM-102 lipid nanoparticles) and 25 micrograms of imelasomeran, a single-stranded, 5’-capped mRNA encoding the omicron BA.1 variant spike

protein of SARS-CoV-2 (embedded in SM-102 lipid nanoparticles).

In addition to elasomeran and imelasomeran, this vaccine also contains the excipients SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose and water for injections. Polyethylene glycol/macrogol (PEG) is included as part of PEG2000-DMG.

The finished product is packaged in multidose vials (type 1 or type 1 equivalent glass), containing 2.5 mL dispersion, each with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal). The product is available in a pack size of 10 multidose vials. The vaccine is supplied ready-to-use at 0.1 mg/mL and no dilution of the product is required.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current regulations.

II.2 ACTIVE SUBSTANCES

(1) Elasomeran

rINN: Elasomeran (CX024414 mRNA)

For details refer to the UK PAR for Spikevax (mRNA-1273) dispersion for injection (PLGB 53720/0002) on the MHRA website or the EPAR for Spikevax on the EMA website.

(2) Imelasomeran

rINN: Imelasomeran (CX031302 mRNA)

CX031302 mRNA is not the subject of a European Pharmacopoeia monograph.

CX-031302 is the mRNA that encodes for the pre-fusion stabilised spike (S) protein of SARS-Cov-2 Omicron BA.1 sub-variant. The CX-031302 mRNA is considered to be the active substance in the vaccine. The active substance is a clear, colourless solution, essentially free of visible particulates.

The manufacturer has provided the molecular sequence of CX-031302 mRNA which includes the 5’ cap, the 5’ untranslated region (UTR), the Open Reading Frame (ORF), the 3’ UTR, and the 3’ polyA tail. The S protein is stabilized in the so-called pre-fusion conformation by two amino acid mutations.

CX-031302 mRNA is readily soluble in water and salts, demonstrated solubility >2 mg/mL to around 6 mg/mL in 32.5 mM sodium acetate, pH 5.0, solution.

CX-031302 mRNA is intended for further processing into mRNA-1273.529 LNP-B intermediate, a mRNA/lipid-based product. The manufacturer has provided a table of its general properties which is satisfactory.

Manufacture, process controls and characterisation of CX-031302 mRNA

An adequate description of the manufacturing process and in-process controls has been provided, where manufacture essentially consists of *in vitro* enzymatic RNA transcription from starting materials and subsequent purification, with associated controls and process parameters.

Raw materials are supplied from approved, qualified suppliers and are released prior to use per controlled incoming material specifications and current GMP guidelines. Compendial raw materials are listed with representative Certificates of Analysis and Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE) statements. Non-compendial raw materials are described, with specifications provided. The information provided is sufficient.

The starting materials are adenosine triphosphate, cytidine triphosphate, guanosine triphosphate, modified uridine triphosphate, 5' Cap and the DNA template (linearised plasmid) from which the RNA is transcribed.

The DNA template is produced from an *Escherichia coli* cell line, involving various manufacturing steps and released according to specifications. The manufacture and testing of the linearised plasmid is suitably described, as is the manufacture and control of the master and working cell banks. Plasmid purification and linearisation are suitably described, and sufficient control demonstrated. The linearised plasmid is released according to specifications and the testing proposed is considered suitable.

Process validation data provided are acceptable, demonstrating consistent manufacturing under suitable control. Comparability between CX-031302 and CX-024414 mRNA active substance manufacturing process control has been demonstrated, although there is a specific obligation to provide additional information on stability studies and comparability assessment for CX-031302 at active substance manufacturing sites.

The manufacturer has sufficiently characterised the mRNA active substance using a range of analytical methods such that suitable specifications are set. This includes the characterisation of any impurities, which are controlled to suitable levels. All potential known impurities have been identified and characterised.

Control and batch analysis
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications, although there is a specific obligation to provide comparative data from the current and new mRNA purity assays for CX-031302 mRNA and CX-024414 mRNA. Batch analysis data are provided and comply with the proposed specification.

Container closure system
Suitable specifications have been provided for the container closure system. The primary packaging has been shown to comply with current regulations.

Stability
Appropriate stability data have been generated supporting a suitable shelf life when stored in the proposed packaging.

mRNA-1273 LNP Intermediate
For details refer to the UK PAR for Spikevax (mRNA-1273) dispersion for injection (PLGB 53720/0002) on the MHRA website or the EPAR for Spikevax on the EMA website.

mRNA-1273.529 LNP-B Intermediate
mRNA-1273.529 lipid nanoparticle (LNP) is a mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-031302) that encodes for the pre-fusion

stabilised Spike (S) protein of SARS-CoV-2 Omicron BA.1 sub-variant. mRNA-1273.529 LNP-B is prepared in a multi-step process incorporating the CX-031302 mRNA and the lipids to form LNPs.

The name, function and quantity of each component in mRNA-1273.529 LNP-B has been provided. The CX-031302 mRNA is detailed in the previous section. The LNPs comprise four lipids to encapsulate and protect the mRNA: SM-102 (the custom-manufactured ionisable lipid) is positively charged to drive lipid to interact with the mRNA; cholesterol is included to provide structure and stability to the particles; the zwitterionic lipid, distearoylphosphatidylcholine (DSPC), is incorporated to increase the fusogenic properties of the particles; the polyethylene glycol-lipid conjugate, PEG2000-DMG, confers steric stabilisation of the nanoparticles. The structures of the lipid components have been provided.

mRNA-1273.529 LNP-B is a white to off-white LNP dispersion. The mRNA-1273.529 LNP-B may contain visible, white or translucent product-related particulates.

The manufacturer has provided a table of the general properties of mRNA-1273.529 LNP-B, which is satisfactory.

Manufacture, process controls and characterisation of mRNA-1273.529 LNP-B
The responsibilities of each facility involved in manufacture, testing and release of mRNA-1273.529 LNP-B and intermediates have been provided. An adequate description of the manufacturing process and controls has been presented for each manufacturing site.

Sufficient information has been provided on all materials, including compendial, non-compendial and excipients used for the manufacturing process of mRNA-1273.529 LNP-B. The manufacturer has adequately characterised the lipid excipients; the techniques used are as approved for the Original mRNA-1273 LNP.

The cholesterol used in the drug substance is plant-based and not from an animal source. Suitable Certificates of Analysis have been provided, as have specifications for non-compendial materials.

The critical process parameters associated with the manufacture of mRNA-1273.529 LNP-B have been described. Adequate microbial control is also in place and in-process hold conditions have been provided. The manufacturing process is supported by process validation.

The manufacturer has characterised the mRNA-1273.529 LNP-B and the techniques used have been satisfactorily described. Potential product-related and process-related impurities that may arise during manufacture or storage have been identified and described. Potential impurities are controlled. A specific obligation to provide comparative and extended characterisation data for Omicron mRNA-1273.529 LNP-B batches, prototype mRNA-1273 LNP and other variant mRNA-1273 LNPs, including potential impurities associated with the Omicron mRNA-1273.529 LNP-B product has been agreed.

Control, batch analysis and reference standards of mRNA-1273.529 LNP-B
A release specification has been provided for mRNA-1273.529 LNP-B and the manufacturer has committed to revise the specification once further batch analysis data becomes available.

The analytical procedures used for testing mRNA-1273.529 LNP-B and intermediates have been validated and adequately described.

Batch analysis data confirm compliance with the proposed specification. In addition, batch release data have been provided for several batches of mRNA-1273.529 LNP-B, confirming comparable results with mRNA-1273 LNP-B batches (containing CX-024414 mRNA) and consistency of mRNA-1273.529 LNP-B manufacture.

The same reference standards used for the characterisation of the mRNA were employed for the characterisation of mRNA in the mRNA-1273.529 LNP-B. No additional reference standards relating to the manufacture of mRNA-1273.529 LNP-B are required when compared with the already approved mRNA-1273 LNP-B.

Container closure system
The mRNA-1273.529 LNP-B is stored frozen in single-use bags as already approved for mRNA-1273 LNP. The primary packaging has been shown to comply with compendial standards.

Stability
The manufacturer has provided sufficient stability data to support the proposed shelf-life of mRNA-1273 LNP-B and mRNA-1273.529 LNP-B for the subsequent manufacture of the mRNA-1273.214 drug product.

II.3 DRUG PRODUCT

Spikevax bivalent Original/Omicron is a sterile, preservative-free, white to off-white frozen dispersion intended for administration by intramuscular (IM) injection. The drug product contains an equal mass of the mRNA-1273 LNP-B (containing CX-024414, Original) and mRNA-1273.529 LNP-B (containing CX-031302, Omicron BA.1). The drug product is supplied in a multidose vial presentation, containing 5 doses per vial. The vaccine is supplied ready-to-use at 0.1 mg/mL and no dilution of the product is required.

Spikevax bivalent Original/Omicron is presented in type 1 glass vials or type 1 equivalent glass vials, closed with chlorobutyl stoppers and sealed with aluminium overseals. Each vial contains 3.2 mL fill volume to allow withdrawal of 5 doses of 0.5 mL (each containing 50 micrograms mRNA). The drug product vials are packaged in 10 multidose vials in a carton.

Pharmaceutical development
A satisfactory account of the pharmaceutical development of mRNA-1273.214 has been provided. The approach to defining critical quality attributes was described, as well as process risk assessment strategy and characterisation studies.

The Spikevax bivalent Original/Omicron (mRNA-1273.214) manufacturing process consists of the thawing the mRNA-1273 LNP-B intermediate (containing CX-024414 mRNA) and mRNA-1273.529 LNP-B intermediate (containing CX-031302 mRNA), pooling equal quantities of the two mRNA-lipid complexes, followed by dilution with a formulation buffer. The subsequent steps include filtration and aseptic filling.

Comparability assessment of drug product batches manufactured at different sites was performed according to ICH Q5E, including clinical trial and process performance qualification batches of the drug product from different sites. It is noted that the manufacturing process for the clinical trial batches of mRNA-1273.214 was different to the

final commercial process. In addition to release testing, the manufacturer has evaluated accelerated stability and extended characterisation testing. Supportive stability data from the monovalent mRNA-1273 drug product has been used. Process consistency was confirmed for mRNA-1273.214, including microbial control.

Compatibility with the container closure system and syringes relies on the Spikevax mRNA-1273 drug product, since no changes have been made to the container closure systems. The excipients are the same as those used in approved Spikevax (monovalent vaccine). All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

The Spikevax bivalent Original/Omicron (mRNA-1273.214) manufacturing process is a conventional aseptic process that includes the following basic steps: thawing the mRNA-1273 LNP-B and mRNA-1273.529 LNP-B intermediates, pooling equal quantities of the two mRNA-lipid complexes, dilution to 0.1 mg/mL, clarification, sterile filtration, aseptic filling into vials followed by stoppering and capping, visual inspection, labelling and packing, and freezing. An alternative interim freezing step before labelling the vials has been introduced, with additional thaw, labelling and freezing steps.

A representative batch formula has been provided.

The control of the manufacturing process has been adequately described and is based on the current approved process, other than the additional mixing and dilution step for the bivalent vaccine. In-process controls and process parameters for each manufacturing step are provided. After manufacturing, vials undergo 100% visual inspection for defects.

Adequate information on critical process parameters and in-process controls has been provided. The control strategy for drug product manufacture has been described through critical and non-critical parameters which have target values and manufacturing limits represented by proven acceptable ranges (PARs). The microbial control strategy is satisfactory.

Drug product process performance qualification studies have been performed at the manufacturing sites. Three sites are already used for the approved Spikevax drug product, with an additional site introduced for manufacture of the bivalent Original/Omicron drug product. Satisfactory process qualification of the aseptic manufacturing steps for all the vial filling lines has been performed using media fills.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of excipients

The same excipients are used as for the approved Spikevax. The components of the LNP-B include SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG). The other excipients are trometamol (Tris), trometamol hydrochloride (Tris-HCl), acetic acid, sodium acetate trihydrate, sucrose and water for injections.

The quality of excipients is appropriate for use in the Spikevax bivalent Original/Omicron based on their intended use. None of the excipients are of human or animal origin.

Control, batch analysis and reference standards of drug product

The finished product specification is given and includes relevant control parameters suitable for the finished product, although a specific obligation is made for justification of the mRNA ratio limits in release testing. In addition, the specification limits should be revised for the new mRNA purity assay, with provision of comparability data for CX-031302 mRNA, mRNA-1273.529 LNP, mRNA-1273.214 DP and for CX-024414 mRNA, mRNA-1273 LNP and mRNA-1273 DP.

The analytical procedures used, including compendial and non-compendial methods, to assess the RNA and lipid content, identity, purity, safety and stability of Spikevax bivalent Original/Omicron have been adequately described. Validation of the analytical methods used for the control of the drug product are satisfactory for ensuring compliance with the relevant specifications, although specific obligations have been agreed for mRNA ratio limits and the new mRNA purity assay.

The impurity profile of Spikevax bivalent Original/Omicron is very similar to mRNA-1273 Lipid Nanoparticle (LNP-B) and mRNA-1273.529 LNP-B. No additional impurities are anticipated to form or be introduced during the manufacture of drug product. Each of the impurities discussed for mRNA-1273 LNP is present in Spikevax bivalent Original/Omicron.

Batch data have been provided that comply with the release specification and demonstrate consistent results.

The reference standards described for the mRNA and mRNA-LNP intermediate will also serve as reference standards for the drug product. A primary reference material and working reference material have also been described and characterised, which is satisfactory.

Independent Batch testing

Independent batch testing provides additional assurance of quality before a batch is made available to the market. Independent batch testing is a function that is undertaken by an Official Medicines Control Laboratory (OMCL) and the UK National Institute for Biological Standards and Control (NIBSC) is responsible for this function.

Independent batch testing is product-specific: it requires specific materials and documentation from the manufacturer and comprises laboratory-based testing and review of the manufacturer’s test data. If all tests meet the product specifications, a certificate of compliance is issued by the OMCL. NIBSC will undertake the independent batch release for this product.

Container closure system
The bulk drug product is dispensed into clear type 1 borosilicate glass vials or clear type 1 equivalent glass vials, closed with a 20 mm chlorobutyl rubber stopper and 20 mm flip-off blue matte aluminium seal. Vials are then packaged in a secondary carton containing a total of ten multidose vials per carton, with a tamper-evident seal.

The container closure system is the same as that used for the current approved Spikevax (except the colour of the seal) and complies with the relevant quality standards of the Ph. Eur.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Statistical modelling for degradation of mRNA purity was also used to support the shelf-life claim for the bivalent mRNA-1273.214 finished product.

Based on accelerated stability results for the bivalent finished product mRNA-1273.214 and clinical stability batch data, along with previous stability data for the monovalent drug product mRNA-1273, a shelf-life of 9 months at -50ºC to -15ºC for the unopened multidose vial is recommended.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for a maximum of 30 days. Within this period, up to 12 hours may be used for transportation.

Once thawed, the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 24 hours after removal from refrigerated conditions.

Punctured multidose vial
Chemical and physical in-use stability has been demonstrated for 6 hours at 2ºC to 25ºC after initial puncture (within the allowed use period of 30 days at 2ºC to 8ºC and 24 hours at 8ºC to 25ºC). From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product on batches of Spikevax bivalent Original/Omicron 0.1 mg/mL dispersion for injection.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The applicant has committed to meet specific obligations (SOBs) to provide additional data once available (SOBs 1-5, refer to Section VI of this report for further details).

The grant of a Conditional Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
The following non-clinical studies were submitted with this line extension application:
- Four pharmacology studies

- Two pharmacokinetic studies
- One general toxicity study.

The general toxicity study (in rats) was conducted in accordance with current Good Laboratory Practice (GLP).

Terms for substances used in the studies below are defined as follows:
- CX-024414 is mRNA that encodes for the pre fusion stabilised spike protein of the initial SARS-CoV-2 virus (SARS-CoV-2-S-2P).
- CX-031302 is mRNA that encodes for the pre-fusion stabilised spike protein of SARS-CoV-2 B.1.1.529 (omicron variant, also known as BA.1).
- **mRNA-1273** is a monovalent vaccine that contains a single mRNA (CX-024414) that encodes for wild type SARS-CoV-2 S-2P (S-2P).
- **mRNA-1273.529** is a monovalent vaccine that contains a single mRNA (CX-031302) that encodes SARS-CoV-2 S-2P for BA.1 (S-2P.529). mRNA-1273.529 vaccine encoded the following substitutions: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K and L981F.
- **mRNA-1273.214** is a bivalent vaccine that contains the two mRNAs, CX-024414 and CX-031302.

III.2 Pharmacology

New data are provided from the following studies:
1. Study MOD-5156, a study of immunogenicity of omicron vaccines in mice
2. Study MOD-5019, a further study of immunogenicity of omicron vaccines in mice
3. Study WASHU-01-MOD-5020, a study in mice of protection from challenge with omicron-SARS CoV-2
4. Study VRC-220-857, a study in rhesus monkeys of immunogenicity and protection from SARS-CoV2 omicron challenge.

Study MOD-5156

This study evaluated immunogenicity in mice of vaccines containing mRNAs encoding for different immunogens in SARS CoV-2 virus. Table 1 summarises the study design of this study.

Table 1: Study Design for Study MOD-5156

Study Report Group (n = 8/group)	Primary Series (Dose 1 and 2)			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	
1	PBS Control	0	Day 1, 22	**Serum (Day 21)** Antibody responses (ELISA) **Serum (Day 36):** Antibody responses (ELISA, PSVN assay)
2	mRNA-1273	1		
3	mRNA-1273.529	1		
6	mRNA-1273.214	1		

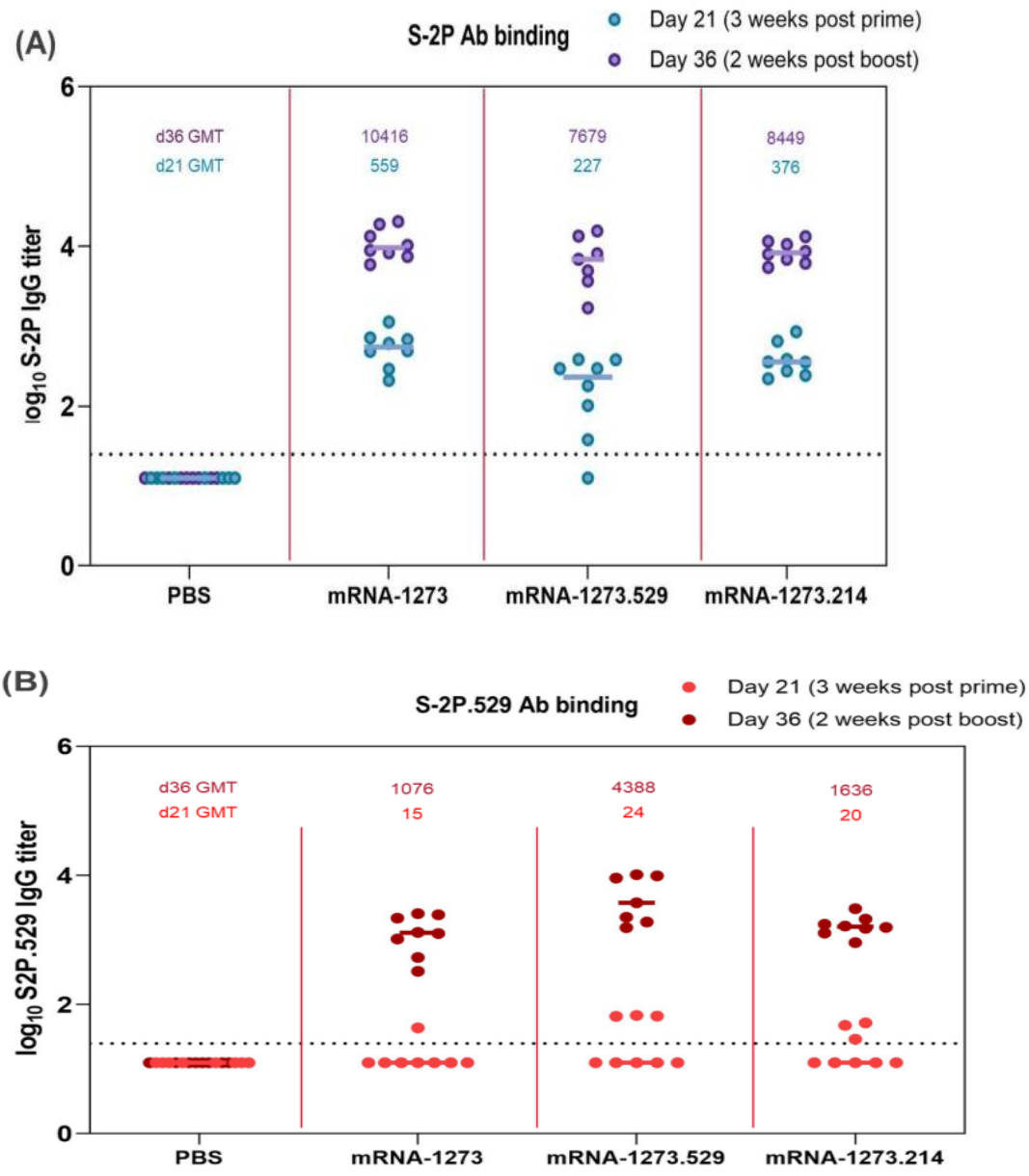
Abbreviations: ELISA = enzyme-linked immunosorbent assay; IM = intramuscular; mRNA = messenger RNA; NA = not applicable; PBS = phosphate-buffered saline; PSVN = pseudovirus neutralization.

[a] mRNA-1273.214 was a 1:1 bench side mix of separately formulated mRNA-1273 and mRNA-1273.529.

Results

IgG responses against S-2P and S-2P.529 proteins were seen in response to each of mRNA-1273 and mRNA-1273-529 (Figure 1A-B): numbers in the box in each of the figures (e.g. 10416 and 559) are the geometric mean titre values. S-2P IgG geometric mean titres increased 18-34 fold two weeks after the second dose with geometric mean titres values ranging from 7679 to 10146 (Figure 1A). S-2P.529 geometric mean titres increased by 71 to 183 fold two weeks after the second dose with geometric mean titres values ranging from 1076 to 4388 across groups (Figure 1B). There were no notable differences in S-2P titre values across treatment groups.

