EMA/429527/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005791/II/0111/G

Invented name: Spikevax

Common name: COVID-19 mRNA vaccine

Marketing authorisation holder (MAH): Moderna Biotech Spain, S.L.

Timetable	
Description	**Planned date**
Start of procedure	07 Aug 2023
CHMP Rapporteur Assessment Report	30 Aug 2023
CHMP members comments	1 Sep 2023
Updated CHMP Rapporteur Assessment Report	12 Sep 2023
Opinion	14 Sep 2023

Procedure resources	
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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 30 June 2023 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A
B.II.b.2.a	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	Type IB	None
B.II.d.1.z	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	Type IB	None

B.I.a.6.a (Type II): Addition of a new strain (Omicron XBB.1.5, andusomeran) resulting in six new monovalent presentations: Spikevax XBB.1.5 0.1 mg/mL dispersion for injection (2.5 mL multidose glass (EU/1/20/1507/011) or cyclic olefin polymer (EU/1/20/1507/012) vials, both in pack sizes of 10 vials), Spikevax XBB.1.5 50 micrograms dispersion for injection (0.5 mL single dose glass vials in pack sizes of 1 (EU/1/20/1507/013) and 10 vials (EU/1/20/1507/014)) and Spikevax XBB.1.5 50 micrograms dispersion for injection in a pre-filled syringe (0.5 mL single dose in pack sizes of 1 (EU/1/20/1507/015) and 10 syringes (EU/1/20/1507/016)). As a result, the SmPC, labelling and package leaflet, and Annex A are updated accordingly.

The finished product mRNA-1273.815 is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-038839 mRNA active substance that encodes for the pre fusion stabilized Spike protein of the SARS-CoV-2 Omicron XBB.1.5 variant.

B.II.b.2.a (Type IB): To use Analytical testing site, Microsynth AG, Balgach Switzerland, as an alternative site responsible for Reverse Transcription Sanger Sequencing (RTSS) batch quality control testing for identity of the finished product (Spikevax XBB.1.5 -multidose vial (EU/1/20/1507/011, EU/1/20/1507/012 only)). This site is registered for RTSS identity testing of the RNA active substance and finished product intermediate of already authorised presentations.

B.II.d.1.z (Type IB): To add an action limit of ≥ 85% to the specification '% RNA Encapsulation' on labelled drug product (LDP) as a requirement for release, when Process Alternative 2 is used (for EU/1/20/1507/011- 016).

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A.

2. Introduction

Moderna developed the Spikevax vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs). The emergence of SARS-CoV-2 variants with multiple mutations have led Moderna to develop variant vaccine constructs.

There are several approved formulations of Spikevax vaccine targeting the Wuhan (original) strain, and Omicron BA.1 and BA.4-5.

To assist in the continued management of COVID-19, and taking into account the ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants, a new Omicron (XBB.1.5) monovalent variant vaccine is the subject of this variation.

3. Quality aspects

3.1. Introduction

The monovalent finished product is presented as a dispersion for injection containing 100 micrograms/mL of andusomeran as active substance, embedded in lipid nanoparticles. The finished product is a white to off-white sterile dispersion for injection in a preservative-free buffer at pH 7.5 for intramuscular administration.

Andusomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

Other ingredients are: 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
The product is available in six presentations: Spikevax XBB.1.5 0.1 mg/mL dispersion for injection (2.5 mL multidose glass (EU/1/20/1507/011) or cyclic olefin polymer (EU/1/20/1507/012) vials, both in pack sizes of 10 vials), Spikevax XBB.1.5 50 micrograms dispersion for injection (0.5 mL single dose glass vials in pack sizes of 1 (EU/1/20/1507/013) and 10 vials (EU/1/20/1507/014)) and Spikevax XBB.1.5 50 micrograms dispersion for injection in a pre-filled syringe (0.5 mL single dose in pack sizes of 1 (EU/1/20/1507/015) and 10 syringes (EU/1/20/1507/016)).

3.2. Active substance – andusomeran

General information

To introduce the new monovalent vaccine, the MAH submitted data to support implementation of the omicron variant XBB.1.5 mRNA (CX-038839) manufacture.

CX-038839 (INN; andusomeran) is the mRNA that encodes for the pre-fusion stabilized Spike protein for 2023-novel Coronavirus (SARS-CoV-2) XBB.1.5 variant. The XBB.1.5 sub variant is a sub-lineage of the Omicron variants. XBB.1.5 is a recombinant of two BA.2 sub-lineages, with an additional spike receptor-

binding domain (RBD) change, S486P. The S protein is stabilized in the so-called pre-fusion conformation by two amino acid mutations, K982P and V983P.