Figure 1: Binding Antibody Responses in BALB/c Mice After Primary Series

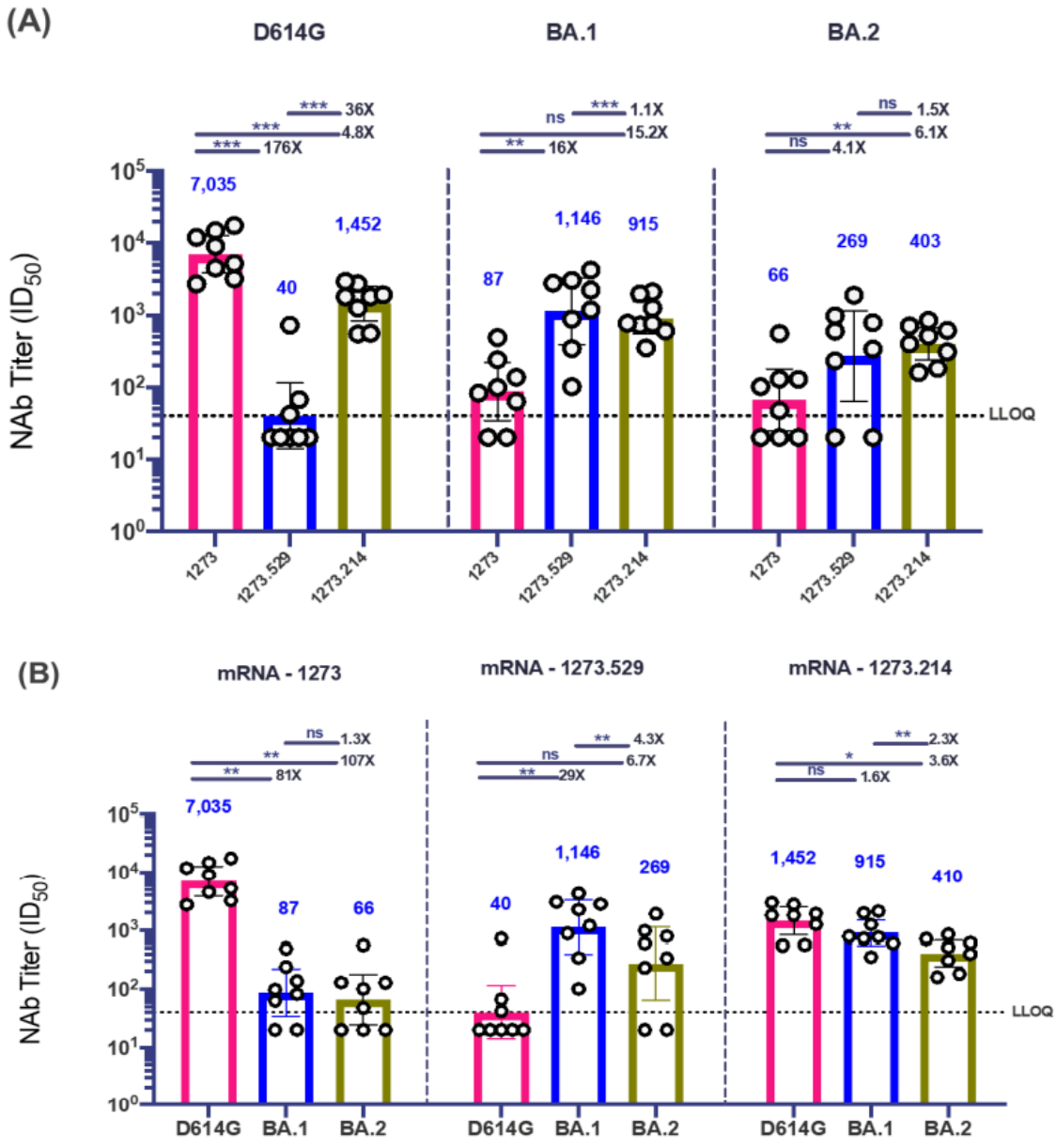


Abbreviations: Ab = antibody; GMT = geometric mean titer; IgG = immunoglobulin G; mRNA = messenger RNA; PBS = phosphate-buffered saline; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; S-2P.529 = Omicron-specific S-2P.

On day 36 (two weeks after the second dose), mice vaccinated with bivalent mRNA-1273.214 or monovalent mRNA-1273.529 achieved higher titres than those vaccinated with monovalent mRNA-1273. However, serum neutralizing antibody responses against BA.1 or

BA.2 were higher in mice vaccinated mRNA-1273.529. mRNA-1273 elicited robust responses against Wuhan D614G but a minimal response against BA.1 and BA.2, while mRNA-1273.529 showed high neutralisation responses against BA.1 and BA.2, but minimal response against Wuhan D614G (Figure 2B). mRNA-1273.214 showed robust neutralization against Wuhan D614G, BA.1 and BA.2 and overall, provided the broadest neutralization coverage across the variants evaluated.

Figure 2: Neutralizing Antibody Responses in BALB/c Mice After Primary Series (Day 36)



Abbreviations: ID_{50} = infectious dose 50; LLOQ = lower limit of quantification; mRNA = messenger RNA; NAb = neutralizing antibody; ns = not significant.
Note: Statistical analysis performed was nonparametric t-test; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Study MOD-5019

The aim of this study was to evaluate immune responses to vaccines in female BALB/c mice aged 6-8 weeks, dosed by intramuscular injection. Table 2 summarises the study plan.

Table 2: Study Design for Study MOD-5019

Study Report Group (n = 8/group)	Primary Series (Dose 1 and 2)			Booster 1 (Dose 3)			Booster 2 (Dose 4)			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	
Three Doses Administered										**All groups: Blood (Days 21, 36, 49):** Antibody responses (ELISA, PSVN) **Groups 1-4 (3 doses): Sacrifice (Day 64):** Serum: Antibody responses (ELISA, PSVN assay) Spleen and LN: Antigen-specific B cell response **Groups 5-8 (4 doses): Sacrifice (Day 93):** Serum: Antibody responses (ELISA, PSVN assay)
1	PBS Control	0	Day 1, 22	PBS	0	Day 50	NA			
2	mRNA-1273	0.25		mRNA-1273	0.25					
3	mRNA-1273	0.25		mRNA-1273.529	0.25					
4	mRNA-1273	0.25		mRNA-1273.214[a]	0.25					
Four Doses Administered										
5	PBS Control	0	Day 1, 22	PBS	0	Day 50	PBS	0	Day 78	
6	mRNA-1273	0.25		mRNA-1273.529	0.25		mRNA-1273.529	0.25		
7	mRNA-1273	0.25		mRNA-1273	0.25		mRNA-1273	0.25		
8	mRNA-1273	0.25		mRNA-1273	0.25		mRNA-1273.529	0.25		

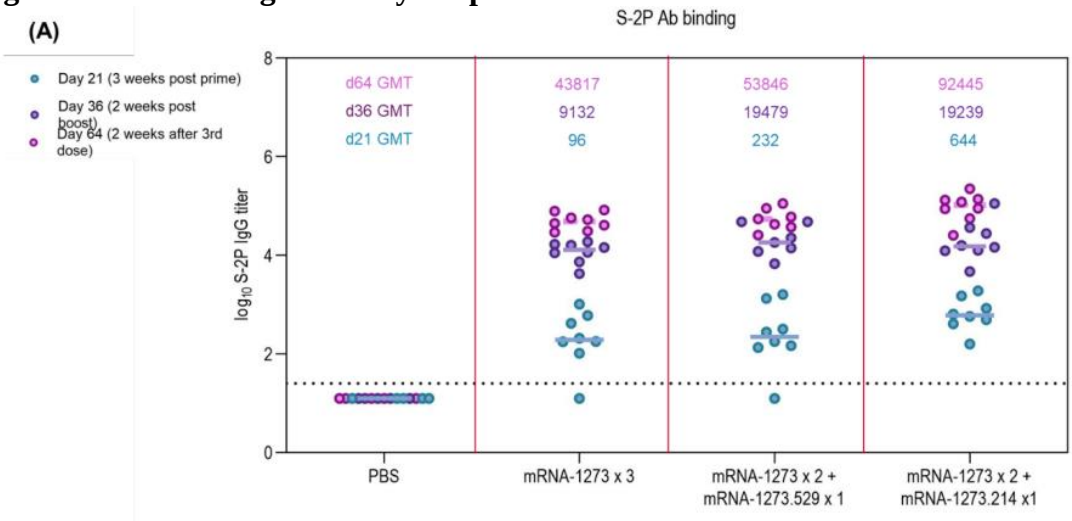
Abbreviations: IM = intramuscular; LN = lymph node; mRNA = messenger RNA; NA = not applicable; PBS = phosphate-buffered saline; PSVN = pseudovirus neutralization.

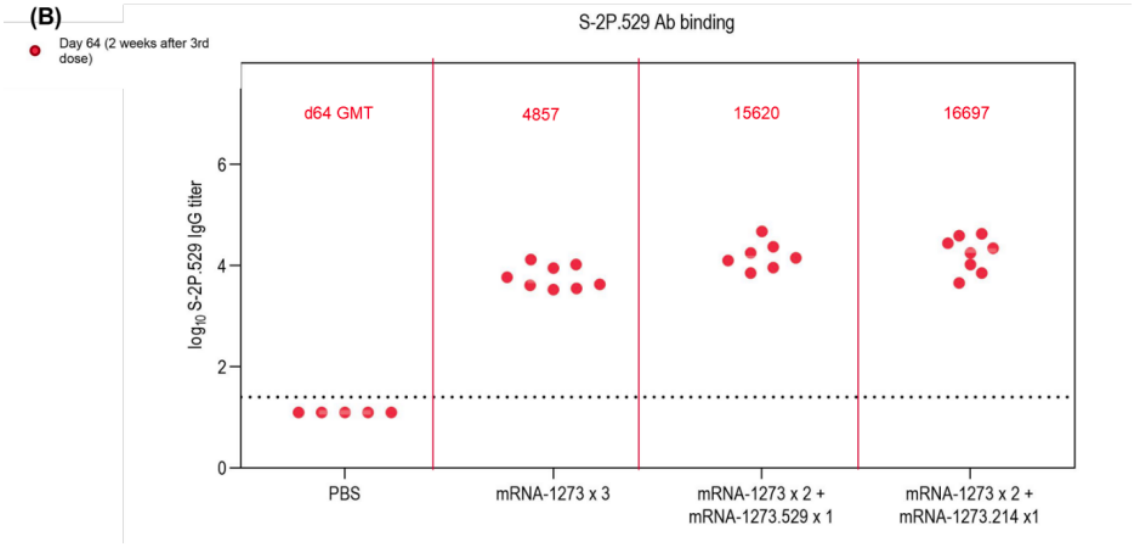
[a] mRNA-1273.214 was a 1:1 bench side mix of separately formulated mRNA-1273 and mRNA-1273.529.

Results

A binding IgG response was seen after two doses of mRNA-1273, as shown in Figure 3. Figure 3A shows results for S-2P binding and Figure 3B for SP-529 binding respectively, i.e. for the Wuhan and Omicron variant spike proteins, respectively. As above, the numbers in the box in each of the figures (e.g. 43817, 9132 and 96) are the geometric mean titre values. In mice given three doses of mRNA-1273, booster responses were seen to its specific antigen; in those given two doses of mRNA1273 and a booster dose of either mRNA-1273.529 or mRNA-1273.214, similar booster responses were also seen to each antigen.

Figure 3 Binding Antibody Responses in BALB/c Mice After Dose 3

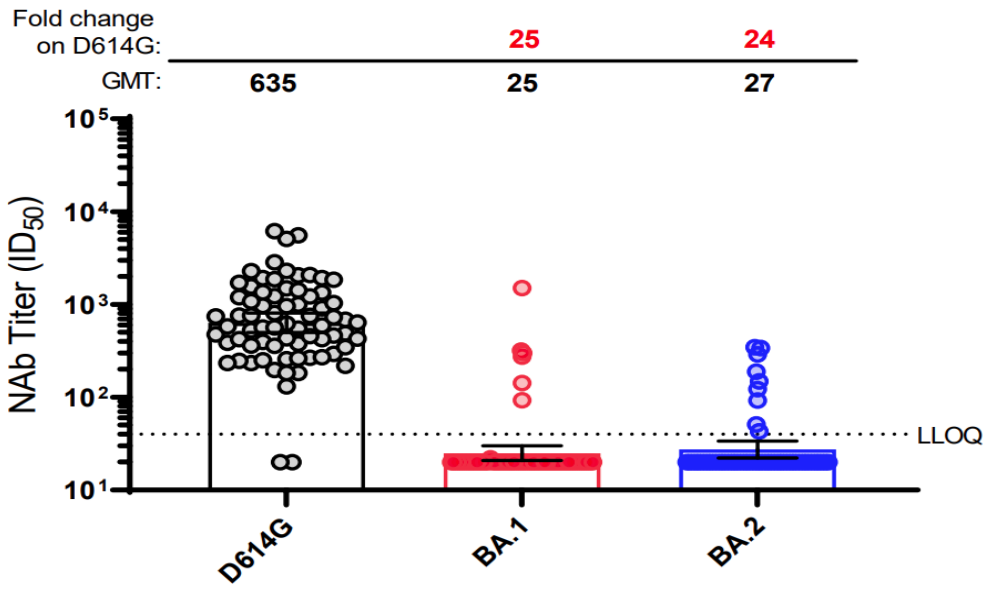




Abbreviations: Ab = antibody; GMT = geometric mean titer; IgG = immunoglobulin G; PBS = phosphate-buffered saline; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; S-2P.529 = Omicron-specific S-2P.

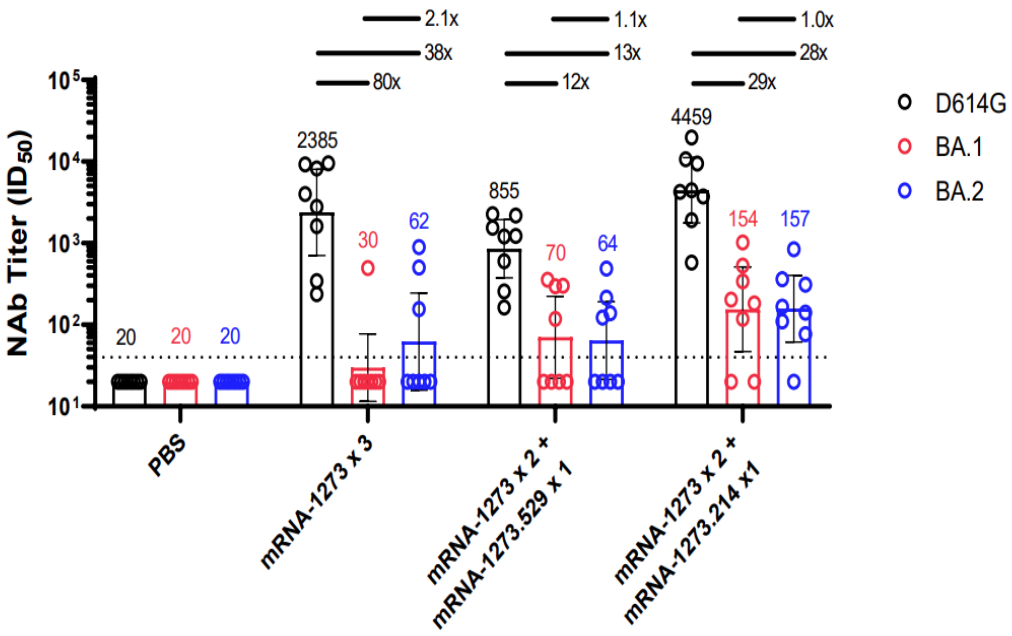
There was minimal neutralizing antibody responses against BA.1 and BA.2 before any booster dose (Figure 4), however on day 64 (two weeks after dose 3), mice boosted with mRNA-1273 showed robust neutralizing antibody titres against D614G (4-fold increase from day 49) but minimal increase in neutralizing antibody titres against BA.1 and BA.2 (Figure 5). Mice boosted with mRNA-1273.529 showed minimal increase in neutralizing antibody titres against D614G but higher neutralizing antibody titres against BA.1 and BA.2. Mice boosted with mRNA-1273.214 had higher neutralizing antibody titres against all 3 variants (D614G, BA.1, and BA.2).

Figure 4: Neutralizing Antibody Responses to BALB/c Mice Before Dose 3 [All groups combined]



Abbreviations: GMT = geometric mean titer; ID50 = infectious dose 50; LLOQ = lower limit of quantification; NAb = neutralizing antibody.
Note: Mice received 0.25 µg mRNA-1273 on Day 1 and Day 22 (primary series; Dose 1 and 2).

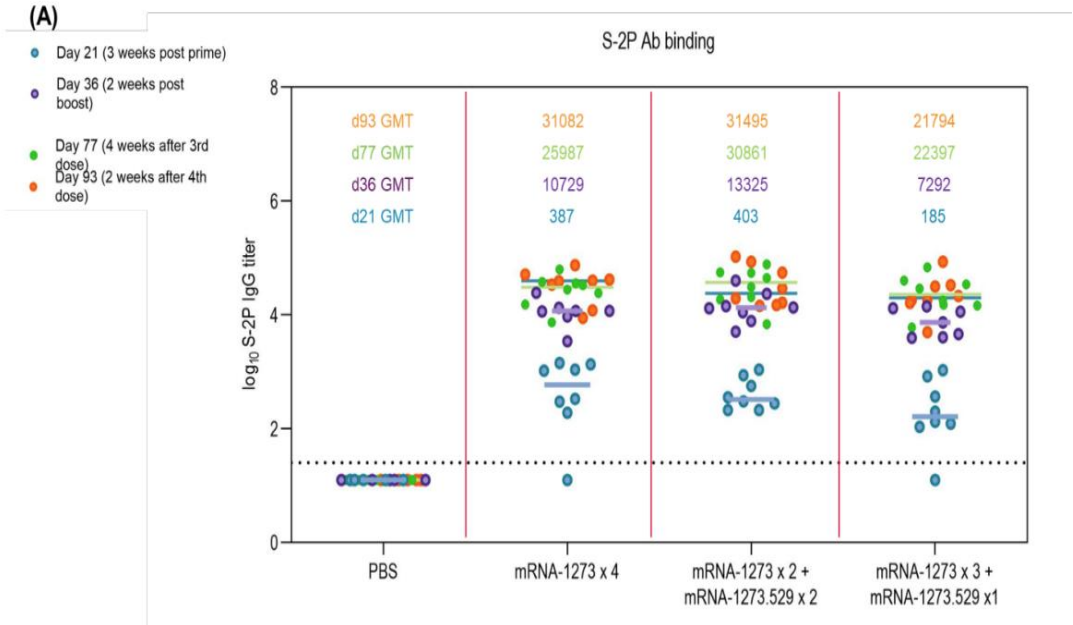
Figure 5: Neutralizing Antibody Responses to BALB/c Mice After Dose 3

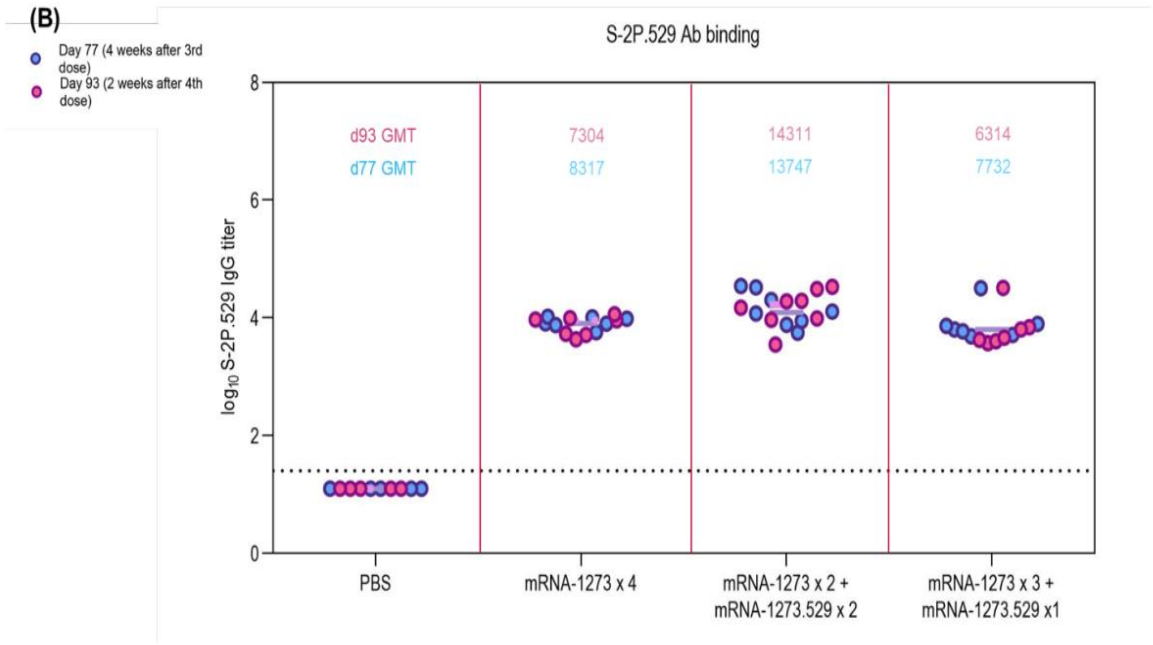


Abbreviations: GMT = geometric mean titer; ID50 = infectious dose 50; NAb = neutralizing antibody.
Note: The dotted line represents the lower limit of quantification.

Boosting with BA.1-matched mRNA-1273.529 and mRNA-1273.214 induced antigen-reactive B cells to S-2P.529 in the draining lymph node, while boosting with mRNA-1273 did not.
No notable increases in S-2P or S-2P.529 IgG geometric mean titres were seen with the fourth dose; this was likely due to the already high level of pre-existing immunity in mice.

Figure 6: Binding Antibody Responses in BALB/c Mice After Dose 4



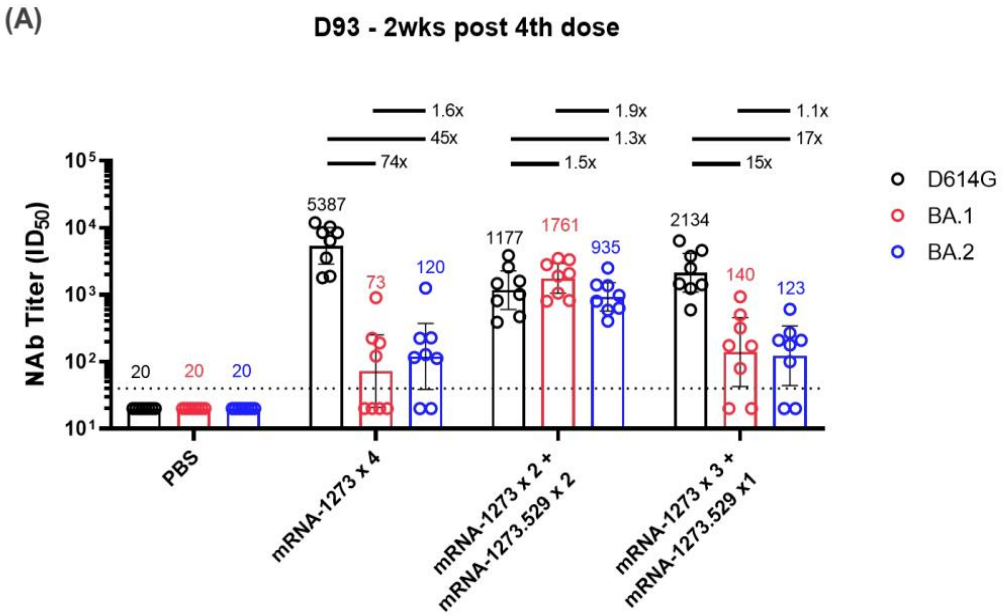


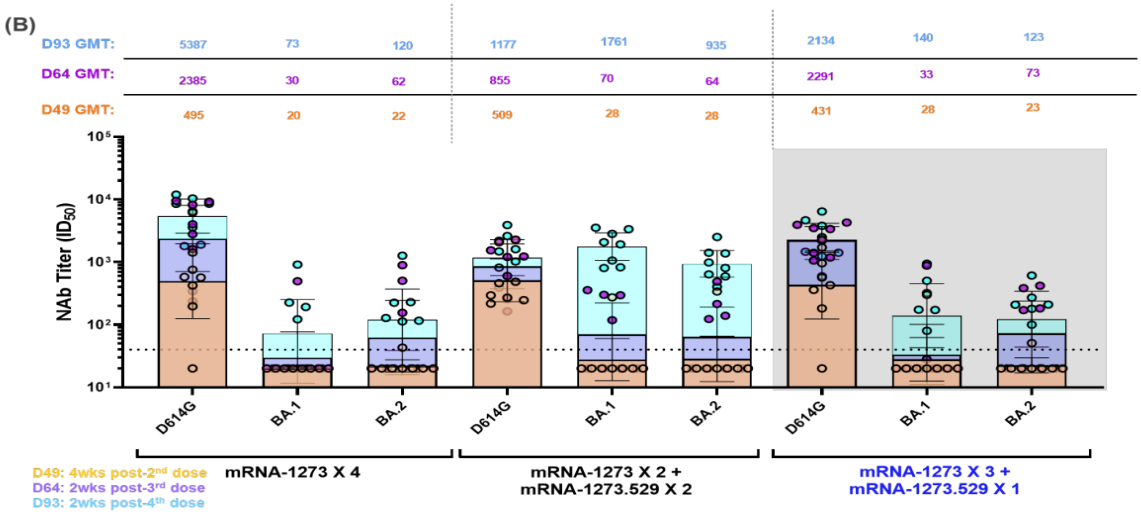
Abbreviations: Ab = antibody; GMT = geometric mean titer; IgG = immunoglobulin G; PBS = phosphate-buffered saline; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; S-2P.529 = Omicron-specific S-2P.

A single booster of mRNA-1273.529 (dose 4) after three doses of mRNA-1273 resulted in similar neutralizing antibody responses against BA.1 and BA2 to those after dose 3 with mRNA-1273.529 (Figure 7A-B9A-B), where no marked increase in neutralisation titres was seen.

Mice boosted twice with mRNA-1273.529 (doses 3 and 4) did not further increase in neutralizing antibody titres against D614G, while marked increases in neutralizing antibody titres were seen against BA.1 and BA.2 (Figure 7A-B), suggesting that Omicron-specific memory B cells measured after the third dose of mRNA-1273.529 responded to the fourth dose of mRNA-1273.529, resulting in a dramatic increase in neutralizing antibodies against BA.1 and BA.2.

Figure 7: Neutralizing Antibody Responses in BALB/c Mice After Dose 4





Abbreviations: D = day; GMT = geometric mean titer; ID_{50} = infectious dose 50; NAb = neutralizing antibody.
Notes: The dotted line represents the lower limit of quantification.
(A) Neutralizing antibody titers on Day 93 (2 weeks post Dose 4)
(B) Neutralizing antibody titers on Days 49 (2 weeks post Dose 2), Day 64 (2 weeks post Dose 3) and Day 93 (2 weeks post Dose 4) overlayed.

Conclusion

Use of mRNA-1273 in mice did not lead to responses against BA.1 or BA.2, whereas use of mRNA-1273.214 (bivalent vaccine) did lead to higher neutralizing antibody titres against all three variants (D614G, BA.1 and BA.2) compared with the mice boosted with either monovalent vaccine (mRNA-1273 or mRNA-1273.529). Boosting with the bivalent vaccine resulted in more robust immunogenicity against SARS-CoV-2 variants compared to boosting with each monovalent vaccine.

Study WASHU-01-MOD-5020

In this study, testing in mice was extended to evaluate antibody responses and protection with different vaccine constructs from challenge with SARS CoV-2 omicron variant. Different strains of mice (BALB/c, K18-hACE2 and 129S2) were used for three different experiments.

mRNA-1273 was given at doses of 0.1, 0.25, 1 and 5 µg and mRNA 1273-529 at 0.1 or 1 µg. These were given as a two-dose regimen with or without a boost of mRNA-1273 , mRNA-1273. In addition, a noncoding mRNA (0.1, 0.25 and 5 µg), UNFIX-01, was used as a negative control with a further group also given saline. All mRNA vaccines were given in 50 µl as an intramuscular injection in the hind leg. The Applicant noted that the low dose used in this testing in mice (0.1 µg) resulted in titres similar to those in human sera after completion of a primary 2-dose series with mRNA-1273.

Table 3 below summarises the testing used in this series of experiments.

Table 3: Endpoint Analyses for WASHU-01-MOD-5020

Analysis	Samples Collected	Method
IgG binding (S and RBD)	Serum	ELISA
Serum neutralizing antibody response	Serum	FRNT
Serum neutralizing antibody response	Serum	PSVN
Viral burden	Nasal wash, nasal turbinates, lung	qRT-PCR
Cytokine and chemokine analysis	Lung	Protein measurement
Lung pathology	Lung tissue	Histopathology
T-cell responses	Spleen	T-cell stimulation and intracellular cytokine staining

Abbreviations: ELISA= enzyme-linked immunosorbent assay; FRNT = focus reduction neutralization; IgG = immunoglobulin G; PSVN = pseudovirus neutralization; qRT-PCR = quantitative reverse transcription polymerase chain reaction; RBD = receptor -binding domain; S = spike

Testing in BALB/c mice

Female BALB/c mice, aged 6-8 weeks, were used for immunogenicity testing (see Table 4 for summary details).

Table 4: Treatment Regimen for Study MOD-5020: BALB/c Mice

Cohort	Mouse Strain (Female)	Primary Series			Collection Time Points
		Treatment	Dose Level (µg)	Dose Schedule	
3	BALB/c	PBS Control	0.1	Day 1, Day 22	**Serum (Day 21, Day 36):** Antibody responses (ELISA, PSVN) **Spleen (Day 36):** T-cell response (ICS)
			1		
		mRNA-1273	0.1		
			1		
		mRNA-1273.529	0.1		
			1		

Abbreviations: ELISA = enzyme-linked immunosorbent assay; ICS = intracellular cytokine staining; mRNA = messenger RNA; PBS = phosphate-buffered saline; PSVN = pseudovirus neutralization.

Results*:*

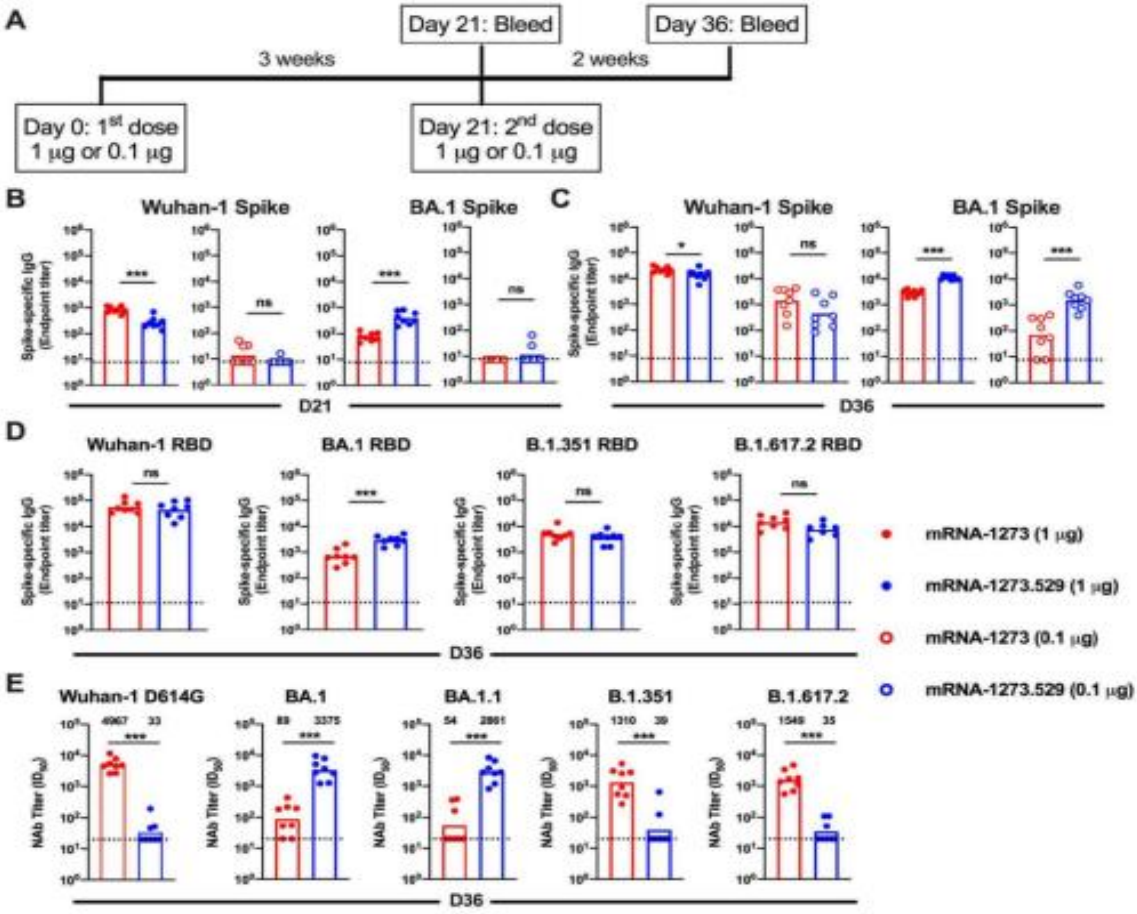
IgG responses are shown in Figure 5. In mice given 1 µg of mRNA-1273, homologous Wuhan S-specific titres were approximately11-fold higher than those against heterologous BA.1, while heterologous Wuhan and homologous BA.1 S-specific titres were similar after vaccination with 1 µg of mRNA-1273.529 (Figure 8B). At the lower dose of mRNA-1273 and mRNA-1273.529, titres against both Wuhan and BA.1 were near the limit of detection.

At day 36, two weeks after the second dose, either dose of mRNA-1273 produced higher IgG titres (8-20-fold) against homologous Wuhan S compared with heterologous BA.1 S (Figure 8C). Two doses of 0.1 µg mRNA-1273.529 resulted in higher titres (3-fold) against homologous BA.1 S compared with heterologous Wuhan, while heterologous Wuhan-I and homologous BA. 1 S-specific IgG titres were similar after two doses of 1 µg mRNA-1273 .529 (Figure 8C). Additionally, two doses of 1 µg mRNA-1273 or mRNA-1273.529 produced similar titres against Wuhan RBD, B.1.351 RBD and B.1.617.2 RBD (Figure 8D). Homologous BA. I RBD-specific titres were 4-fold higher in mice given mRNA-1273 .529 (1 µg) compared to those vaccinated with mRNA-1273 (Figure 8D).

Neutralizing antibody response was seen against Wuhan D614G after a 2-dose primary series of 1 µg mRNA-1273, with slightly lower neutralizing antibody titres (4-fold reduction) against B.1.351 or B.1.617.2. The serum neutralizing activity was reduced (59-92-fold lower) against BA.1 and BA.1.1 compared with Wuhan D614G (Figure 8E).

Mice given two doses of 1 µg mRNA-1273.529 had high neutralization antibody titres against BA.1 and BA.1.1, but lower levels (87-102-fold less) against Wuhan D614G, B.1.351 and B.1.617.2 (Figure 8E). Overall, the Applicant noted that these data suggest that a primary series with a BA.1-matched vaccine (mRNA-1273.529) induces robust neutralizing activity against BA.1 and BA.1.1, but not against other previous SARS-Co V-2 variants.

Figure 8 Antibody Responses in BALB/c Mice After Immunization with mRNA-1273 and mRNA-1273-529 Vaccines



Abbreviations: D = day; ID_{50} = 50% infectious dose; IgG = immunoglobulin G; mRNA = messenger RNA; NAb = neutralizing antibody; ns = not significant; RBD = receptor-binding domain.

Notes: Statistical analyses were performed as follows: Mann-Whitney test (**B-E**; ns; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

T cell responses in splenocytes taken from mice at day 36 (two weeks after their second dose) and restimulated with two separate peptide pools that together encompass the peptide library of the WA-1 S protein showed no differences between CD4 and CD8 cytokine production to Wuhan-I S glycoprotein in mice given either vaccine. There was no evidence of CD4 Th-2 skewed responses in either group.

Testing in Kl 8-hACE2 mice:
To evaluate the antibody response and protection against BA.l, seven-week old Kl 8-hACE2 female mice, were administered two intramuscular injections of 0.1 or 5 µg control mRNA (UNFIX-01) or mRNA-1273, 3 weeks apart. K18-hACE2 mice express human angiotensin converting enzyme-2 receptors and are reported to be susceptible to severe infection on exposure to SARS-CoV-2 variants. Table 5 outlines the experiment.

Table 5 Treatment Regimen for Study WASHU-K18MOD7AB and WASHU-K18MOD3/4: K18-hACE2 Mice

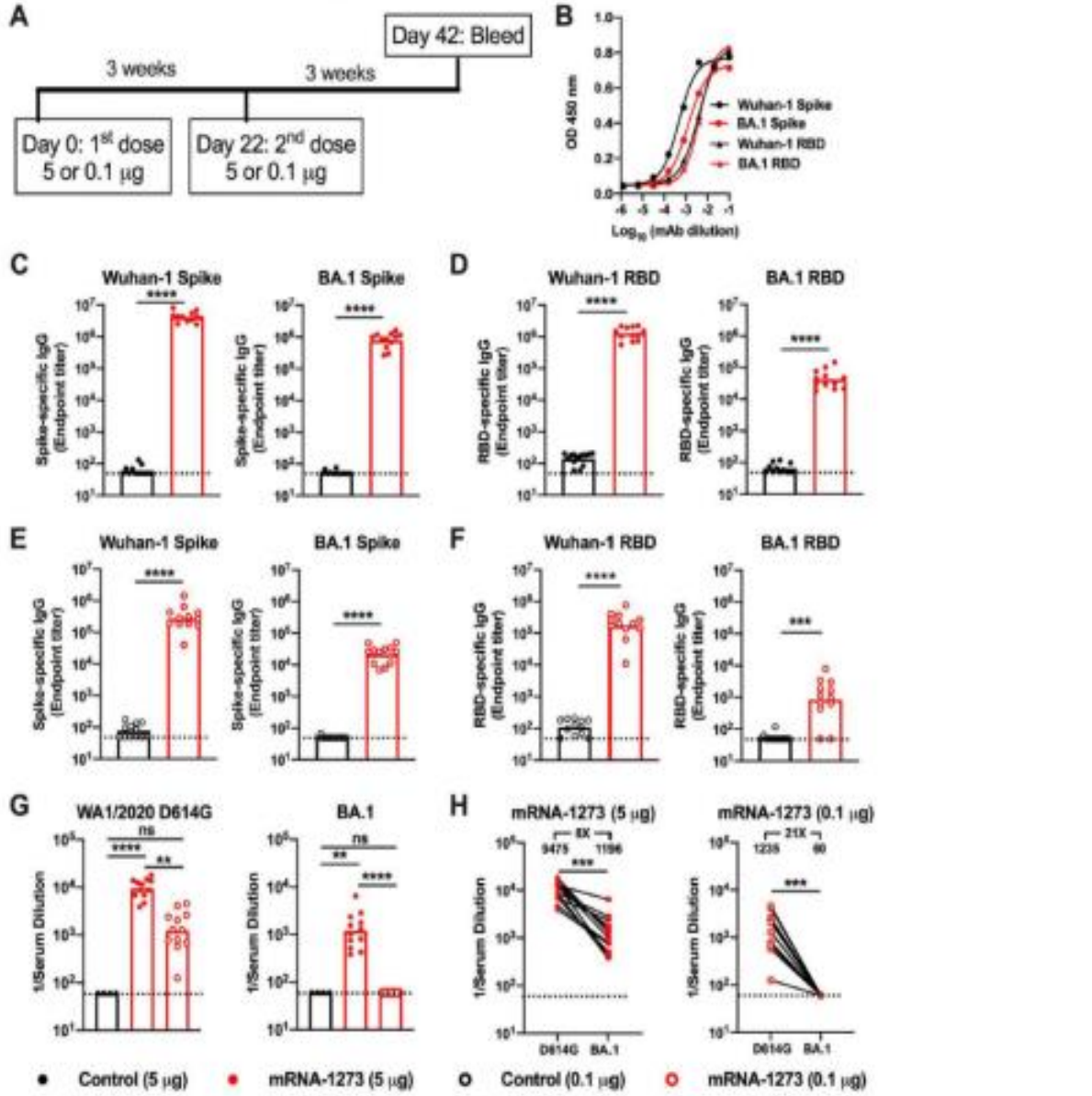
		Primary Series			Boost			Challenge		
Cohort	Mouse Strain (Female)	Treatment	Dose Level (µg)	Dose Schedule	Treatment	Dose Level (µg)	Dose Schedule	Variant (10^4 FFU)	Time Point	Collection Time Points
1	K18-hACE2	mRNA control	0.1	Day 0, Day 21	N/A			WA1/2020 D614G or BA.1	Day 56/57	**Serum (Day 42):** Antibody responses (ELISA, FRNT) **Sacrifice (Day 62/63)** Body weight Viral burden (qRT-PCR) Cytokine/chemokine analysis Histopathology
			5							
		mRNA-1273	0.1							
			5							
2	K18-hACE2	mRNA control	0.25	Day 0, Day 21	mRNA control	1	Day 134/156	BA.1	Day 162/184	**Serum (Day 133/155 pre-boost; Day 160/182 post-boost):** Antibody response (FRNT) **Sacrifice (Day 168/190):** Viral burden (qRT-PCR)
			5			1				
		mRNA-1273	0.25		mRNA-1273	1				
			5			1				

Abbreviations: ELISA = enzyme-linked immunosorbent assay; FFU = focus-forming units; FRNT = focus reduction neutralization; mRNA = messenger RNA; N/A = not applicable; qRT-PCR = quantitative reverse transcription polymerase chain reaction.

Results
IgG responses were seen against both the Wuhan and BA.1 S proteins after two doses of mRNA-1273 (Figure 9C-F).

At 0.1 µg, titres were approximately 10-fold lower than at 5 µg. In both mRNA-1273 dose groups, Wuhan S- and RBD-specific titres were higher than those against BA.1. Responses against both WA1/2020 D614G and BA.1 were seen after two doses of 5 µg mRNA-1273 (Figure 9G). At 0.1 µg mRNA-1273, neutralizing antibody geometric mean titres against WAI/2020 D614G were ~8-fold less compared to at 5 µg mRNA-1273. In both mRNA-1273 groups, serum neutralizing activity was reduced against BA.1 compared with WA1/2020 D614G (Figure 9H). At 5 µg, the neutralizing titre was ~8-fold lower against BA.1 and at 0.1 µg, titres were at least 20-fold lower against BA.1, with all values assigned to the limit of detection.
.

Figure 9: Antibody Responses of mRNA Vaccines in K18-hACE2 Mice



Abbreviations: ANOVA = analysis of variance; IgG = immunoglobulin G; mAb = monoclonal antibody; mRNA = messenger RNA; ns = not significant; OD = optical density; RBD = receptor-binding domain.

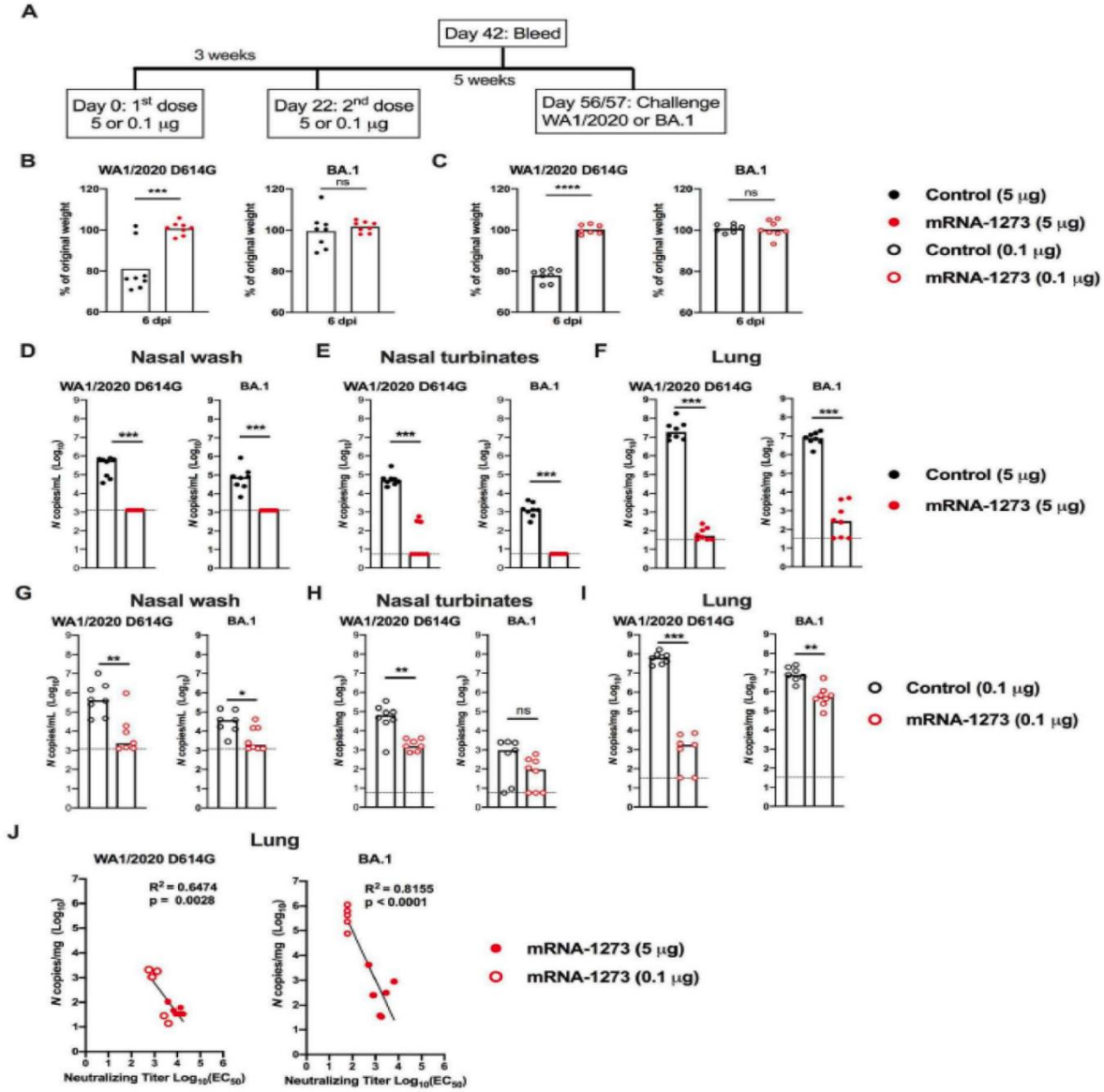
Notes: Statistical analyses performed were as follows: Mann-Whitney test (**C-F**); 1-way ANOVA with Dunn's post-test (**G**); and Wilcoxon signed-rank test (**H**); ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

When mice were challenged with WA1/2020 D614G or BA.1, weight loss occurred in the controls: this was prevented in mice given either 0.1 or 5 µg of mRNA-1273 (Figure 10B and C). BA.1-challenged mice did not lose weight in the six days post-infection and so no demonstration of a protective effect of the vaccine was possible using this measure.

There was a reduced viral burden in those challenged with BA.1 compared to those challenged with WA1/2020 D614G. Control (unvaccinated) mice challenged with BA.1 had reduced levels of viral burden in nasal washes compared to mice challenged with WA1/2020 D614G (Figure 10D-F) by ~10-fold (10(5)-10(6) N copies per ml reducing to 10(4)-10(5) N copies per ml) (Figure 10D and Figure 10G). In nasal turbinates, BA.1 viral load was ~100-fold lower than WA1/2020 D614G (10(3) versus 10(5) N copies per mg; Figures 2E and 2H). In lungs, BA.1 viral load was approximately10-fold lower than WAI/2020 D614G ((10(7) to 10(8) N copies per ml) versus 10(6) to 10(7) N copies per mg; Figures 10F and 10I).

In vaccinated mice, 5 µg mRNA-1273 led to robust protection against WA1/2020 D614G and BA.1 (Figure 10D-I). WA1/2020 D614G viral RNA was not detected in the nasal wash (Figure 10D) and low levels of WAl/2020 D614G were seen in nasal turbinates (three of seven mice; Figure 10E) and lungs (four of seven mice; Figure 10F). In the 5 µg group, BA.1 viral RNA was not detected in the nasal wash or nasal turbinates, while low levels of BA.1 were observed in the lung (five of seven mice). A reduced dose of 0.1 µg mRNA-1273 received some protection against WA1/2020 D614G and BA.1 infection, as depicted in Figures 10G, H and I); the level of infection was reduced (100-100,000-fold) compared with the unvaccinated control group. Serum neutralizing antibody titres were inversely correlated with the viral load in the lung for both SARS-Co V-2 variants (Figure 10J), where the burden of infection generally decreased as the neutralizing antibody titres increased. The highest levels of infection were seen in BA.1-challenged mice, with low neutralizing antibody titres after vaccination with 0.1 µg mRNA-1273.

Figure 10: Protection Against SARS-CoV-2 Infection After mRNA Vaccination in K18-hACE2 Mice



Abbreviations: dpi = days post-infection; EC_{50} = half maximal effective concentration; mRNA = messenger RNA; ns = not significant; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Notes: Statistical analyses were performed as follows: unpaired t test (**B, C**); Mann-Whitney test (**D-I**); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Source: Ying et al 2022b, Figure 2.

In control (unvaccinated) mice, exposure to WAl/2020 D614G or BA.1 infection resulted in an inflammatory response with increased expression of several pro-inflammatory cytokines and chemokines, including G-CSF, GM-CSF, IFNγ, IL-1β, IL-6, CXCLl, CXCL5, CXCL9, CXC10, CCL2, CCL4 and TNFα in lung homogenates, when evaluated six days after the challenge. 0.1 and 5 µg mRNA-1273 each diminished this inflammatory response to the WAl/2020 D614G challenge; however, no protection was seen in mice challenged with BA.1 where levels of pro-inflammatory cytokines and chemokines in the lung were similar to those observed in controls).

Histological analysis of lung sections revealed severe pneumonia characterised by immune cell infiltration, alveolar space consolidation, vascular congestion and interstitial oedema in controls challenged with WAl/2020 D614G. After BA.1 challenge, mRNA control mice showed less lung pathology, with focal airspace consolidation and immune cell infiltration; these results are consistent with reduced pathogenicity of BA.1 compared to WAl/2020 D614G. Mice given 0.1 or 5 µg mRNA-1273 did not develop lung pathology after challenge with WAl/2020 D614G: findings were consistent with uninfected mice. After challenge with BA.1, 5 µg mRNA-1273 protected against mild pathological changes associated with infection. Protection against BA.1 was not seen in mice that received 0.1 µg mRNA-1273, where lung pathology findings were similar to those observed in controls with patchy immune cell infiltration, airway space thickening, and mild alveolar congestion.

Approximately 17-19 weeks after two doses of 0.25 or 5 µg mRNA vaccines, blood was collected and mice boosted with 1 µg mRNA-1273. Preboost neutralizing antibody titres against WA1/2020 D614G and BA.1 were 5-10-fold lower in mice given 0.25 µg mRNA-1273 compared to mice given 5 µg. In mice given 5 µg mRNA-1273, neutralizing activity was reduced against BA.1 compared with WAl/2020 D614G (7-14-fold lower). No difference was seen between the 2 SARS-CoV-2 variants for mice given 0.25 µg with two of four mice showing no neutralizing activity against BA.1 at the 1/60 limit of detection. One month after boosting with 1 µg mRNA-1273, serum neutralizing titres rose against both WAl/2020 D614G and BA.1: titres against BA.1 were reduced (8-20-fold lower) compared with those against WAl/2020 D614G.

Four weeks after boosting with 1 µg mRNA-1273, mice were challenged with BA.1 and viral load measured in the upper and lower respiratory tract. In boosted mice, viral load was lower than in controls. In those primed with 5 µg mRNA-1273, BA.1 viral RNA was not detected in the nasal wash or nasal turbinates and low levels of BA.1 were seen in the lungs (5 of 8 mice). In those primed with 0.25 µg mRNA-1273, low levels of BA.1 were seen in the nasal wash (one of four mice), nasal turbinates (three of four mice) and lungs (four of four mice). Evaluation of viral load six days post-infection showed that a boost of 1 µg mRNA-1273 improves neutralizing antibody response and reduces BA.1 viral load in the upper and lower respiratory tract.

<u>Testing in 129S2 mice:</u>
These mice were used in a challenge experiment in which they were infected with the Omicron variant of SARS CoV-2 virus and their immune response to vaccination characterised. The mice are able to be infected with virus that engages murine angiotensin converting enzyme-2. The study design is presented in below in Table 6.

Ten to eleven weeks after the initial two doses of mRNA-1273, there were high levels of neutralizing antibody titres against WA1/2020 N501 Y/D614G (Figure 11B), compared with 9-18-fold lower serum pre-boost neutralizing antibody titres against BA.1 or BA.2 (Figure

11B). One month after boosting with mRNA-1273 or mRNA-1273.529, neutralizing antibody titres against WAl/2020 N501 Y/D614G were ~2-6-fold higher than pre-boost values (Figure 11C-D). Three to four weeks after boosting with mRNA-1273.529, neutralizing antibody titres against BA.1 and BA.2 were 15 to 32-fold and 11to18-fold higher than pre-boost values, respectively, while a 2-8-fold (BA.1) and 5 to 17-fold (BA.2) increase versus pre-boost values was seen in mice boosted with mRNA-1273 (Figure 11E-F).

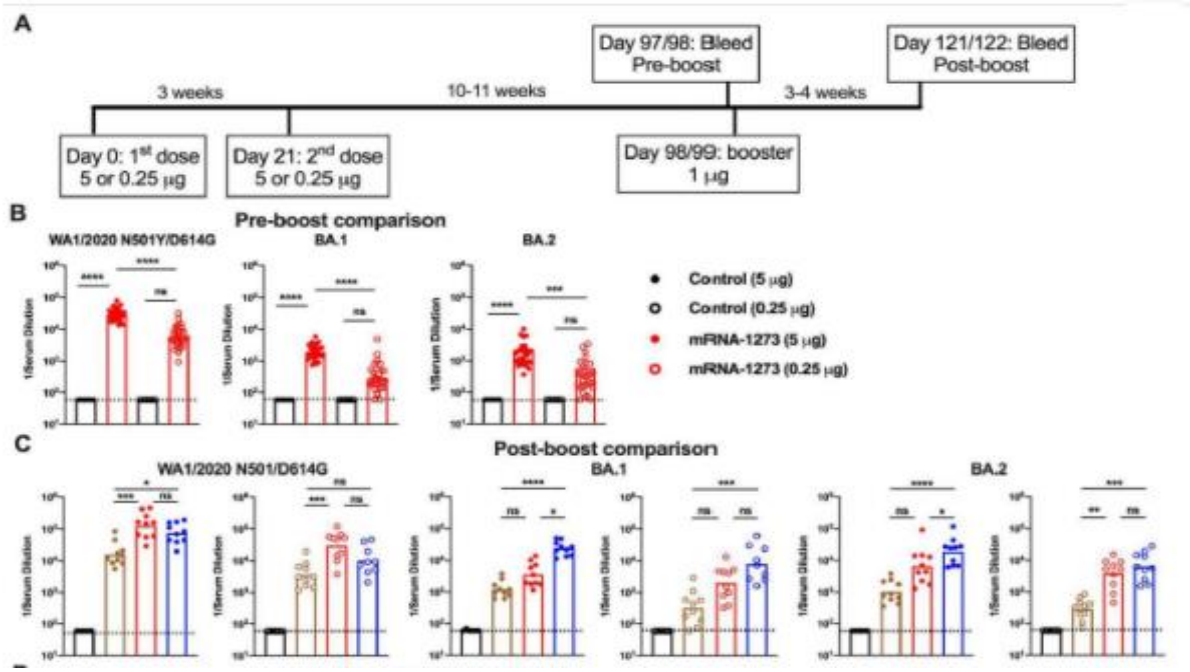
Table 6: Treatment Regimen for WASHU-129MOD5/6: 129S2 Mice

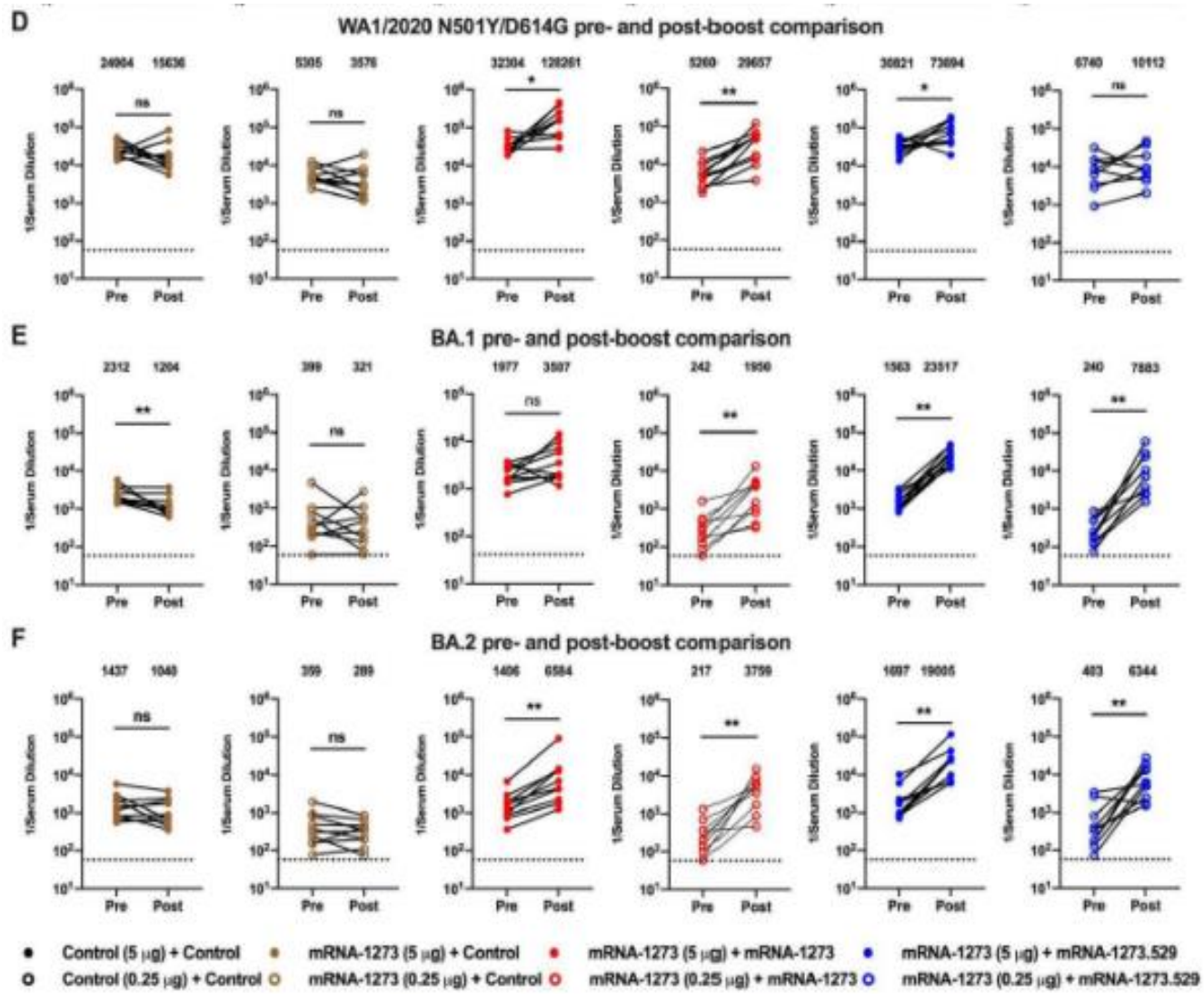
Cohort	Mouse Strain (Female)	Primary Series			Boost			Challenge		Collection Time Points
		Treatment	Dose Level (µg)	Dose Schedule	Treatment	Dose Level (µg)	Dose Schedule	Variant (10^5 FFU)	Time Point	
4	129S2	mRNA Control	5	Day 0, Day 21	mRNA Control	1	Day 98, Day 99	WA1/2020 N501Y/D614G or BA.1	Day 124/126	**Serum (Day 97/98 pre-boost; Day 121/122 post-boost):** Antibody response (FRNT) **Sacrifice (Day 127/129):** Viral burden (qRT-PCR) Cytokine/chemokine analysis
			0.25		mRNA Control	1				
		mRNA-1273	5		mRNA Control	1				
					mRNA-1273	1				
					mRNA-1273.529	1				
			0.25		mRNA Control	1				
					mRNA-1273	1				
					mRNA-1273.529	1				

Abbreviations: FFU = focus-forming units; FRNT = focus reduction neutralization; mRNA = messenger RNA; qRT-PCR = quantitative reverse transcription polymerase chain reaction.

The Applicant noted that these data suggest that boosting with mRNA-1273 or mRNA-1273.529 both result in enhanced neutralizing antibody responses against BA.1 and BA.2, with higher neutralizing antibodies produced after boosting with a BA.1-matched vaccine.

Figure 11: Booster Doses of mRNA-1273 or mRNA-1273.529 Enhance Neutralizing Antibody Responses in 129S2 Mice





Abbreviations: ANOVA = analysis of variance; mRNA = messenger RNA; ns = not significant.

Notes: Statistical analyses were performed as follows: 1-way ANOVA with Dunn's post-test (**B, C**); Wilcoxon test (**D, E**); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Five weeks after boosting with 1 µg mRNA-1273 or mRNA-1273.529, mice were challenged with WAl/2020 N501Y/D614G or BA.1 virus. Three days post-infection, BA.1 viral RNA levels in the upper and lower respiratory tract in control (unvaccinated) mice were approprimately100-fold lower than RNA levels seen in unvaccinated control mice given WAl/2020 N501 Y/D614G, indicating lower pathogenicity of BA.1.

In mice primed with 0.25 or 5 µg mRNA-1273 and boosted with mRNA-1273 or mRNA-1273.529, WAl/2020 N501 Y/D614G viral load was reduced compared to controls (100,000-1,000,000-fold. In mice primed with 5 µg mRNA-1273 and boosted with mRNA-1273 or mRNA-1273 .529, BA.1 viral RNA levels were low (near the limit of detection) with no differences between groups. However, differential protection against BA.1 was noted in mice primed with 0.25 µg mRNA-1273 and boosted with mRNA-1273 or mRNA-1273.529. While BA.1 viral load was generally reduced in the upper and lower respiratory tract in mice primed with 0.25 µg mRNA-1273 and boosted with mRNA-1273 or mRNA-1273.529, there was a trend toward lower BA.1 viral load in the nasal turbinates in mice boosted with mRNA-1273.529 and BA.1 viral load in the lungs was reduced by 27-fold in mice boosted with mRNA-1273.529 compared to that in mice boosted with mRNA-1273.

Cytokine and chemokine responses in lung homogenates were evaluated three days after challenge with WAl/2020 N501 Y/D614G or BA.1. After challenge, mice primed with mRNA-1273 and boosted with mRNA-1273 or mRNA-1273.529 generally had lower levels of proinflammatory cytokines and chemokines compared with control (unvaccinated) mice. In control (unvaccinated) mice, the inflammatory response after BA.1 challenge was diminished compared with that after WAl/2020/N501 Y/D614G, consistent with lower pathogenicity of BA.1 in mice. After BA.1 challenge, mice that had been given 5 µg mRNA-1273 and boosted with any of the mRNA vaccines, showed reduced levels of chemokines and cytokines compared to control (unvaccinated) mice; the company noted that these data indicate that boosting with homologous mRNA-1273 or heterologous mRNA-1273.529 results in increased protection against BA.1-induced inflammation. The inflammatory response induced by BA.1 in mice primed with 0.25 µg mRNA-1273 and boosted with control mRNA was similar to that in control (unvaccinated) mice; however, lower levels of cytokines and chemokines were seen in mice primed with 0.25 µg mRNA and boosted with mRNA-1273.529 compared to those boosted with mRNA-1273.

Conclusion of Study WASHU-01-MOD-5020
Overall, it was noted that boosting with a BA.1-matched vaccine (mRNA-1273.529) resulted in modestly enhanced protection against BA.1-induced inflammatory response in 129S2 mice; this was consistent with the virology data.

Mice were protected against both SARS-CoV-2 variants by the higher dose of vaccines used: neutralizing antibodies induced by the low dose primary series of mRNA-1273 showed less inhibitory activity against BA.1 and this was reflected in breakthrough infections in the upper and lower respiratory tracts. Cytokine and histology analyses confirmed the low-to-minimal protection against BA.1 in mice by the low-dose of mRNA-1273. Serum neutralizing titres were increased one month after boosting with mRNA-1273, although the response to BA.1 was lower than the response to WAl/2020. Boosting mice, with mRNA-I273.529, which had received a primary series of mRNA-1273, resulted in enhanced neutralizing antibody responses against BA.1 and in enhanced protection against BA.1-induced inflammatory response.

The Applicant concluded that boosting with either mRNA-1273 or mRNA-1273.529 enhanced protection against BA.1 infection: differences in protection were limited and either vaccine gave protection against the historical WAl/2020 variant while offering increased neutralizing titres and protection against BA.1 and BA.2.

Study VRC-220-857
The aim of this study was to determine the effect of boosting with mRNA-1273.529 (Omicron spike) approximately nine months after a two-dose regimen of mRNA-1273 (four weeks apart) in rhesus monkeys. This tested whether vaccination elicited increased immunity and protection against omicron challenge.

Table 7 and Figure 12 below summarise the procedures used in this study.

Table 7: Treatment Regimen for Study VRC-20-857

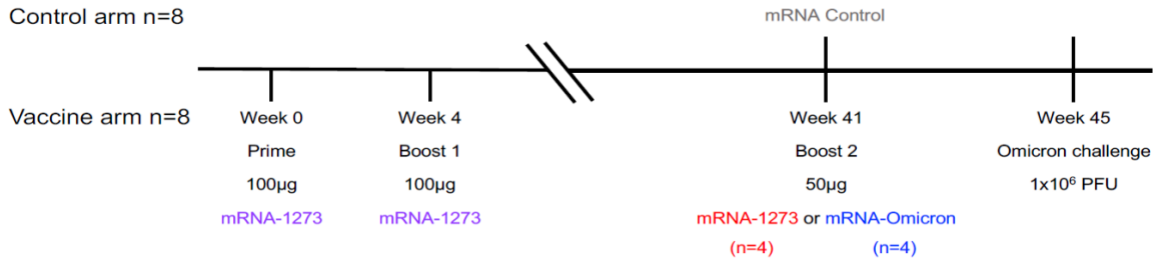
Group	Number of Animals	Vaccination Schedule			Pre-Challenge Collection	Challenge (Week 45)[a]	Post-Challenge Collection
		Prime Dose 1 (Week 0)	Prime Dose 2 (Week 4)	Boost (Week 41)			
1	8	N/A	N/A	UNFIX-01 50 µg	Sera: Weeks 6, 41, 43 NW, BAL: Weeks 8, 39, 43	SARS-CoV-2 Omicron	BAL: Days 2, 4, 8 NS: Days 1, 2, 4, 8 Oral Swab: Day 2 Lung tissue: Day 8[b]
2	4	mRNA-1273 100 µg	mRNA-1273 100 µg	mRNA-1273 50 µg			
3	4			mRNA-1273.529 50 µg			

Abbreviations: BAL = bronchoalveolar lavage; mRNA = messenger RNA; N/A = not applicable; NS = nasal swab(s); NW = nasal wash(es); PFU = plaque-forming units; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UNFIX-01 = untranslated factor 9.

[a] Animals were challenged with a total dose of 1×10^6 PFU of SARS-CoV-2 Omicron. The viral inoculum was administered as 7.5×10^5 PFU in 3 mL intratracheally and 2.5×10^5 PFU in 1 mL intranasally in a volume of 0.5 mL distributed evenly into each nostril.

[b] Two out of 4 animals from groups 2 and 3 were euthanized for tissue collection.

Figure 12: Experimental Schema for Study VRC 20-857



Abbreviations: mRNA = messenger RNA; PFU = plaque-forming units.

Results

Two weeks after the second dose, binding antibody titres were highest against Wuhan followed by Delta, then Beta, then Omicron. Geometric mean titres (GMTs) to Wuhan and omicron were 8×10(19) and 3×10(15) respectively: these were markedly decreased by week 41 (pre-boost) at 2×10(12) and 2×10(8) for Wuhan and Omicron, respectively. A similar pattern was observed when measuring binding to the receptor binding domain (RBD) of the same variants, with titres to Omicron of 7×10(11) at week 6 and 8×10(7) AUC at week 41. At week 41 (following either boost), S-binding titres were close to the same level as at week 6: titres to Omicron were lower than the other variants. At week 6, neutralizing titres assessed by live virus assay, were highest to D614G followed by Delta, then Beta, then Omicron. Titres to all variants decreased by week 41.

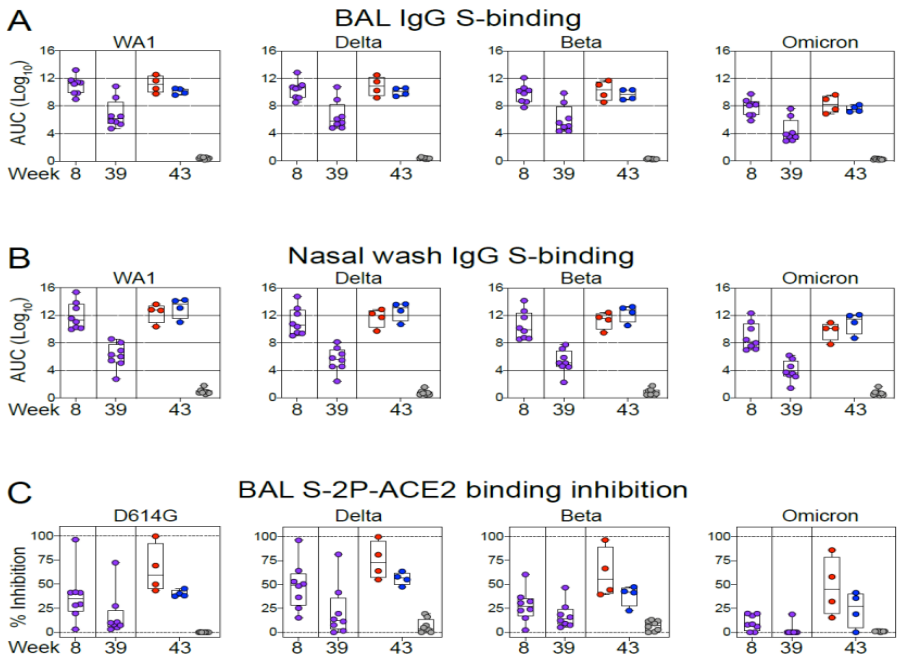
Following a boost with either test article, neutralizing titres to D614G and Delta were similar to those at week 6 and titres to Beta and Omicron were greater than at week 6. Following either boost, pseudovirus neutralizing titres to Beta and Omicron were greater than at week 6. This included an increase in Omicron titres from 320 GMT to 2980 GMT in the mRNA-1273 boost group and to 1930 GMT in the mRNA-1273.529 boost group.

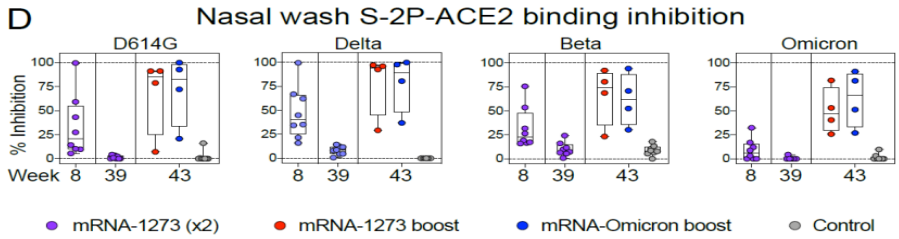
Antibody avidity over time was measured to assess whether the increased neutralizing titres after the boost could be attributed to antibody maturation. Antibody avidity to Omicron S-2P increased from 0.44 to 0.67 from weeks 6 to 41.

In bronchoalveolar lavage fluid and nasal washes, IgG S-binding titres were highest in Wuhan, then Delta, then Beta and then Omicron (Figure 3). In bronchoalveolar lavage fluid, week 39 (pre-boost) MTs were 6.8×10(6), 4.0×10(6), 1.3×10(6) and 2.5×10(4) for Wuhan, Delta, Beta and Omicron, respectively. Compared to that of Wuhan, these titres correlated with a 2-fold reduction for Delta, a 5-fold reduction for Beta, and a 275-fold reduction for Omicron. At week 43 (following either boost), titres were increased by 3-4 logs for all variants. In nasal washes, week 8 titres decreased from approximately 10(11) for Wuhan, Delta and Beta to 1.3×10(6), 3.7×10(5) and 1.9×10(5) for Wuhan, Delta and Beta, respectively, at week 39. Omicron titres were lower than Wuhan titres (and those of other variants) and decreased from 8.8×10(8) to 8.7×10(3). Either boost increased nasal antibody titres by approximately seven logs at week 43 with GMTs of approximately10(12) for Wuhan, Delta and Beta and approximately 10(10) for Omicron.

In measures of ACE2 inhibition (used as a measure of antibody function), bronchoalveolar lavage fluid expressed 25-50% median binding inhibition for all variants at week 8, except for Omicron S-2P, in which binding inhibition was low to undetectable (Figure 13C). There was a decrease in ACE2 binding inhibition (<15%) for all variants by week 39, followed by an increase after either the mRNA-1273 or mRNA-1273.529 boost. Despite an increase in ACE2 inhibition of Omicron S-2P following the boost, it was still lower than all the other variants. ACE2 inhibition was low to undetectable in the upper airway at week 39 (following the primary series). After either boost, there was an increase in ACE2 S-2P binding inhibition across all variants, including Omicron, to values higher than the initial peak at Week 8 (Figure 13D).

Figure 13: Mucosal Antibody Response to Boosting with mRNA-1273 or mRNA-1273.529





Abbreviations: ACE2 = angiotensin-converting enzyme 2; AUC = area under the curve; BAL = bronchoalveolar lavage; IgG = immunoglobulin G; mRNA = messenger RNA; NHP = non-human primate; S = spike; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; WA1 = USA-WA1/2020.

Note: Circles indicate individual NHPs. Boxes represent the interquartile range with the median denoted by a horizontal line. Dotted lines are for visualization purposes and denote 4-$\log_{10}$ increases in binding titers (A-B) or 0% and 100% inhibition (C-D). Eight controls and 8 vaccinated NHPs were split into 2 cohorts post-boost.

Source: Gagne et al 2022b, Figure 2

B-cell binding was measured using different variants of concern to assess mobilisation of cross-reactive memory B-cells. At week 6, 63% of the total S-2P–specific memory B-cell responses were dual-specific and capable of binding both Wuhan and Omicron probes, with 33% binding to Wuhan alone and 4% binding to Omicron alone. The total S-specific memory B-cell compartment decreased approximately 90% (as a fraction of all class-switched memory B-cells) by week 41. The dual-specific population remained the largest group within the S-binding pool.

At week 43 (following either boost), there was expansion of the total S-specific memory B-cell compartment (similar to that at week 6). After boosting with mRNA-1273, 71% of all S-2P–specific memory B-cells were dual-specific for Wuhan and Omicron and 24% were specific for Wuhan alone. After boosting with mRNA-1273.529, 81% of all S-2P–specific memory B-cells were dual-specific for Wuhan and Omicron and 12% were specific for Wuhan only. These results indicate that either boost expanded cross-reactive dual-specific (Wuhan and Omicron-positive) B-cells.

To further explore the effect of boosting on anamnestic B-cell responses, the activation status of S-binding memory B-cells was phenotyped. Wuhan S-2P– and/or Omicron S-2P-binding memory B-cells predominantly had an activated memory phenotype immediately after both the second and third doses.

In testing for cross-reactivity of B-cells for Delta and Omicron, at week 6, 68% of all Delta S-2P and/or Omicron S-2P memory B-cells were dual-specific; the remainder of S-binding memory B-cells, however, largely bound Delta alone. Following the booster, occurrence of dual-specific cells increased to 76% for mRNA-1273 and 85% for mRNA-1273.529.

Frequencies of memory B-cells specific for Wuhan and Delta or Beta were also assessed. Approximately 95% of all Wuhan and/or Delta-binding memory B-cells were dual-specific after either boost. Findings were similar to those with Wuhan and Beta S-2P probes, in which the dual-specific population was 85% at week 6 and 90% following the boost. mRNA-1273.529 boost resulted in very few detected B-cells, which only bound Wuhan epitopes when co-stained for Delta or Beta.

S-2P–specific T-cell responses were measured in blood and bronchoalveolar lavage fluid. Vaccination with mRNA-1273 elicited T helper 1 (Th1), T-follicular helper (Tfh) and low-level CD-8 T-cell responses at the peak of the response (week 6) that decreased over time. There was little to no response from T helper 2 cells. Vaccination with either mRNA-1273 or mRNA-1273.529 boost increased Tfh responses. T helper 1 and CD-8 T-cells in bronchoalveolar lavage fluid were detected at week 8 and were undetectable levels at week

39 (pre-boost. These responses were increased with either the mRNA-1273 or mRNA-1273.529 boost (week 43).

In blood, mRNA-1273 elicited S-2P–Specific T-cell responses: T helper 1 (Th1), T-follicular helper (Tfh) and low-level CD-8 T-cell responses were seen at the peak of the response (Week 6) that decreased over time. There was little to no response from T helper 2 cells. Each of mRNA-1273 and mRNA-1273.529 increased Tfh responses. In bronchoalveolar lavage fluid, T helper 1 and CD-8 T-cells were detected at week 8 and decreased to undetectable levels at week 39 (pre-boost). These responses were increased at week 43 with either the mRNA-1273 or mRNA-1273.529 boost.

Four weeks after either booster, monkeys were challenged with 1×10(6) PFU of SARS-CoV-2 omicron. In measures of subgenomic (sg) RNA two days later, control (i.e. unvaccinated) monkeys had geometric mean copy numbers of 1×10(6) sgRNA per ml of bronchoalveolar lavage fluid, whereas those that had been vaccinated had mean copy numbers of 3×10(2) and 2×10(2) sgRNA per ml for the mRNA-1273 and mRNA-1273.529 cohorts. All vaccinated monkeys had undetectable levels of sgRNA N by day 4 post-infection and copy numbers in controls (unvaccinated monkeys) had decreased to 3×10(5) per ml. At day 4 post-infection, five of eight controls had detectable virus in nasal swabs compared with three of eight vaccinated monkeys. No clear difference was noted between the boost cohorts. By day 8 post-infection, four of eight controls had detectable sgRNA N (including two with increased copy numbers), while none of the vaccinated monkeys had detectable sgRNA. In the throat, sgRNA N was present on day 2 post-infection in only one of eight vaccinated monkeys (in either boost group) compared to six of eight controls. No virus was detected in the bronchoalveolar lavage fluid of any vaccinated monkey, while 8 of 8 controls had detectable virus on day 2 and seven of eight were positive at day 4 post-infection. One of eight boosted monkeys had culturable virus from nasal swabs. In controls, two of eight (on day 2 post-infection) and three of eight (day 4 post-infection) had culturable virus in the nose.

Following the Omicron challenge, two monkeys from each of the vaccinated groups and four monkeys from the control group were killed and the amount of SARS-CoV-2 nucleocapsid in the lungs was assessed by immunohistochemistry: the degree of inflammation was assessed by hematoxylin and eosin (H&E) staining. Variable amounts of nucleocapsid antigen were detected in the lungs of controls. The viral antigen (when present) was often associated with the alveolar capillaries and occasional nearby immune cells.

For all vaccinated monkeys there was no evidence of any viral antigen. Monkeys from each group showed histopathological alterations rated as minimal-to-mild or mild-to-moderate. Inflammation was characterised by mild and patchy expansion of alveolar capillaries, generalised alveolar capillary hypercellularity, mild and regional type II pneumocyte hyperplasia, and (less frequently) scattered collections of immune cells within some alveolar spaces. Control monkeys had moderate-to-severe pathology with often diffuse alveolar capillary expansion, diffuse hypercellularity, moderate type II pneumocyte hyperplasia, and multiple areas of perivascular cellular infiltration (cuffing). Protection against the omicron variant was robust in the lungs, regardless of boost selection at the time point evaluated.

Conclusion of results of Study VRC-220-857

The data showed that boosting with mRNA-1273 or mRNA-1273.529 leads to comparable and significant increases in neutralizing antibody responses against all variants of concern, including Omicron. Boosting was important for enhancing mucosal antibody binding and neutralisation responses and cross-reactive cells were expanded following a boost with either

mRNA-1273 or mRNA-1273.529. Control of virus replication in lower airways was seen with either boost with no viral antigen in lungs of any vaccinated monkeys; the boosted monkeys had histopathological changes rated as either minimal-to-mild or mild-to-moderate.

Overall conclusion of the pharmacolgy studies

Overall, it is concluded that there are sufficient non-clinical data to support the application and no further primary pharmacology studies are required.

III.3 Pharmacokinetics

Pharmacokinetic studies

Distribution

A revised report (Study 5002121) into distribution of the vaccine components after intramuscular dosing in rats was submitted. This study was conducted with mRNA1647, a different mRNA product which encodes for antigens from cytomegalovirus. It is expected that distribution of mRNA is dependent on the lipid nanoparticle composition, which is the same for mRNA1647 and mRNA-12734: although different, these vaccines are expected to distribute similarly and findings with one can be read across to the other. The report concluded as follows.

The analyte mRNA1647 was quantifiable in the majority of tissues examined and in plasma 2 hours post-dose; peak concentrations were reached between 2-24 hours post-dose in tissues with exposures above that of plasma. The highest mRNA-1647 exposure was observed in muscle (i.e. site of injection), followed by proximal (popliteal) lymph nodes, axillary distal lymph nodes and spleen, suggesting the mRNA-1647 distribution to the circulation by lymph flow. All other tissues tested, except for spleen (higher than plasma) and eye (slightly higher than plasma), have demonstrated exposures comparable or below that measured in plasma.

Metabolism

Study NCS-BAA-2022-10

This study sought to evaluate metabolism of the lipid SM-102, in cryopreserved hepatocytes from male Sprague-Dawley rats, male cynomolgus monkeys and humans (male and female).

10 μM SM-102 was incubated with 1 million hepatocytes per ml for up to 24 hours and then chromatographic and mass spectral techniques were applied to separate, then identify SM-102 and potential metabolites. Some samples were incubated with hepatocytes that had been denatured by boiling in order to aid identification of signals from SM-102. Chromatographic peaks observed to be unique to the hepatocyte samples were subjected to mass spectrometric assessment.

A list of predicted metabolites was prepared given the structure of SM-102. By using molecular weight analyses of ions of putative metabolites, structures were confirmed and a list of metabolites created.

Table 8 and Figure 14 below provides a summary of the metabolites detected listed by retention time and species and the proposed biotransformations. Five metabolites M1, M3, M4, M6 and M7 were detected, resulting from ester hydrolysis of the straight chain and branched aliphatic chains and beta-oxidation of the ester hydrolysis, as depicted below. Metabolite M3 was not detected in rat hepatocytes but was detected in monkey and human hepatocytes. No human specific metabolites were detected.

Table 8: Summary of Metabolite Profiling of SM-102 Human, Rat and Non-Human Primate (NHP) Hepatocytes

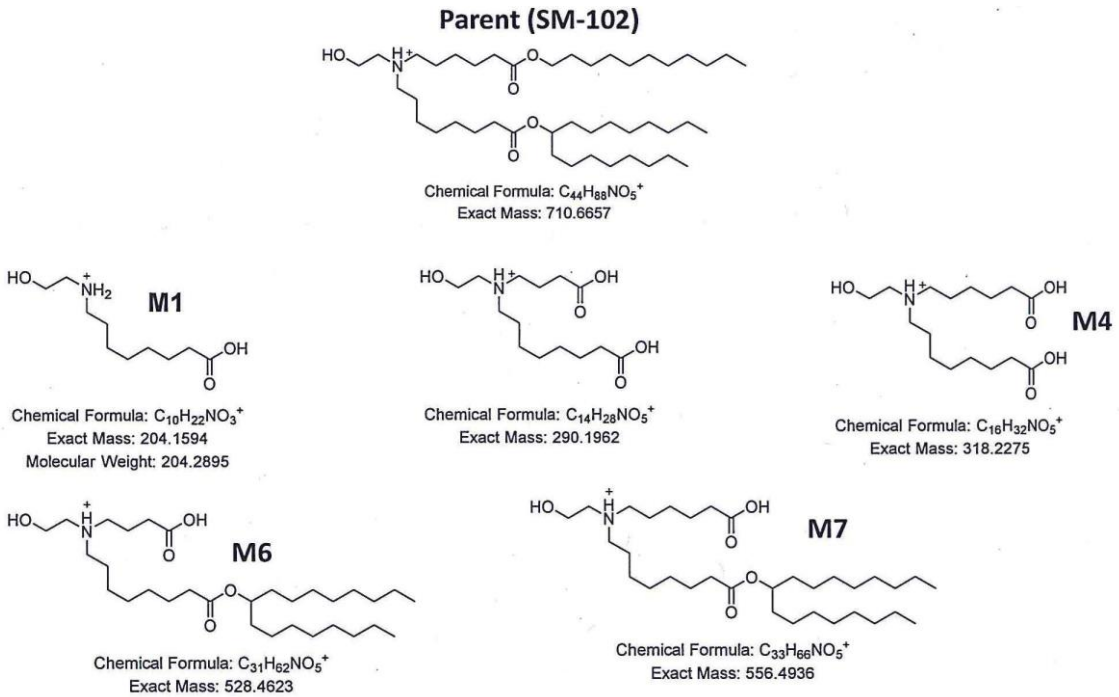
Metabolite ID	RT	Observed m/z	Theoretical m/z	Error	Elemental Composition	Proposed Biotransformation	Human	Rat	NHP
M1	3.2	204.1591	204.1592	-0.48	C10H22NO3	N Dealkylation + Hydrolysis	Y	Y	Y
M3	6.2	290.1961	290.1962	0.34	C14H28NO5	Ester Hydrolysis (2X)+ B-oxidation(2X)	Y*	N	Y
M4	6.9	318.2269	318.2275	1.8	C16H32NO5	Ester Hydrolysis (2X)	Y	Y	Y
M6	15.1	528.4614	528.4623	1.7	C31H62NO5	Ester Hydrolysis(1X) + B-oxidation (1X)	Y	Y	Y
M7	16.4	556.4934	556.4936	0.35	C33H66NO5	Ester Hydrolysis(1X)	Y	Y	Y
Parent	19.2	710.6660	710.6657	0.42	C44H88NO5	NA	Y	Y	Y

- Labels for metabolites are consistent with In vivo Rat Met ID – Y – Detected , N Below Detection limit
- M2, M5, M8-M12(*In vivo*) were not detected in *in vitro samples*

* Confirmed based on RT and HRMS – Low signal for MS/MS

- Abundances (EIC signal) of all the metabolites are at least similar or less in human hepatocytes compared to rat and NHP hepatocytes

Figure 14



Study QV-02236-DA-RE

Male rats were administered a single intravenous infusion of SM-102 (2.1 mg) and plasma, bile and urine were analysed for the presence of metabolites. Plasma, bile and urine samples were collected pre-dose and up 24 hours post-dose.

Unchanged SM-102 and 12 metabolites were identified in plasma, bile and urine; of these, 9 metabolites were detected in the plasma, 12 in the bile and 5 in the urine.

The proposed biotransformation scheme for SM-102 in rats is shown in Figure 15 below.

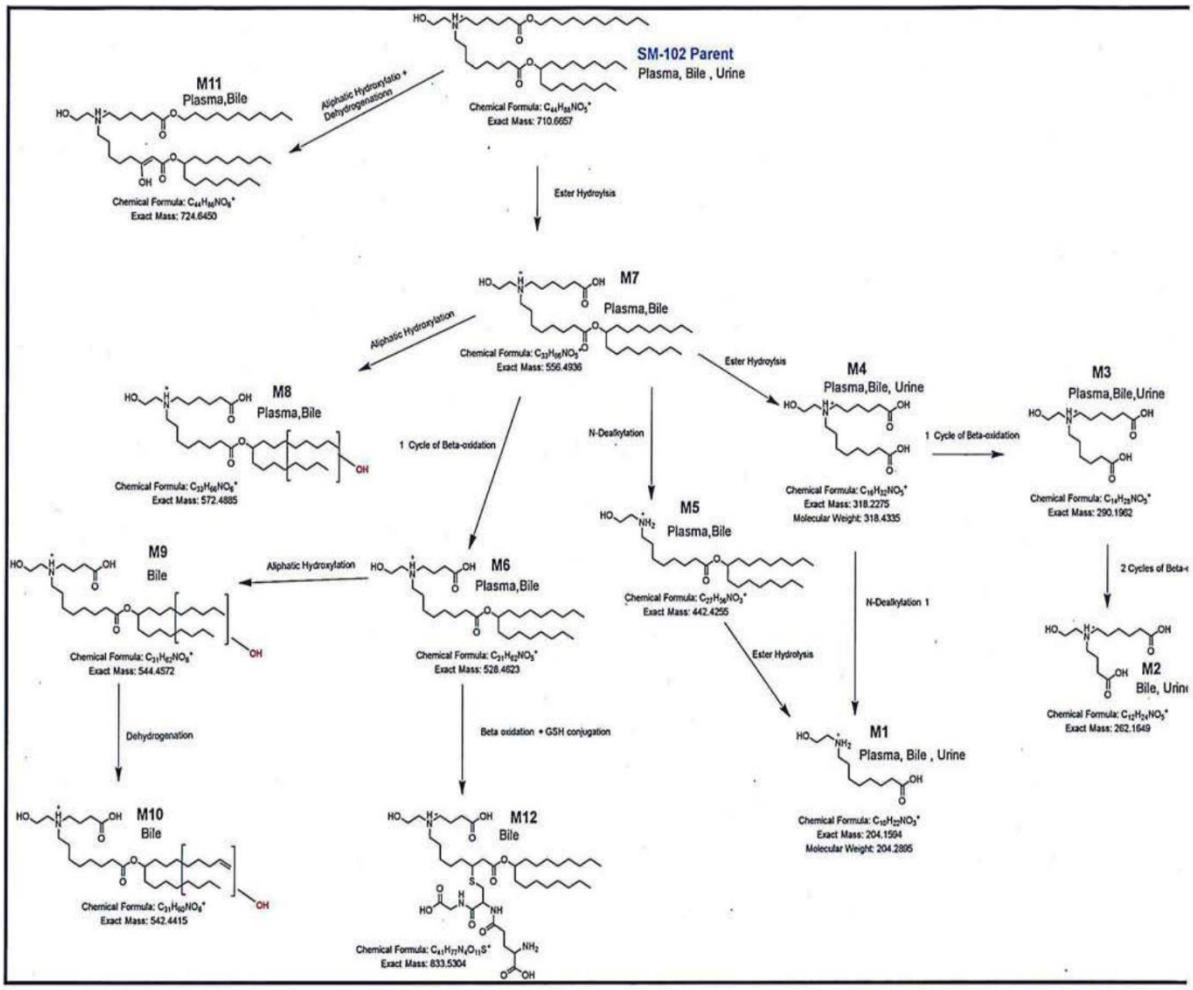


Figure 15: Proposed biotransformation scheme for SM-102 in rats

High concentrations of SM-102 (approximately 22,500 ng/ml) were found in plasma at 2 hours after dosing, which declined to approximately 42 ng/ml at 24 hours. The main circulating species was intact SM-102 (>95%). The highest concentrations in bile were seen at 2 hours after dosing, declining at 24 hours.

Metabolites and unchanged SM-102 were cleared via both the renal and hepatic routes of elimination, except that unchanged SM-102 was hardly detected in urine. SM-102 concentrations fell to <10% and <1 % of the maximum level by 6 and 24 hours post dose, respectively.

Conclusion of pharmacokinetics

The metabolic fate of SM-102 representing a component of the lipid nanoparticle, was described in two studies, one *in vitro* and one *in vivo*, in rats. The main component detected after an intravenous dose was SM-102, with the proposed metabolic route described of ester hydrolysis and elimination of oxidative metabolites by each of the biliary and urinary routes. SM-102 was cleared within 24 hours and was hardly excreted at all unchanged in urine. These data suffice to support dosing of SM-102 as a component of the vaccine.

III.4 Toxicology

Single-dose toxicity

No new single dose toxicity studies were provided and none were required for this application.

Repeat-dose toxicity

No toxicity data were provided for the bivalent vaccine mRNA 1273-214 and this is acceptable.

The original approved vaccine used data from multiple repeat-dose toxicity studies with a range of different vaccine constructs using the same lipid nanoparticle and a non-compliant GLP study with mRNA-1273. The MAH has now presented a new GLP-compliant study with mRNA-1273 (Study 2308-245). This study is summarised below and the data presented suffices to support the bivalent vaccine.

Rats were given either 0 or 40 μg mRNA-1273 as an intramuscular injection of 0.2 ml on study days 1, 29 and 57: the control group were given a buffer solution with sucrose. Post mortem evaluations were scheduled on days 58 and 71, with the latter being a recovery group.

Rats were monitored for clinical observations, body weights, food and water consumption and body temperature; ophthalmic examinations were undertaken and blood was drawn for haematological, coagulation and clinical chemistry evaluations. At post mortem, evaluations were made of organ weights and macroscopic and microscopic examinations were undertaken. Blood was taken on the day of necropsy (i.e, days 58 or 71) for use in determining antibody: serum was analysed for anti-spike S1 protein specific antibodies by ELISA - this part of the study was not intended to be in compliance with GLP.

There were no new safety concerns identified. There were two unexpected deaths in the control group; the concern that these rats may have been misdosed and received the active vaccine arises, however, as all those rats in the active vaccine group survived without any significant toxicity, this explanation for the deaths (i.e. toxicity arising from misdosing) is not likely.

III.5 Ecotoxicity/Environmental Risk Assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medical Products for Human Use (EMEA/CHMP/SWP4447100), due to their nature vaccines and lipids are unlikely to resulting a significant risk to the environment. Therefore, environmental risk studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

III.6 Discussion on the non-clinical aspects

The grant of a Conditional Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

Data from Part G and Part F of Study mRNA-1273-P205 were submitted to support this application. Study mRNA-1273-P205 is an ongoing phase 2/3 study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants.

The study is in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new clinical efficacy data have been submitted for this application and none were required.

In support of the application, the following was submitted:

IV.5 Immunogenicity

In support of the application pivotal data from Study mRNA-1273-P205 (also referred to as Study 205 in this report) were submitted. This is an ongoing open-label study to evaluate the immunogenicity, safety, and reactogenicity of mRNA candidate variant vaccines administered as booster doses. The global protocol currently includes 6 parts. Part F and Part G are the most relevant for this application.

- **Study Participants**

Key inclusion criteria

- Male or female, at least 18 years of age at the time of consent
- Female participants of childbearing potential could be enrolled if not currently breastfeeding, with a negative pregnancy test on Day 1, and adequate contraception from 28 days prior to Day 1 until 3 months post-vaccination
- Parts F and G: participants had received a primary series of mRNA-1273 (2 doses of 100 µg). This was followed by a 50 µg booster dose of mRNA-1273 at least 3 months before enrolment.

Key exclusion criteria

- Had significant exposure to someone with SARS-CoV-2 infection in the past 14 days
- Has known history of SARS-CoV-2 infection within 3 months prior to enrolment
- Acutely ill or febrile within 72 hours of screening
- Currently has symptomatic acute or unstable chronic disease requiring medical or surgical care, to include significant change in therapy or hospitalization for worsening disease, at the discretion of the investigator
- Has a current or previous diagnosis of immunocompromising condition to include human immunodeficiency virus, 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 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.

- Additional safety exclusions included history of myocarditis/pericarditis within 2 months; bleeding disorder; known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse event to the vaccine or its excipients

Comment
Although there was no upper age limit, the eligibility criteria define an adult population which is likely to be younger and fitter than the population to be initially targeted for a bivalent booster. No immunocompromised or pregnant individuals were included.

- **Treatments**

Study vaccine was administered as a single dose on Day 1. The route was intramuscular injection into the deltoid muscle. Participants in Part G received a 50 µg booster dose of Spikevax bivalent Original/Omicron (mRNA-1273.214) and participants in Part F (cohort 2) received a 50 µg booster dose of the original Spikevax monovalent vaccine (mRNA-1273).

- **Objectives and endpoints**

Table 1: Part G objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate **non-inferiority** of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) when administered as a second booster dose against the **Omicron** variant (B.1.1.529) based on geometric mean titre (GMT) ratio and seroresponse rate (SRR) difference at Day 29 or Day 91 • To demonstrate **superiority** of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) administered as a second booster dose against the **Omicron** variant (B.1.1.529) based on GMT ratio at Day 29 or Day 91 • To demonstrate **non-inferiority** of the antibody response of a second booster dose of mRNA-1273.214 compared to mRNA-1273 (50 µg) when administered as a second booster dose against the **ancestral** SARS-CoV-2 based on GMT ratio at Day 29 or Day 91	• Geometric mean titre (GMT) ratio of Omicron-specific GMT of mRNA-1273.214 over the Omicron-specific GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91 • Seroresponse rate (SRR*) difference between mRNA-1273.214 against Omicron variant and mRNA-1273 against Omicron variant at Day 29 and Day 91 • GMT ratio of ancestral SARS-CoV-2 GMT of mRNA-1273.214 over ancestral SARS-CoV-2 GMT of mRNA-1273 (Part F, Cohort 2, 50 µg mRNA-1273) at Day 29 and Day 91
• To evaluate the safety and reactogenicity of mRNA-1273.214	• Solicited local and systemic reactogenicity adverse reactions (ARs) during a 7-day follow-up period after vaccination • Unsolicited adverse events (AEs) during the 28-day follow-up period after vaccination • Serious AEs (SAEs), medically-attended AEs (MAAEs), AEs leading to withdrawal and AEs of special interest (AESIs) from Day 1 to end of study
Key secondary	
• To demonstrate non-inferiority based on the SRR against ancestral SARS-CoV-2 of a second booster dose of mRNA-1273.214 compared	• SRR difference between mRNA-1273.214 against ancestral SARS-CoV-2 and mRNA-1273 against ancestral SARS-CoV-2 at Day 29 and Day 91

Objectives	**Endpoints**
to a second booster dose of mRNA-1273 (50 μg) at Day 29 or Day 91	
Secondary	
• To evaluate the immunogenicity of mRNA-1273.214 booster compared to mRNA-1273 booster administered as a second booster dose at all timepoints post-boost	• GMT ratio of mRNA-1273.214 and mRNA-1273 against the Omicron variant at all timepoints post-boost • SRR difference between mRNA-1273.214 against the Omicron variant and mRNA-1273 against the Omicron variant at all timepoints post-boost • GMT ratio of mRNA-1273.214 and mRNA-1273 against ancestral SARS-CoV-2 and other variants at all timepoints post-boost • SRR difference between mRNA-1273.214 against ancestral SARS-CoV-2 and other variants and mRNA-1273 against ancestral SARS-CoV-2 and other variants at all timepoints post-boost
• To compare the immune response of mRNA-1273.214 as a second dose against the Omicron variant compared to the priming series of mRNA-1273	GMT ratio and SRR difference of mRNA-1273.214 as a second booster dose against the Omicron variant compared to the priming series of mRNA-1273 against the ancestral SARS-CoV-2 (historical control group)
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: o Primary case definition per the P301 (COVE) study o Secondary case definition based on the CDC criteria: the presence of one of the CDC-listed symptoms 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 anti-nucleocapsid antibody after a negative test at time of enrolment

Objectives	Endpoints
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Characterise the SARS-CoV-2 genomic sequence of viral isolates and compare with the vaccine sequence • Characterise the immune responses to vaccine breakthrough isolates
• To characterise the cellular immune response of mRNA-1273.214 as a booster against SARS-CoV-2 and other variants	• T-cell and B-cell response after the mRNA-1273.214 booster

- **Bioanalytical methods**

A summary of the qualified and the validated analytical methods used for the assessment of clinical endpoints is provided below:

Table 2: Overview of Bioassays for the Assessment of Clinical Endpoints

Assay Name	Methodology	Study Number(s)
SARS-CoV-2 Pseudotyped Virus Neutralization[b]	PsV neutralization	P205 (Part A), P201 (Part B), P205 (Part F and G), and P301 (Historical Control Primary Series)[c],
MSD (VAC123)[d]	MSD multiplex	P205 (Part F and G)

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

[a] The Omicron assay has been validated and the validation report has been submitted to Center for Biologics Evaluation and Research. Given that the SRR definition depends on the assay LLOQ, and that the Delta assay is currently fit-for-purpose pending final validation, the SRR for Delta is not discussed in this report.

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

[c] P301 Part A PsVNA against Delta only available at Day 57.

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

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

- **Randomisation**

The primary study objectives of Part G involved a non-randomised comparison with participants from Part F who received a second booster dose of 50 µg mRNA-1273 following

100 µg mRNA primary series and a booster dose of 50 µg mRNA-1273. Enrolment of Part G began upon completion of enrolment of Part F.

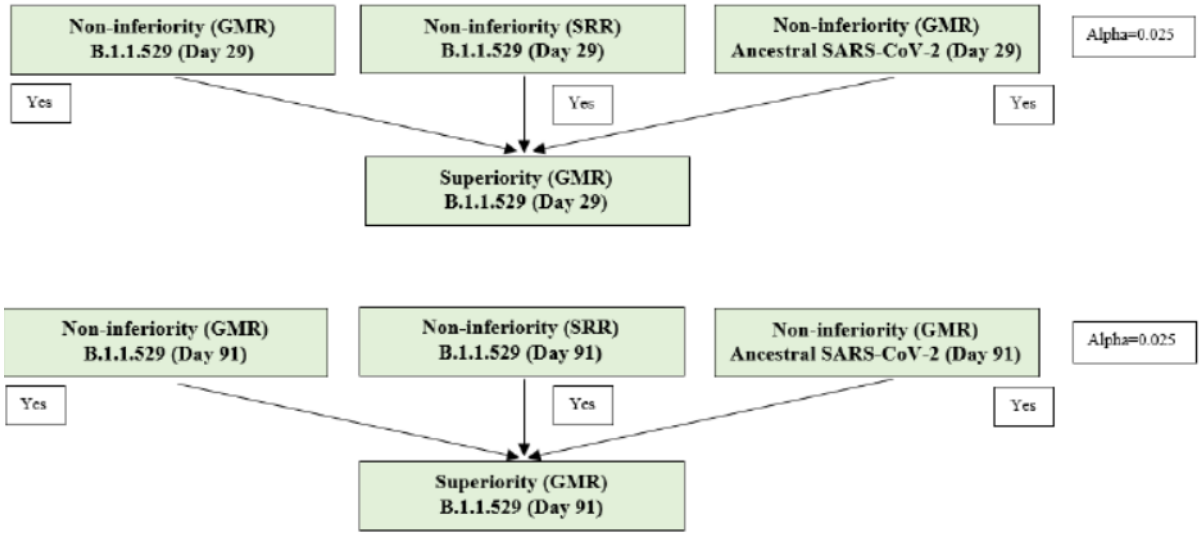
Comment
Though a randomised comparison would have been preferable, the comparison of the two cohorts is considered acceptable bearing in mind that the inclusion criteria were the same for important factors and the timing of enrolment only differed by 18 days.

- **Blinding (masking)**

The study was unblinded

- **Statistical methods**

Figure 1: Statistical Hypotheses Testing Strategy for Part G



An analysis of covariance (ANCOVA) model was performed to assess the difference in immune response between mRNA-1273.214 and mRNA-1273. The analyses of GMT were adjusted for age and baseline titres. The pre-specified non-inferiority criteria were 0.67 and 10% for GMT ratio (GMR) and SRR, respectively.

Table 3: Definitions of immunogenicity analysis sets

Set	Description
Full Analysis Set (FAS)	The FAS consists of all participants who receive investigational product (IP).
Per-Protocol Set for Immunogenicity (PPSI)	The PPSI consists of all participants in the FAS who received the planned dose of study vaccination and no major protocol deviations that impact key or critical data. The PPSI will be used as the primary analysis set for analyses of immunogenicity for immunobridging.
PPSI – SARS-CoV-2 negative (PPSI-Neg)	Participants in the PPSI who have no serologic or virologic evidence of SARS-CoV-2 infection at baseline, i.e., who are SARS-CoV-2 negative, defined by both

Set	Description
Full Analysis Set (FAS)	The FAS consists of all participants who receive investigational product (IP).
	negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid PPSI-Neg will be the primary analysis set for analyses of immunogenicity for between-booster comparisons.

Results

The results are available for a data cut-off date of 27 April 2022, which corresponds to the interim analysis at Day 29.

Participant flow

Table 4: Participant Disposition in full analysis set (all participants who receive investigational product)

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

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

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

- **Recruitment**

The study is being conducted at 23 sites in the US. Enrolment was 18 February 2022 to 8 March 2022 for Part F and 8 March 2022 to 23 March 2022 for Part G.

Conduct of study

Protocol amendments

Amendment 6 (17 March 2022) was made before enrolment of Part G was complete. The amendment modified the statistical hypothesis testing by adding non-inferiority testing against the Omicron variant (B.1.1.529) and the ancestral strain, and superiority testing against the Omicron variant, at Day 29 and 91.

Table 5: Summary of Reasons for Exclusion from Per-Protocol Immunogenicity Set — 2nd Booster Dose: mRNA-1273.214, mRNA-1273

	Part G mRNA-1273.214 50 ug (N=437)	Part F Cohort 2 mRNA-1273 50 ug (N=377)
Full Analysis Set	437	377
Per-Protocol Immunogenicity Set, n (%)	428 (97.9)	367 (97.3)
Excluded from Per-Protocol Immunogenicity Set, n (%)	9 (2.1)	10 (2.7)
Reasons for Exclusion, n (%) [1]		
Received incorrect vaccination	0	0
Had no Immunogenicity Data at Baseline	1 (0.2)	0
Had no Immunogenicity Data at Day 29	8 (1.8)	5 (1.3)
Had Immunogenicity Data at Day 29 Out of Window	0	2 (0.5)
Had Major Protocol Deviations	0	2 (0.5)
History of HIV infection	0	1 (0.3)

Percentages are based on the number of subjects in the Full Analysis Set.
[1] A subject who has multiple reasons for exclusion is listed under the reason that appears earliest.

- **Baseline data**

Table 6: Subject Demographics and Baseline Characteristics - Per-Protocol Immunogenicity SARS-CoV-2 Negative Set (PPSI-Neg)

	Part G mRNA-1273.214 50 ug (N = 334)	Part F mRNA-1273 50 ug (N = 260)
Median age (min, max) (years)	61.0 (20, 88)	63.0 (21, 96)
Proportion ⩾ 65 years (%)	41.6	46.2
Gender: M / F (%)	43.4 / 56.6	48.5 / 51.5
Race (%)		
White	87.1	90.0
Black or African American	7.2	4.2
Asian	3.3	4.2
Multiracial	1.8	0
Other/not reported/unknown	0.6	1.5
Mean BMI (kg/m2)	29.9	30.6
Pre-booster PCR positive , n (%)	0	0
Pre-booster Elecsys Anti-SARS-CoV-2 positive (%)	0	0
Time between dose 2 of primary series and 1st booster dose (days)		
Mean (SD)	266.4 (64.32)	255.4 (51.75)
Median (min, max)	247.5 (143, 457)	242.0 (172, 435)
Time between 1st booster dose and 2nd booster dose (days)		
Mean (SD)	136.8 (35.11)	133.3 (22.29)
Median (min, max)	136.0 (88, 408)	133.0 (90, 310)

- **Numbers analysed**

Table 7: Number of Subjects in Each Analysis Set

	Part G mRNA-1273.214 50 ug n (%)	Part F Cohort 2 mRNA-1273 50 ug n (%)
All Enrolled	440	379
Full Analysis Set [1]	437 (99.3)	377 (99.5)
Modified Intent-to-Treat (mITT) Set [1]	340 (77.3)	267 (70.4)
Per-Protocol Efficacy Set [1]	339 (77.0)	266 (70.2)
Per-Protocol Immunogenicity Set [1]	428 (97.3)	367 (96.8)
Per-Protocol Immunogenicity Sensitivity Set [1]	428 (97.3)	369 (97.4)
Per-Protocol Immunogenicity SARS-CoV-2 Negative Set [1]	334 (75.9)	260 (68.6)
Safety Set	437	377
Solicited Safety Set [2]	437 (100)	351 (93.1)

[1] Numbers are based on planned treatment group and percentages are based on the number of subjects enrolled.
[2] Numbers are based on planned treatment group and percentages are based on the number of safety subjects.

- **Outcomes and estimation**

Neutralizing antibody results

Table 8: Ancestral SARS-CoV-2 (D614G) and Omicron (BA.1) Neutralizing Antibody Titres (ID50) - Per-Protocol Immunogenicity – SARS-CoV-2 Negative Set

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

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold-rise; GMR = geometric mean ratio; GMT = geometric mean 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.

[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 is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibody titer information, seroresponse 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] 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the 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.

Source: Tables 14.2.1.1.14.8, Table 14.2.2.1.1.8, and Table 14.2.2.1.2.8.

A sensitivity analysis which excluded participants who had SARS-CoV-2 infection after the booster dose and up to Day 29 was also performed. This excluded 10 participants from Part G and 3 participants from Part F. The GMT and ratio of geometric mean titres (GMR) results were consistent with the primary analysis set. The ID50 neutralizing body (NAb) GMR against omicron was 1.742 (97.5% CI: 1.488, 2.039) and the ID50 NAb GMR against ancestral was 1.199 (97.5% CI: 1.063, 1.353).

Table 9: Ancestral SARS-CoV-2 (D614G) and Omicron (BA.1) Neutralizing Antibody Titres (ID50) - Per-Protocol Immunogenicity – SARS-CoV-2 Positive Set

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

Abbreviations: CI = confidence interval; GLSM = geometric least squares mean; GMFR = geometric mean fold-rise; GMR = geometric mean ratio; GMT = geometric mean 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.

[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 is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ. For participants without pre-Dose 1 antibody titer information, seroresponse 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] 97.5% CI was calculated by stratified Miettinen-Nurminen method adjusted by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the 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.

Source: Table 14.2.1.1.12.8, Table 14.2.2.1.9.8, and 14.2.2.1.10.8.

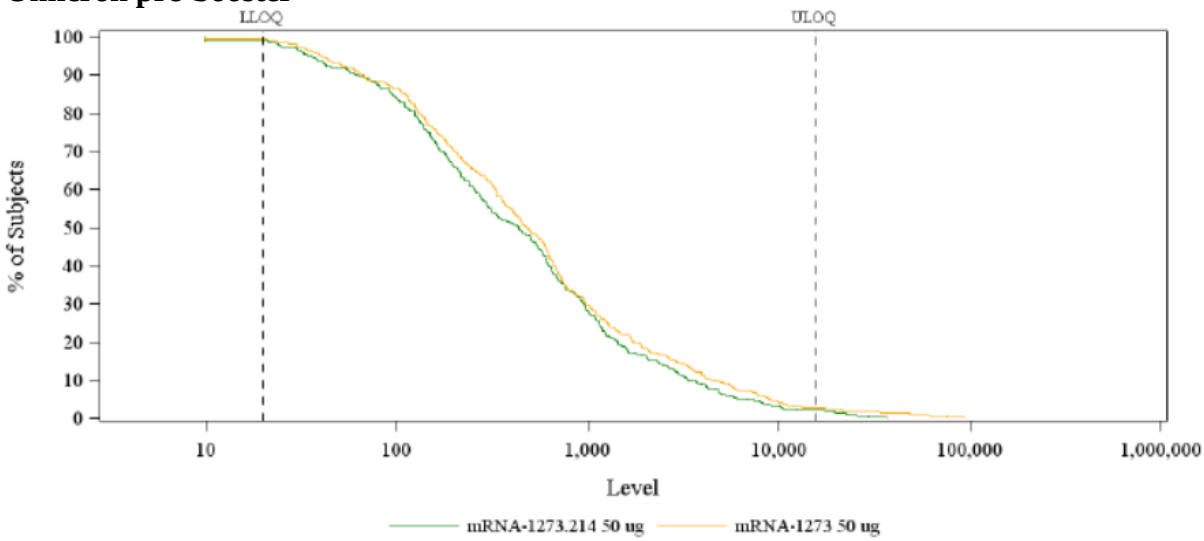
Table 10: Ancestral SARS-CoV-2 (D614G) and Omicron (BA.1) Neutralizing Antibody Titres (ID50) - Summary of 4-fold increases from pre-2nd booster (Day 1) baseline to Day 29 by baseline SARS-CoV-2 status

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

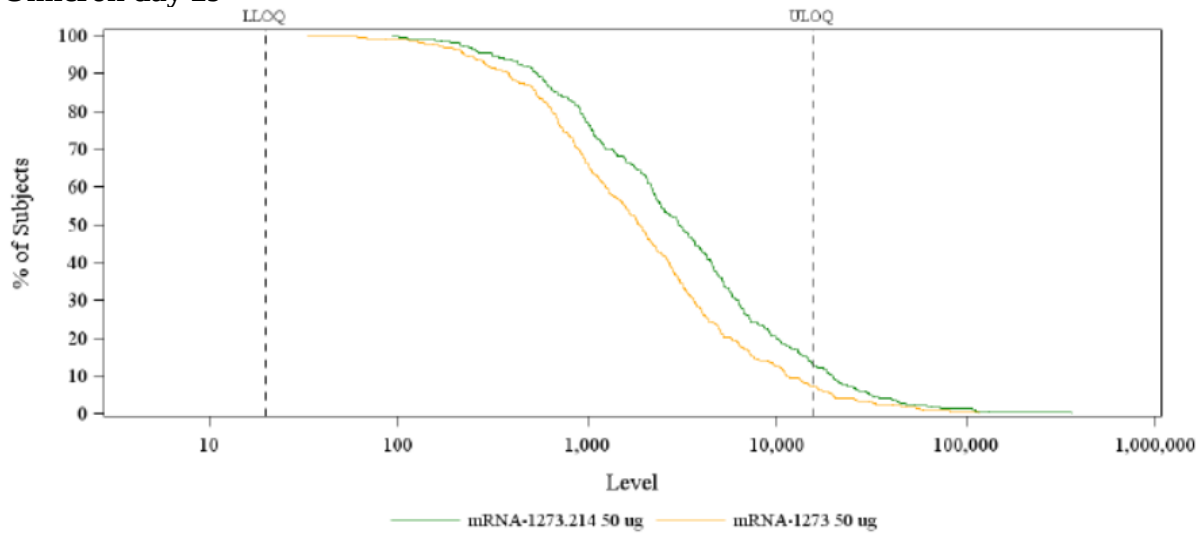
* ≥ 4-fold increase from baseline at participant level is defined as a ≥ 4 x LLOQ for participants with baseline undetectable antibody level, or a 4-times or higher antibody level ratio in participants with pre-existing antibody levels
Source: Table 14.2.1.1.14.8

Figure 2: Reverse Cumulative Distribution Function of Pseudovirus Neutralizing Antibody PsVNA ID50 - per-Protocol immunogenicity set (participants with and without prior SARS-CoV-2 infection)

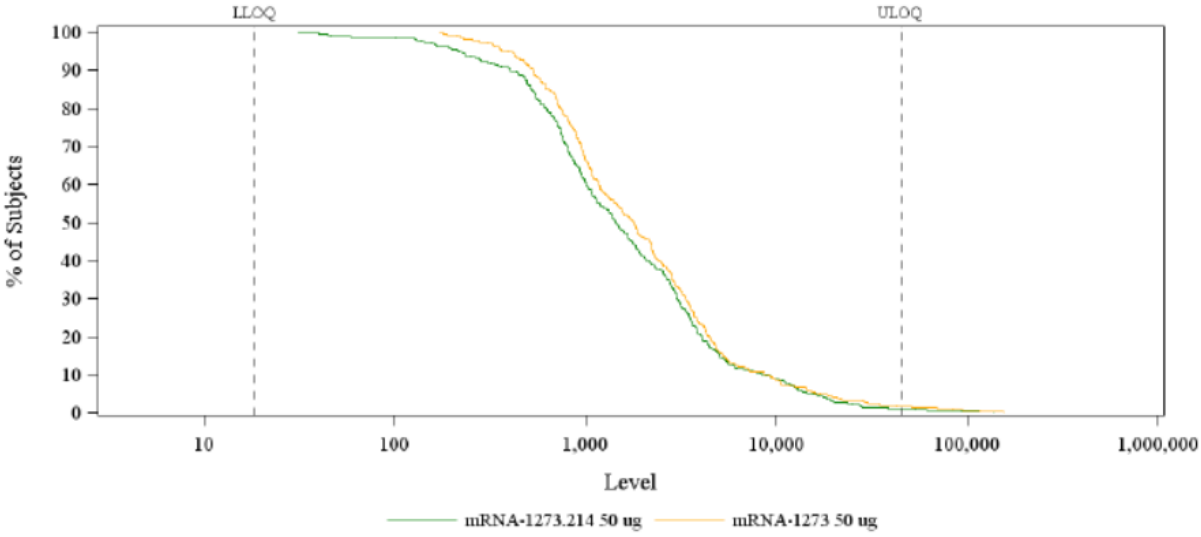
Omicron pre-booster



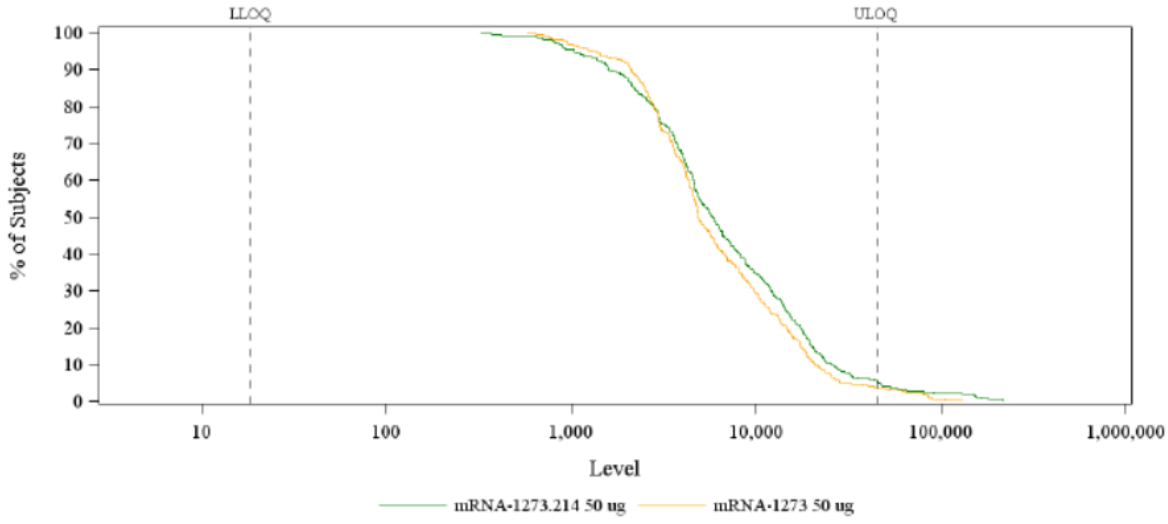
Omicron day 29



Ancestral pre-booster



Ancestral day 29



Effect of age

In the over 65 years subgroup of the PPSI-Neg set, GMT ratios against omicron BA.1 and ancestral virus were in line with the primary analysis set (see table below). A similar pattern was observed in the PPSI-Pos set over 65 years subgroup.

Table 11: Ancestral SARS-CoV-2 (D614G) and Omicron Neutralizing Antibody Titres (ID50) - Per-Protocol Immunogenicity – SARS-CoV-2 Negative Set - ≥ 65 years

PsVNA ID50	Omicron variant		Ancestral SARS-CoV-2	
	Part G mRNA-1273.214 N=139	Part F mRNA-1273 N=120	Part G mRNA-1273.214 N=139	Part F mRNA-1273 N=120
Pre-booster				
n	139	120	139	120
GMT	319.220	373.387	1521.888	1819.661
95% CI	(252.175, 404.089)	(293.768, 474.585)	(1235.411, 1874.794)	(1514.116, 2186.863)
Day 29				
n	139	120	139	120
GM level	2590.107	1811.192	7271.891	7377.897
95% CI	(2078.986, 3226.888)	(1450.053, 2262.274)	(6008.651, 8800.709)	(6203.211, 8775.030)
GLSM	2721.119	1710.573	7723.676	6880.361
95% CI	(2352.114, 3148.015)	(1462.237, 2001.085)	(6922.044, 8618.144)	(6114.782, 7741.792)
GMR	**1.591**		**1.123**	
95% CI	(1.284, 1.971)		(0.955, 1.319)	
⩾ 4-fold increase from baseline (pre-booster) n (%)	102 (73.4)	67 (55.8)	76 (54.7)	56 (46.7)
95% CI	(65.2, 80.5)	(46.5, 64.9)	(46.0, 63.1)	(37.5, 56.0)

Neutralizing antibody against omicron subvariants BA.4/5

The applicant has conducted exploratory analyses of neutralization against BA.4 and BA.5 in the three immunogenicity analysis populations (according to baseline SARS-CoV-2 status):

Table 12: Summary of Neutralizing Antibody Geometric Mean Titres for Omicron BA.4, BA.5 Variant – Comparison Between mRNA-1273.214 50 µg and mRNA-1273 50 g 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.

Additional analyses by age were conducted and are presented in the table below.

Table 13: Summary of Pseudovirus Neutralizing Antibody BA 4/5 ID50 Titres Based on Pre-Booster Baseline - Per-Protocol Immunogenicity, SARS-CoV-2 Negative Set (Age Group: >=65 Years)

Parameter Timepoint Statistic	mRNA-1273.214 50 ug (N=139)	mRNA-1273 50 ug (N=120)
[redacted]		
Baseline (Pre-Booster)		
n[1]	139	120
GM Level	132.058	161.306
95% CI [2]	(101.752, 171.391)	(129.119, 201.515)
Median	146.261	142.970
Min, Max	(5.00, 4444.98)	(5.00, 4550.99)
Day 29		
n[1]	139	120
GM Level	816.647	588.025
95% CI [2]	(655.380, 1017.595)	(482.690, 716.345)
Median	896.660	621.685
Min, Max	(12.32, 8572.44)	(30.76, 8700.95)
N1	139	120
GMFR	6.184	3.645
95% CI [2]	(5.395, 7.089)	(3.149, 4.220)

CI = confidence interval, GM = geometric mean, GMFR = geometric mean fold rise (post-baseline / baseline titers).
N1 = Number of subjects with non-missing data at baseline and the corresponding post-baseline timepoint.
Antibody values reported as below the lower limit of detection (LOD) are replaced by 0.5 x LOD.
[1] Number of subjects with non-missing data at the timepoint (baseline or post-baseline).
[2] 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.

Binding antibody results

Day 29 IgG binding antibody response data for multiple variants are available from Part G and Part F (cohort 2). In the ≥65 years group, the pattern of results for binding antibody against variants is consistent with the overall results.

Table 14: Summary of Binding Antibody Specific to SARS-CoV-2 Spike Protein by MSD Assay Based on Pre-Booster Baseline - Per-Protocol Immunogenicity SARS-CoV-2 Negative Set

	Omicron Variant		Ancestral SARS-CoV-2		Alpha Variant	
	P205 Part G	P205 Part F	P205 Part G	P205 Part F	P205 Part G	P205 Part F
Antibody: MSD (VAC123) bAb	mRNA-1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)	mRNA1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)	mRNA-1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)
Pre-booster, n	331	256	332	259	332	259
Observed GM level (95% CI)[a]	50655.927 (45583.372, 56292.960)	55961.844 (50768.815, 61686.057)	253731.553 (230052.946, 279847.322)	280186.866 (255545.533, 307204.275)	183544.862 (166028.649, 202909.056)	207233.058 (188611.265, 227693.401)
Day 29, n	292	239	313	251	308	250
GLSM (95% CI)	209858.615 (198169.736, 222236.952)	168686.787 (158454.185, 179580.187)	884978.378 (839674.114, 932727.016)	761984.392 (718960.954, 807582.401)	668710.370 (634902.081, 704318.937)	562715.291 (531543.650, 595714.950)
GMR (95% CI)	1.244 (1.143, 1.354)		1.161 (1.074, 1.256)		1.188 (1.100, 1.283)	

	Beta Variant		Delta Variant		Gamma Variant	
	P205 Part G	P205 Part F	P205 Part G	P205 Part F	P205 Part G	P205 Part F
Antibody: MSD (VAC123) bAb	mRNA-1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)	mRNA-1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)	mRNA-1273.214 50 µg (N=334)	mRNA-1273 50 µg (N=260)
Pre-booster, n	332	259	332	259	332	259
Observed GM level (95% CI)[a]	113986.467 (103400.922, 125655.694)	125811.778 (114408.266, 138351.921)	160021.236 (145267.097, 176273.887)	176050.555 (160244.776, 193415.341)	121087.417 (109783.228, 133555.578)	136347.211 (124198.876, 149683.817)
Day 29, n	306	252	310	252	307	252
GLSM [Estimated GM level] (95% CI)	408454.565 (387526.328, 430513.025)	354483.033 (334714.357, 375419.275)	546566.964 (520177.789, 574294.891)	494689.007 (468536.105, 522301.721)	443654.796 (420473.235, 468114.405)	374273.107 (352956.042, 396877.634)
GMR (95% CI)	1.152 (1.066, 1.245)		1.105 (1.027, 1.189)		1.185 (1.095, 1.283)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval, GLSM = Geometric least squares mean, GMR = geometric mean ratio, GMT = geometric mean titer; LLOQ = lower limit of quantification; LS = least square; MSD = Meso Scale Discovery; n = number of participants with non-missing data at the corresponding timepoint; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
The log-transformed antibody levels are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (<65, ≥65 years) and pre-booster antibody titer level (in log 10 scale). The treatment variable corresponds to each individual study arm dose. The resulted LS means, difference of LS means, and confidence intervals are back transformed to the original scale for presentation.
[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.
Source: Table 14.2.1.2.13.8 and Table 14.2.3.1.1.8.

Overall conclusions on clinical immunogenicity

The pivotal immunogenicity data to support this application are from Part G and Part F (cohort 2) of study mRNA-1273-P205. Parts G and F enrolled adults (≥18 years of age) who had previously received two 100 µg doses of mRNA-1273 as primary series, and one 50 µg dose of mRNA-1273 as a first booster at least 3 months prior to enrolment. The participants in Part G and Part F received a 50 µg second booster dose of mRNA-1273.214 and mRNA-1273, respectively, on Day 1.

The primary efficacy analysis set was the per-protocol immunogenicity set with negative baseline SARS-CoV-2 status (PPSI-Neg set); this comprised 334 and 260 participants from Parts G and F, respectively. At baseline in the PPSI-Neg set, there were no major imbalances. More than 40% of participants were over 65 years of age.

The study met its primary endpoints in the primary analysis population (PPSI-Neg set) at Day 29 (interim analysis, data cut-off date of 27 April 2022). For neutralization against Omicron BA.1 strain, mRNA-1273.214 was superior to mRNA-1273 with a GMR of 1.75 (97.5% CI: 1.49, 2.04). For neutralization against ancestral SARS-CoV-2, non-inferiority was demonstrated with a GMR of 1.22 (97.5% CI: 1.08, 1.37). The results in the baseline SARS-

CoV-2 positive subgroup and in the ≥ 65 years subgroup were consistent with the primary analysis. These results suggest that mRNA-1273.214 is associated with a superior neutralizing antibody response against the omicron BA.1 strain and a similar neutralizing antibody response against the ancestral virus compared to mRNA-1273, irrespective of age or the presence of antibodies to natural infection.

The applicant conducted analyses of neutralization against omicron BA.4 and BA.5 strains. Though the analyses were exploratory and therefore there was no multiplicity adjustment, the results suggest that a second booster with mRNA-1273.214 should provide a superior neutralizing antibody response against BA.4/5 compared to a second booster with mRNA-1273. The results in the ≥ 65 years subgroup are consistent with the overall results.

Day 29 IgG binding antibody data were provided for Parts G and F against Omicron, ancestral, Alpha, Beta, Delta and Gamma variants. Though the analyses are exploratory and therefore there was no multiplicity adjustment, the binding antibody data suggest that mRNA-1273.214 could provide a superior antibody response compared to mRNA-1273 against the variants that dominated previously.

In conclusion, the immunogenicity study design and conduct were acceptable and the study met its primary endpoints at Day 29. A second booster dose of mRNA-1273.214 is associated with a superior neutralizing antibody response against the Omicron BA.1 strain and a similar neutralizing antibody response against the ancestral virus compared to a second booster dose of mRNA-1273. Results of exploratory analyses suggest that a second booster dose of mRNA-1273.214 should provide a superior neutralizing antibody response against BA.4/BA.5 compared to a second booster dose of mRNA-1273.

IV.6 Clinical safety

The clinical safety data to support this application are from study mRNA-1273-205 (for a description of the study design see above section IV.5, Clinical Aspects, Immunogenicity). The reactogenicity and safety data from Part G (mRNA-1273.214 50 µg second booster) and Part F cohort 2 (mRNA-1273 50 µg second booster) were compared. Data from an interim analysis, with a data cut-off date of 27 April 2022 (median follow-up of six weeks) has been submitted.

Patient exposure

Table 15: Summary of Study Duration —- Safety Set

	Part G mRNA-1273.214 50 ug (N=437) n(%)	Part F Cohort 2 mRNA-1273 50 ug (N=377) n(%)
Number of Subjects, n (%)		
Received Injection	437 (100)	377 (100)
>= 28 Days Since Injection	436 (99.8)	377 (100)
>= 56 Days Since Injection	0	285 (75.6)
>= 2 Months Since Injection	0	114 (30.2)
>= 3 Months Since Injection	0	0
Follow up Time from Injection (Days)		
Mean (SD)	43.1 (4.13)	57.9 (4.08)
Median	43.0	57.0
Q1, Q3	41.0, 45.0	56.0, 62.0
Min, Max	22, 51	51, 66

Solicited adverse reactions

Table 16: Summary of Participants with Solicited Adverse Reactions within 7 Days After the Injection by Grade (Solicited Safety Set)

	P205 Part G	P205 Part F
Solicited Adverse Reaction Category Grade	mRNA-1273.214 50 µg (N=437) n (%)	mRNA-1273 50 µg (N=351) n (%)
Solicited adverse reactions - N1	437	351
Any solicited adverse reactions	380 (87.0)	301 (85.8)
95% CI	83.4, 90.0	81.7, 89.2
Grade 1	220 (50.3)	184 (52.4)
Grade 2	125 (28.6)	89 (25.4)
Grade 3	35 (8.0)	28 (8.0)
Grade 4	0	0
Solicited local adverse reactions - N1	437	351
Any solicited local adverse reactions	347 (79.4)	279 (79.5)
95% CI	75.3, 83.1	74.9, 83.6
Grade 1	291 (66.6)	239 (68.1)
Grade 2	41 (9.4)	28 (8.0)
Grade 3	15 (3.4)	12 (3.4)
Grade 4	0	0
Pain - N1	437	351
Any	338 (77.3)	269 (76.6)
Grade 1	303 (69.3)	241 (68.7)
Grade 2	31 (7.1)	24 (6.8)
Grade 3	4 (0.9)	4 (1.1)
Grade 4	0	0
Erythema (redness)[a] - N1	437	351
Any	30 (6.9)	13 (3.7)
Grade 1	15 (3.4)	5 (1.4)
Grade 2	6 (1.4)	6 (1.7)
Grade 3	9 (2.1)	2 (0.6)
Grade 4	0	0
Swelling (hardness)- N1	437	351
Any	30 (6.9)	23 (6.6)
Grade 1	17 (3.9)	13 (3.7)
Grade 2	8 (1.8)	5 (1.4)
Grade 3	5 (1.1)	5 (1.4)
Grade 4	0	0
Axillary swelling or tenderness - N1	437	351
Any	76 (17.4)	54 (15.4)
Grade 1	71 (16.2)	46 (13.1)
Grade 2	4 (0.9)	4 (1.1)
Grade 3	1 (0.2)	4 (1.1)
Grade 4	0	0
Solicited systemic adverse reactions - N1	437	351
Any solicited systemic adverse reactions	307 (70.3)	232 (66.1)
95% CI	65.7, 74.5	60.9, 71.0
Grade 1	167 (38.2)	124 (35.3)
Grade 2	116 (26.5)	92 (26.2)
Grade 3	24 (5.5)	16 (4.6)
Grade 4	0	0
Fever[b] - N1	436	351
Any	19 (4.4)	12 (3.4)
Grade 1	14 (3.2)	9 (2.6)
Grade 2	4 (0.9)	3 (0.9)
Grade 3	1 (0.2)	0
Grade 4	0	0

Headache - N1	437	350
Any	192 (43.9)	144 (41.1)
Grade 1	150 (34.3)	112 (32.0)
Grade 2	37 (8.5)	30 (8.6)
Grade 3	5 (1.1)	2 (0.6)
Grade 4	0	0
Fatigue - N1	437	350
Any	240 (54.9)	180 (51.4)
Grade 1	125 (28.6)	95 (27.1)
Grade 2	100 (22.9)	74 (21.1)
Grade 3	15 (3.4)	11 (3.1)
Grade 4	0	0
Myalgia - N1	437	350
Any	173 (39.6)	135 (38.6)
Grade 1	101 (23.1)	68 (19.4)
Grade 2	62 (14.2)	54 (15.4)
Grade 3	10 (2.3)	13 (3.7)
Arthralgia - N1	437	350
Any	136 (31.1)	111 (31.7)
Grade 1	93 (21.3)	70 (20.0)
Grade 2	39 (8.9)	38 (10.9)
Grade 3	4 (0.9)	3 (0.9)
Grade 4	0	0
Nausea/vomiting - N1	437	350
Any	45 (10.3)	35 (10.0)
Grade 1	39 (8.9)	27 (7.7)
Grade 2	5 (1.1)	8 (2.3)
Grade 3	1 (0.2)	0
Grade 4	0	0
Chills - N1	437	350
Any	104 (23.8)	74 (21.1)
Grade 1	65 (14.9)	46 (13.1)
Grade 2	38 (8.7)	27 (7.7)
Grade 3	1 (0.2)	1 (0.3)
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.

Source: Module 5.3.5.1 Table 14.3.1.1.1.8.

The median duration of solicited adverse events in the mRNA-1273.214 (Part G) and mRNA-1273 (Part F) groups was 3.0 (range 1 to 21) days and 3.0 (range 1 to 22) days, respectively.

The frequency and severity of the solicited local and systemic reactogenicity events were similar for the mRNA-1273.214 and mRNA-1273 treatment groups. At least one grade 3 solicited adverse events was reported by 8% in each group. There were no grade 4 solicited adverse events.

The frequency and severity of solicited adverse events was generally reduced in participants ≥65 years compared to 18 to 64 years.

The pattern of solicited adverse events was very similar when analysed by subgroups according to pre-booster SARS-CoV-2 status.

Reactogenicity outcomes were comparable to those for the solicited safety set of Study P201 Part B which included 330 participants who received a 50 µg first booster of mRNA-1273 after mRNA-1273 primary series (refer to CHMP public assessment report EMEA/H/C/005791/II/0034).

Comment:
At the 50 µg dose, the reactogenicity profile of the bivalent vaccine mRNA-1273.214 when used as a second booster should be similar to the reactogenicity profile of mRNA-1273 when used as a first or second booster. No changes to section 4.8 of the SmPC are required in relation to local or systemic reactogenicity.

Unsolicited adverse events

Table 17: Summary of Unsolicited TEAEs up to the data cut-off date (Safety Set)

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

A treatment-emergent adverse event (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 subjects in the Safety Set.
[1] Subjects without any SAE and with any non-serious TEAE.
[2] Subjects with at least one non-serious TEAE regardless of reporting any SAE or not.

Table 18: Subject Incidence of Unsolicited TEAEs (reported by more than one participant in Part G) by System Organ Class and Preferred Term up to 28 Days After the Injection —Safety Set

System Organ Class Preferred Term	Part G mRNA-1273.214 50 µg (N=437) n (%)	Part F (cohort 2) mRNA-1273 50 µg (N=377) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	81 (18.5)	78 (20.7)
Number of Unsolicited Adverse Events	114	105
Infections and infestations	29 (6.6)	33 (8.8)
COVID-19	5 (1.1)	1 (0.3)
Upper respiratory tract infection	5 (1.1)	9 (2.4)
Coronavirus infection	3 (0.7)	8 (2.1)

System Organ Class Preferred Term	Part G mRNA-1273.214 50 µg (N=437) n (%)		Part F (cohort 2) mRNA-1273 50 µg (N=377) n (%)	
Asymptomatic COVID-19	2	(0.5)	2	(0.5)
Respiratory tract infection viral	2	(0.5)	2	(0.5)
Nervous system disorders	8	(1.8)	5	(1.3)
Headache	7	(1.6)	4	(1.1)
Vascular disorders	2	(0.5)	3	(0.8)
Hypertension	2	(0.5)	3	(0.8)
Respiratory, thoracic and mediastinal disorders	5	(1.1)	2	(0.5)
Cough	3	(0.7)	1	(0.3)
Nasal congestion	2	(0.5)	0	
Oropharyngeal pain	2	(0.5)	0	
Gastrointestinal disorders	4	(0.9)	2	(0.5)
Diarrhoea	3	(0.7)	0	
Skin and subcutaneous tissue disorders	4	(0.9)	7	(1.9)
Musculoskeletal and connective tissue disorders	14	(3.2)	12	(3.2)
Arthralgia	7	(1.6)	7	(1.9)
Myalgia	5	(1.1)	6	(1.6)
General disorders and administration site conditions	21	(4.8)	17	(4.5)
Fatigue	11	(2.5)	12	(3.2)
Injection site pain	4	(0.9)	1	(0.3)
Chills	2	(0.5)	0	
Investigations	3	(0.7)	1	(0.3)
Injury, poisoning and procedural complications	9	(2.1)	4	(1.1)
Procedural pain	3	(0.7)	0	
Wrist fracture	2	(0.5)	0	

A treatment-emergent adverse event (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 subjects in the Safety Set. MedDRA version 23.0.

Medically Attended Adverse Events (MAAEs)

In the mRNA-1273.214 50 µg group (Part G), 58/437 participants (13.3%) had 74 MAAEs up to the data cut-off date. COVID-19 (8/437 [1.8%]) was the most commonly reported MAAE, followed by upper respiratory tract infection (6/437 [1.4%]) and coronavirus infection (non-COVID) (4/437 [0.9%]). Two non-serious MAAEs in two participants were assessed as related to vaccination by the Investigator: moderate fatigue (Day 2); mild dermatitis (Day 7).

In the mRNA-1273 50 µg group (Part F), 85/377 participants (22.5%) had 104 MAAEs up to the data cut-off date. Upper respiratory tract infection (15/377 [4.0%]) was the most commonly reported MAAE, followed by coronavirus infection (9/377 [2.4%]). Three

non-serious MAAEs in 3 participants were assessed as related to vaccination by the Investigator: mild hypertension (Day 13); mild urticaria (Day 18); mild back pain (Day 33).

Comment

Comparison of unsolicited AEs (including medically attended AEs) reported by the mRNA-1273 and mRNA-1273.214 groups does not raise any new safety concerns. A significant proportion appear to be due to reactogenicity. Section 4.8 of the proposed SmPC is in line with that of mRNA-1273 (Spikevax). This is acceptable and no amendments are warranted.

Adverse events of special interest (AESI)

The applicant has conducted Standardised MedDRA Queries (SMQs) of selected unsolicited AEs:

Table 19: Subject Incidence of Select Unsolicited Adverse Event After the Injection by SMQ (Narrow and Broad Scope) — Second Booster Dose: mRNA-1273.214, mRNA-1273 - Safety Set

	Part G	Part F Cohort 2
	mRNA-1273.214	mRNA-1273
SMQ	50 ug	50 ug
Subordinate SMQ	(N=437)	(N=377)
Preferred Term	n (%)	n (%)
Cardiac Arrhythmia	1 (0.2)	1 (0.3)
Arrhythmia Related Investigations, Signs and Symptoms	1 (0.2)	0
Tachycardia	1 (0.2)	0
Cardiac Arrythmia Terms (Including Bradycardia and Tachycardia)	0	1 (0.3)
Heart rate irregular	0	1 (0.3)
Congenital and Neonatal Arrhythmias	0	0
Cardiac Failure	0	2 (0.5)
Cardiac failure	0	1 (0.3)
Oedema peripheral	0	1 (0.3)
Cardiomyopathy	0	1 (0.3)
Cardiac failure	0	1 (0.3)
Hypersensitivity	4 (0.9)	11 (2.9)
Asthma	0	1 (0.3)
Conjunctivitis allergic	0	1 (0.3)
Dermatitis	1 (0.2)	0
Dermatitis contact	1 (0.2)	2 (0.5)
Eczema	0	1 (0.3)
Rash macular	1 (0.2)	0
Rhinitis allergic	0	1 (0.3)
Seasonal allergy	0	3 (0.8)
Urticaria	1 (0.2)	2 (0.5)
Angioedema	1 (0.2)	3 (0.8)
Oedema peripheral	0	1 (0.3)
Urticaria	1 (0.2)	2 (0.5)
Arthritis	9 (2.1)	9 (2.4)
Arthralgia	7 (1.6)	7 (1.9)
Arthritis	0	1 (0.3)
Joint swelling	1 (0.2)	0
Osteoarthritis	1 (0.2)	0
Rheumatoid arthritis	1 (0.2)	0
Spinal osteoarthritis	0	1 (0.3)
Hearing and Vestibular Disorders	0	1 (0.3)
Dizziness	0	1 (0.3)
Haematopoietic Cytopenias	0	1 (0.3)
Anaemia	0	1 (0.3)
Peripheral Neuropathy	0	2 (0.5)
Hypoaesthesia	0	1 (0.3)
Muscular weakness	0	1 (0.3)

In the mRNA-1273.214 arm, an event of moderate tachycardia on Day 7 followed an event of moderate symptomatic COVID-19 on Day 5. The four hypersensitivity events were of mild severity (the event of urticaria was also reported under angioedema); hypersensitivity is listed in section 4.8 of the proposed SmPC.

There were no reports in either group for the following SMQs: Ischaemic heart disease; Embolic and Thrombotic Events; Central Nervous System Vascular Disorders; Convulsions; Demyelinating Disease of Central Nervous System; Thrombophlebitis and Vasculitis.

In order to identify additional potential events of myocarditis/pericarditis, all cases were reviewed with adverse events identified using the narrow and the broad cardiomyopathy standard SMQs, as well as a Custom MedDRA Query (CMQ) (based on MedDRA v.23.0 terms included in the CDC (US Centers for Disease Control and Prevention) working case definitions for acute myocarditis and acute pericarditis). The CMQ analysis did not identify any myocarditis or pericarditis events.

Comment:
The AESI assessment does not identify any new safety concerns.

Serious adverse events (SAEs) and deaths
No deaths were reported in either the 50 μg mRNA-1273.214 (Part G) booster dose group or the 50 μg mRNA-1273 (Part F) booster dose group.

In the mRNA-1273.214 50 μg booster dose group (Part G), 2 participants (0.5%) had one SAE each within 28 days of the booster dose and both SAEs were assessed as not related to vaccination by the Investigator (traumatic fracture on Day 14; prostate cancer confirmed on Day 2). One participant had an SAE beyond 28 days after the booster dose that was assessed by the Investigator as not related to vaccination (severe nephrolithiasis on Day 44).

In the mRNA-1273 50 μg booster dose group (Part F2), one participant (0.3%) had an SAE within 28 days of the booster dose and the SAE was assessed as not related to vaccination by the Investigator (severe spinal osteoarthritis on Day 9). No participants had an SAE beyond 28 days from the booster dose at the time of the data cut-off date.

Safety in special populations
Details of all pregnancies in female participants were to be collected after the start of study treatment and until the end of their participation in the study. No pregnancies were reported in the mRNA-1273.214 50 μg booster dose group or in the mRNA-1273 50 μg booster dose group up to the data cut-off.

Immunological events
There were no reports of anaphylaxis or severe hypersensitivity events.

Discontinuation due to AEs
No participants in either the mRNA-1273.214 group or the mRNA-1273 group discontinued due to a treatment-emergent adverse event.

Post marketing experience
The applicant has provided a summary of post-marketing safety data for mRNA-1273 (Spikevax).

The post-marketing global safety database does not fully distinguish between a third 100 μg dose, indicated for immunocompromised individuals in some settings, and a 50 μg booster dose for immunocompetent individuals. Dose 4 may refer to the first 50 μg booster dose for immunocompromised individuals or may refer to the second booster for immunocompetent individuals.

Cumulatively as of 15 Apr 2022, an estimated total of 633,071,724 doses of mRNA-1273 had been administered, including an estimated 126,556,471 doses administered that were Dose 3 or a subsequent dose. There were 41,625 cases (122,901 events) reported after Dose 3 and 607 cases (1,341 events) after Dose 4. No new safety concerns for Dose 3 or Dose 4 have been identified from the post-marketing safety database to date.

Cumulatively, there were 413 cases (431 events) received of myocarditis and pericarditis following a third dose of mRNA-1273. The cases involved 272 males (65.9%) and 140 females (33.9%), with a mean age of 42.9 years (SD: 16.9) and a median age of 40 years (min: 13/max: 91). The time to onset from vaccination was less than 7 days for 298 (69.1%) of the events. Myocarditis rates continue to appear to be lower following dose 3 compared with dose 2, for both sexes, and for almost all age strata, including the age range reported to be at highest risk (12 to 39 years of age). However, post-marketing data for dose 3 are limited and estimates may change as the demographic characteristics of dose 3 recipients change over time.

The bivalent mRNA-1273.214 vaccine was not marketed in any country at the time of licensing.

Proposals for post authorisation follow up (post marketing surveillance)
Refer to section IV.6, Risk Management Plan.

Overall conclusions on clinical safety
The clinical safety data to support this application are from study mRNA-1273-P205 Part G which investigated a 50 µg second booster dose of mRNA-1273.214. A non-randomised comparison with a 50 µg second booster dose of mRNA-1273 is available from Part F cohort 2. The safety set included 437 participants in Part G and 377 participants in Part F. At the data cut-off date, the median follow-up was 6 weeks. This is sufficient for approval.

The frequency and severity of solicited adverse reactions (ARs) were similar for Part G and Part F. In Part G, the commonest (≥10%) solicited local ARs were pain (77%) and axillary swelling or tenderness (17%). The commonest (≥10%) solicited systemic ARs were fatigue (55%), headache (44%), myalgia (40%), arthralgia (31%), chills (24%), and nausea/vomiting (10%). At least one grade 3 solicited AR was reported by 8% in each group. There were no grade 4 solicited ARs. As expected, the frequency and severity of solicited ARs was generally reduced in participants aged ≥65 years compared to those aged 18 to 64 years.

The pattern of solicited ARs was very similar when analysed by subgroups according to pre-booster SARS-CoV-2 status. Reactogenicity outcomes for Part G were comparable to those for the solicited safety set of study P201 part B which included 330 participants who received a 50 µg first booster of mRNA-1273 after mRNA-1273 primary series. All this suggests that at the 50 µg dose, the reactogenicity profile of mRNA-1273.214 when used as a second booster should be similar to the reactogenicity profile of mRNA-1273 when used as a first or second booster, in individuals who received mRNA-1273 as the primary series.

Unsolicited AEs were reported by 22.4% of Part G and 29.4% of Part F. Grade 3 unsolicited AEs were reported by 1.1% and 0.8%, respectively. There were no grade 4 unsolicited AEs. Between-group comparison of unsolicited AEs (including medically attended AEs) does not raise any new safety concerns. A significant proportion appear to be due to reactogenicity.

The applicant has conducted Standardised MedDRA Queries (SMQs) and customised queries of selected unsolicited AEs of special interest. The analyses do not identify any myocarditis or pericarditis events, or any new safety concerns. There is no reason to think that the risk of myocarditis/pericarditis would be higher for mRNA-1273.214 compared to mRNA-1273, given the similarities in the active substances and excipients. No deaths were reported. Serious adverse events (SAEs) were reported by 3 participants in Part G and one participant in Part F; all are unlikely to be unrelated to vaccination.

There are no clinical pregnancy data for mRNA-1273.214. However, the available post-approval pregnancy data for mRNA-1273 can be extrapolated to mRNA-1273.214 given the similarities in the active substances and excipients; no non-clinical reproductive toxicity data were submitted or are required. mRNA-1273.214 has not been studied in individuals ≤18 years of age and is not recommended for use in adolescents at this time.

In conclusion, based on a clinical safety database of 437 participants with median follow-up of 6 weeks, the reactogenicity profile of mRNA-1273.214 as a 50 µg second booster appears similar to that of 50µg of mRNA-1273 when used as a first or second booster. No new safety concerns are raised.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the Applicant intends to address general safety through continued clinical trial follow-up, a European Post Authorisation Safety Study, an observational study of Spikevax using routinely collected health data in five European countries, a US Post Authorisation safety study, and an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy.

Study key detailed information and milestones are provided in the table below:

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
20-0003 *US*	Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults. Interventional *Ongoing*	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, SARS-CoV-2 spike-specific T-cell responses.	Open-label, dose-ranging study	Healthy male and non-pregnant female participants, ⩾18 years of age	LPLV: 03 Jul 2021 Interim CSR: 01 May 2021 Final CSR Main Study: 01 Nov 2022

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
mRNA-1273-P201 *US*	Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ⩾ 18 Years Interventional *Ongoing*	Safety and 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	Randomized, observer-blind, placebo-controlled study	Generally healthy males and females (⩾18 years of age) with no known history of SARS-CoV-2 infection, enrolled in 2 age cohorts (18 to <55 years of age and 55 years of age and older)	LPLV: 20 Aug 2021 Part A CSR: 01 Mar 2021 Part B CSR: 30 Jun 2022 Part C CSR (final): 30 Sep 2022
mRNA-1273-P203 *US*	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age Interventional *Ongoing*	Evaluate the safety, reactogenicity, and effectiveness	Randomized, observer-blind, placebo-controlled study	Healthy adolescents 12 to < 18 years of age	LPLV: 30 Apr 2024 Interim long-term safety CSR for Part A & B: 30 Sep 2022 Final CSR: 31 Jul 2024
mRNA-1273-P204 *US, Canada*	Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized,	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of	Two-part, open-label, dose-escalation, age de-escalation and	The study population includes healthy children of 3 age groups (6	Study start: 15 Mar 2021 Final CSR: 31 Mar 2024

Study Number *Country(ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age Interventional *Ongoing*	elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	subsequent randomized, observer-blind, placebo-controlled expansion study	years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years) No participants in Part 1 participate in Part 2 of the study	

Study Number *Country(ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
mRNA-1273-P301 *US*	Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Interventional *Ongoing*	Long-term safety data and durability of vaccine effectiveness (VE)	Randomized, stratified, observer-blind, placebo-controlled study	Males and females (⩾ 18 years of age), who are at risk of SARS-CoV-2 infection with no known history of SARS-CoV-2 infection, including participants at increased risk of complications from COVID-19. Participants ⩾ 65 years of age were eligible for enrolment with or without underlying medical conditions that might further increasing their risk of severe COVID-19.	LPLV: 30 Sep 2022 Interim CSR: 15 Oct 2021 Long-term follow-up Part B & C Interim CSR: 31 Dec 2022 Final CSR: 30 Jun 2023
Study mRNA-1273-P304 *US*	A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls.	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of elasomeran. Immunogenicity : neutralizing and binding	Open label single treatment arm study in solid organ transplant recipients and healthy controls	Approximately 240 adult (⩾ 18 years of age) male and female participants (220 kidney or liver transplant recipients, and 20 healthy adults) will be	Protocol submission: 05 Feb 2021 Interim Report: 31 Mar 2023 Final CSR: 31 Jan 2024

Study Number *Country(ies)*	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	Interventional *Ongoing*	antibody titres as surrogate endpoints expected to predict clinical benefit.		enrolled	
mRNA-1273-P903 *US*	Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity. Non-interventional *Ongoing*	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) 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	Secondary database analysis using retrospective analyses of pre-vaccination data as well as prospectively updating data during the vaccination period. It will include estimation of background rates of observed versus expected rates, and self-controlled risk interval analyses.	A sample of pediatric, adolescent and adult individuals enrolled in health plans contributing data to HealthVerity will be used for calculation of background rates. Patients from this dataset as well as additional patients with evidence of SARS-CoV-2 vaccination will be included as vaccine uptake increases.	Protocol submission: 31 Jan 2021 Interim updates: 30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022, 30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Jan 2023 Final study report: 30 Jun 2023.
mRNA-1273-P904 *Denmark, Norway, Italy, Spain,*	Post-Authorization Active Surveillance Safety Study Using Secondary	The overarching research question of this study: Is the occurrence of each adverse	Secondary database analysis of observational data to estimate	Pediatric, adolescent, and adult individuals within the catchment area	Feasibility assessment: 31 Jan 2021 Protocol submission:

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
United Kingdom	Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU. Non-interventional *Ongoing*	event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: - To assess whether vaccination with Spikevax is associated with	incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU.	of participating data partners from the VAC4EU network	30 Jun 2021 Interim updates: 30 Sep 2021, 31 Mar 2022, 30 Sep 2022, 31 Mar 2023 Final study report: 31 Dec 2023

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompro-mised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders			
mRNA-1273-P905 *Denmark, Norway, Italy, Spain, United Kingdom*	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries. Non-interventional Planned	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with	Secondary database analysis comparing birth prevalence of study outcomes for pregnancies with and without COVID-19 Vaccine Moderna exposure.	The study population will encompass all pregnancies, identifiable in the databases, ending in a live or still birth; a spontaneous abortion; or an induced abortion, or an ectopic pregnancy, as identifiable in the participating	Feasibility assessment: 31 Jan 2021; Protocol submission: 30 Jun 2021; Interim updates: 31 Mar 2022, 30 Sep 2022, 31 Mar 2023; Final study report: 31

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna COVID-19 vaccine during pregnancy is associated with an increased risk of: a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy		databases	Dec 2023

mRNA-1273-P901 *US*	Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. Non-interventional *Ongoing*	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease Secondary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna	Prospective cohort study	Individuals ≥12 years of age	Protocol submission: 01 Mar 2021 Interim updates: 14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 14 Jun 2023; 14 Dec 2023 Final study report: 14 Apr 2025

		COVID-19 vaccine in preventing COVID-19 diagnosis by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes) 4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals who			

		are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications) 5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus) 6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in frail individuals 7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing			

		COVID-19 diagnosis in pregnant women 8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis among individuals with a history of COVID-19 diagnosis 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic COVID-19 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic COVID-19			

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease 14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease.			
mRNA-1273-P910 *EU, Countries are yet to be*	Natural history and clinical outcomes of vaccine associated myocarditis	Characterize natural history of and risk factors for myocarditis temporally associated with	Observational cohort study	To be confirmed upon identification of study collaborators	Protocol submission: 26 Apr 2022 Interim report:

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
determined	*Initial development* *Planned*	Moderna COVID-19 vaccination in children and young adults			30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024 Final study report: 28 Feb 2025
mRNA-1273-P911 *United States*	Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) *Initial development* *Planned*	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX).	Observational cohort study	To be confirmed upon identification of study collaborators	Protocol submission: 30 Apr 2022 Interim report: 31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027 Final study report: 31 Oct 2028
mRNA-1273-P205 *US*	A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants Initial	To evaluate the immunogenicity , safety, and reactogenicity of mRNA vaccine boosters for SARS-CoV-2 variants including mRNA-1273.211,	Open-label Phase 2/3 study consisting of 7 parts: A, (1, 2), B, C, D, E, F, and G.	Men and nonpregnant women, at least 18 years of age who previously received 2 doses of Spikevax (with other criteria depending on	Study Start: 28 May 2021 Protocol Submission: 30 Jun 2022 Interim report: 30 Jun 2022

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	development Ongoing	Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, and Spikevax bivalent.		the Part of the study)	LSLV: 22 Jul 2023 Final CSR: 31 Dec 2023
mRNA-1273-P919 *US*	An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy Non-interventional Planned	To assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is associated with prenatal exposure to Spikevax.	Observational cohort database study	An administrative claims data source in the US will be selected that includes capture of longitudinal data on diagnoses, procedures, medications, and vaccines used across all applicable healthcare settings (inpatient, emergency, and outpatient care). Mothers and infants will be linked via a common identifier and date of birth event. Mothers will be included in the study if they have adequate database enrolment to capture all	Protocol submission: 28 Oct 2022 Study completion: 30 Sep 2023 Final study report: 31 Mar 2024

Study Number *Country(ies)*	Study Title Study Type *Study Status*	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
				pregnancy and pre-pregnancy baseline data with no prenatal exposure to major teratogenic infections or medications.	

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a Conditional Marketing Authorisation is recommended for this application.

V USER CONSULTATION

The readability of the Patient Information Leaflet (PIL) text has been evaluated on the basis of a bridging report. This makes reference to a user consultation for Spikevax (mRNA-1273) dispersion for injection, (PLGB 53720/0002; formerly known as COVID-19 Vaccine Moderna dispersion for injection). A PIL mock-up is not required at the time of Conditional Marketing Authorisation of COVID-19 vaccines. The bridging report is accordance with legal requirements.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product as a booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Spikevax bivalent Original/Omicron has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Specific obligations

Description	Due date
1. The MAH should provide additional information on stability studies and comparability assessment for the introduction of CX-031302 at Moderna Train and Lonza Visp (SO1).	30/09/2024
2. The MAH should provide comparative and extended characterisation data for Omicron mRNA-1273.529 LNP-B batches, prototype mRNA-1273 LNP and other variant mRNA-1273 LNPs, including potential impurities associated with the Omicron mRNA-1273.529 LNP-B product, with respect to both the mRNA and LNP components (SO2).	31/12/2022

3. In order to improve the control of drug product, additional data should be provided to justify mRNA ratio limits (SO3).	31/12/2022
4. In order to improve the control of drug product, the MAH should amend the specification limits for the new mRNA purity assay, compared with the current mRNA purity assay (SO4).	31/10/2022
5. Comparative data from both mRNA purity assays should be provided for CX-031302 mRNA, mRNA-1273.529 LNP, mRNA-1273.214 DP and on CX-024414 mRNA, mRNA-1273 LNP and mRNA-1273 DP (SO5).	31/01/2023
6. The MAH should submit the day 91 immunogenicity and safety results from study mRNA-1273-P205 Part G and Part F (cohort 2) (SO6).	31/12/2022

This authorisation has the following post authorisation measure(s) which should be fulfilled by the date(s) shown if a date is specified:

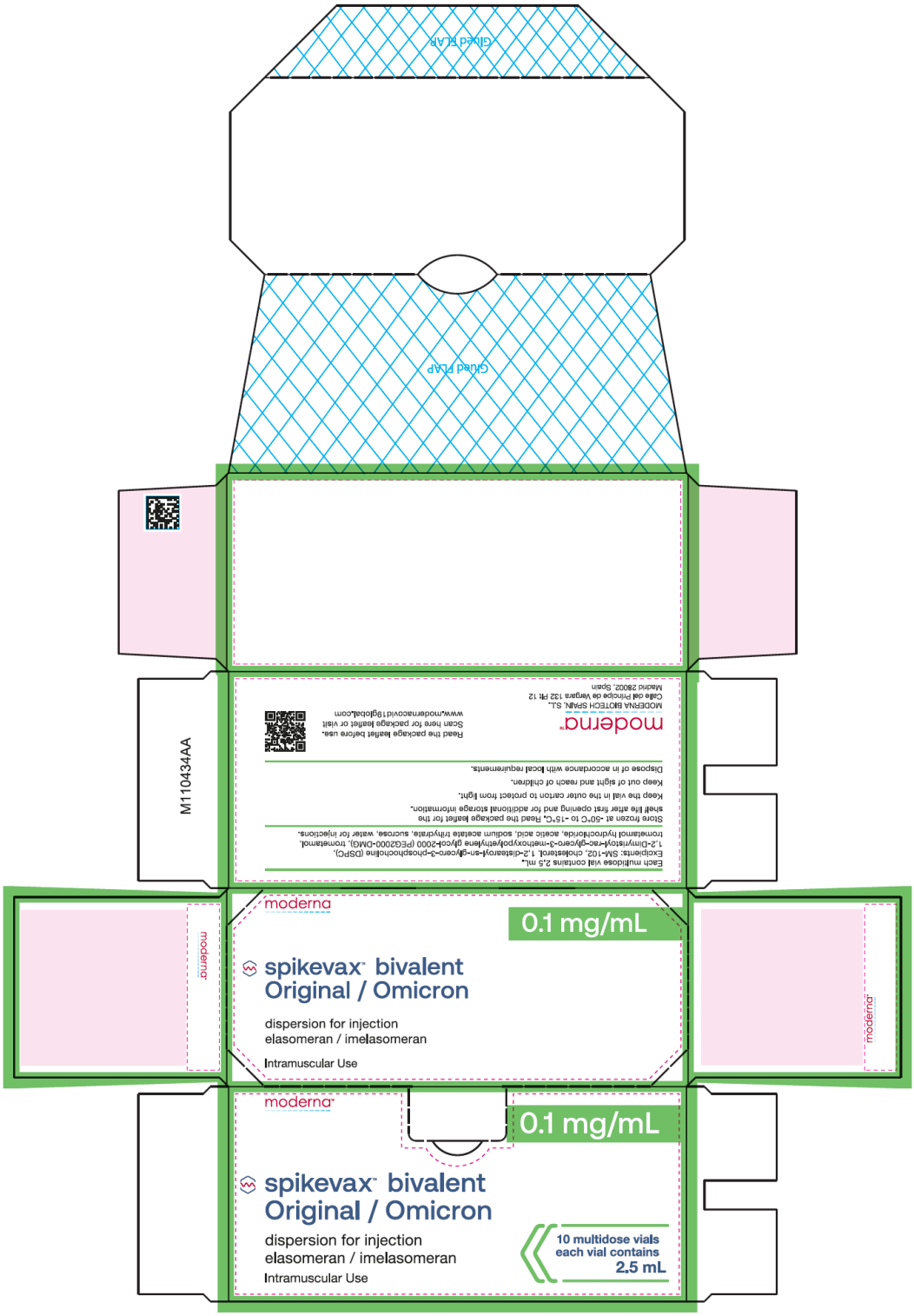
Description	**Due date**
1. Update Section 3.2.P.5.6 {mRNA-1273.214 DP} to include both mRNA-1273 DP and the variants data, as previously included with Sequence 0190.	
2. In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. This should include further evidence to support the comparability of mRNA 1273 LNP and mRNA 1273 LNP-B batches across manufacturing sites, as well as updated stability data mRNA 1273 LNP-B finished product intermediate.	31/12/2023
3. Stability data for the 3-month timepoint for Patheon and Catalent PPQ batches should be provided.	
4. Update to include both CX-024414 mRNA and the variants data, as previously included with Sequence 0190.	
5. Provide equivalency report for the AxiChrom in-house packed Oligo dT chromatography column implementation at Lonza Visp.	
6. Stability data should be provided to support the claimed interim storage time for unlabelled vials (Process Alternative 2).	
7. Provide end-to-end studies for 5°C storage preceded by storage at -20°C (analysed separately) to confirm the consistency of 5°C stability following frozen storage.	
8. The MAH should submit the cellular immunogenicity results from study mRNA-1273-P205 Part G and Part F (cohort 2).	30/09/2023
9. Provide accelerated data for mRNA-1273.214 DP (Catalent site) for comparability with mRNA-1273 DP, generated with SOP-1142.	
10. The MAH should outline how real-world effectiveness data will be collected for Spikevax bivalent Original/Omicron, including data on COVID-19 cases, hospital admissions and whether the vaccine can reduce transmission. The outline and relevant protocol(s) should be submitted within 3 months of grant.	12/11/2022
11. Comparative accelerated stability data for the Omicron mRNA-1273.529 LNP against prototype mRNA-1273 LNP for batches manufactured at the different manufacturing sites (e.g. Norwood, Granada	

and Visp) should be presented to enable a direct comparison of the stability profiles between the prototype and variant mRNA-1273 LNPs.	
12. Data from the first two refiltration batches of bivalent DP to be provided to support reprocessing claim.	
13. Cumulative Process duration to be provided for four PPQ batches from Rovi manufacturing according to Process 2.	
14. The MAH should submit the day 181 immunogenicity and safety results from study mRNA-1273-P205 Part G and Part F (cohort 2).	30/09/2023
15. The MAH should provide the validation report of the BA.4/5 pseudovirus neutralisation assay used to analyse clinical samples from study mRNA-1273-P205 Part G and Part F (cohort 2).	31/03/2023

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PILs for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Glued FLAP
Glued FLAP
M110434AA
moderna
0.1 mg/mL
spikevax bivalent
Original / Omicron
dispersion for injection
elasomeran / imelasomeran
Intramuscular Use
moderna
0.1 mg/mL
spikevax bivalent
Original / Omicron
dispersion for injection
elasomeran / imelasomeran
Intramuscular Use
10 multidose vials
each vial contains
2.5 mL

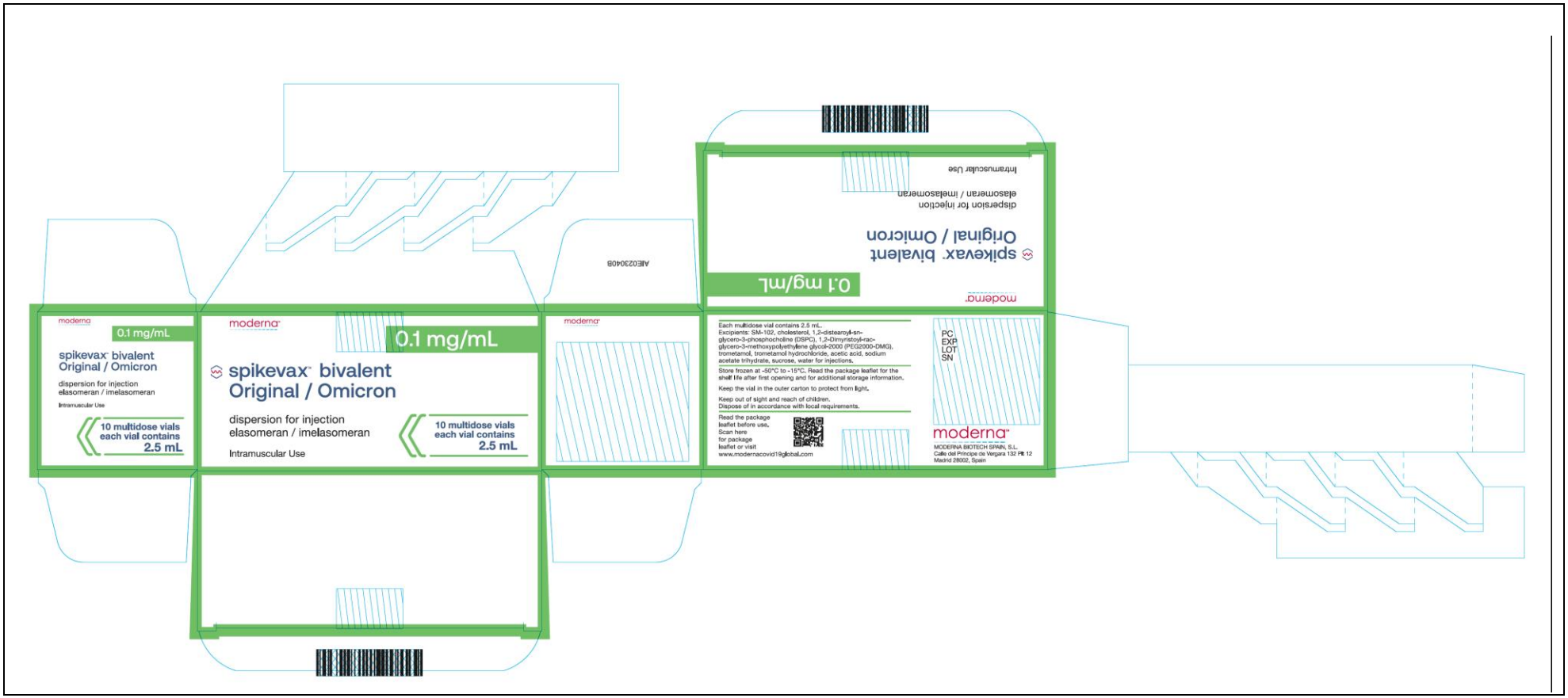

moderna
0.1 mg/mL
spikevax bivalent
Original / Omicron
dispersion for injection
elasomeran / imelasomeran
Intramuscular Use
10 multidose vials
each vial contains
2.5 mL
moderna
0.1 mg/mL
spikevax bivalent
Original / Omicron
dispersion for injection
elasomeran / imelasomeran
Intramuscular Use
10 multidose vials
each vial contains
2.5 mL
moderna
Each multidose vial contains 2.5 mL.
Excipients: SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, water for injections.
Store frozen at -50°C to -15°C. Read the package leaflet for the shelf life after first opening and for additional storage information.
Keep the vial in the outer carton to protect from light.
Keep out of sight and reach of children.
Dispose of in accordance with local requirements.
Read the package leaflet before use.
Scan here for package leaflet or visit
www.modernacovid19global.com
PC
EXP
LOT
SN
moderna
MODERNA BIOTECH SPAIN, S.L.
Calle del Príncipe de Vergara 132 Pl. 12
Madrid 28002, Spain
AIE023040B
0.1 mg/mL
spikevax bivalent
Original / Omicron
dispersion for injection
elasomeran / imelasomeran
Intramuscular Use
moderna

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the Marketing Authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**