CX-038839 mRNA is chemically identical to naturally-occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N1-methylpseudouridine, a naturally-occurring pyrimidine base present in mammalian tRNAs. This nucleoside is included in the CX-038839 mRNA in place of the normal uridine base to minimize the indiscriminate recognition of CX-38839 mRNA by pathogen-associated molecular pattern (PAMP) receptors (e.g., Toll-like receptors). The molecular sequence of CX-038839, including the 5′ cap, the 5′ untranslated region (UTR), the Open Reading Frame (ORF), the 3′ UTR, and the 3′ polyA tail, is provided.

The full sequence of CX-38839 is provided. The 3'UTR for CX-038839 mRNA has been modified with a 24 nt substitution of an 11 nt sequence in the original 3'UTR used in CX-024414 mRNA. This sequence is referred to as the identity and ratio (IDR) sequence. The IDR sequence corresponds to position 3943-3966 in the CX-038839 mRNA sequence.

The information on the structure of mRNA CX-038839 is considered acceptable.

Manufacture

The active substance is manufactured by Lonza AG (Lonzastrasse, 3930 Visp, Switzerland), ModernaTX, Inc. (One Moderna Way, Norwood, MA 02062, USA) and Lonza Biologics, Inc. (101 International Drive Portsmouth, NH 03801, USA)

No new manufacturing sites were introduced with this submission for drug substance and all hold appropriate GMP authorisations.

Description of manufacturing process and process controls

The nominal manufacturing batch size for CX-038839 mRNA at Lonza AG (Visp, Switzerland) and at ModernaTX (Norwood, United States) is 75 L (Scale B) in vitro transcription (IVT) reaction volume. The manufacturing process for CX-038839 is identical to the manufacturing process presented for CX-024414 at the 75 L scale at Lonza Visp and at ModernaTX Norwood, respectively.

Control of materials

Raw materials:
The raw materials used in the manufacture of CX-038839 are identical to the raw materials used for manufacture of CX-024414 (elasomeran, original strain).

Starting material:
The starting materials in the manufacture of CX-038839 mRNA are the linearized plasmid template and the nucleotides ATP, CTP, GTP, N1-Me-ΨTP. The nucleotides are the same nucleotides as used for manufacture of CX-024414 mRNA.

Linearized Plasmid Template:
A unique linearized DNA plasmid template specific for CX-038839 mRNA was manufactured at ModernaTX, Inc. (Norwood, MA, USA). The features of the plasmid template specific for CX-038839 mRNA are consistent with CX-024414 mRNA described in Section 3.2.S.2.3 {CX-024414 - Starting Materials - Lonza Visp} and Section 3.2.S.2.3 {CX-024414 – Starting Materials - US - ROW}, with the exception of the specific sequence of the coding region and the 3'UTR. In addition to the elements described for the 3'UTR of CX-024414, the 3'UTR for CX-038839 mRNA has been modified with a 24 nt substitution in an 11 nt region of the original 3'UTR used in CX-024414 mRNA. This sequence is referred to as the identity and ratio (IDR) sequence, to enable identification and relative ratio determination of individual RNA

components in a bivalent Drug Product. Introduction of the IDR in the 3'UTR enables analytical control using RNAse H guides specifically targeting to the IDR for each RNA and offers the flexibility and efficiency for analytical control of future variant vaccines. These proposed sequences are non-coding and would therefore not be translated into peptides.

The full plasmid DNA sequence and the plasmid map are provided. The host cell line used for manufacture of PL-034023 for CX-038839 mRNA is the same as described for CX-024414 mRNA.

The cell banking system is two-tiered, including a master cell bank (MCB) and a working cell bank (WCB). The manufacturers involved in cell bank production are listed. Manufacture and testing of MCB and WCB was conducted as for the original CX-024414 containing plasmid.

Release results for MCB and WCB are provided including for culture purity, lytic and lysogenic bacteriophages, viability, marker retention, strain identity (for MCB only), plasmid identity, plasmid integrity and plasmid copy number. The analytical procedures used to perform release are also stated. Qualification of MCB and WCB have also been described.

The MCB stability protocol and all available data are provided. The test methods and acceptance criteria are the same as for release testing. All available data show compliance to specification.

PL-034023 is manufactured for CX-038839 mRNA using the same procedure as described for CX-024414 mRNA. The same approach to characterization testing and kanamycin risk assessment described for CX-024414 mRNA was taken for CX-038839 mRNA.

The specification for the linearized plasmid includes: appearance, concentration, plasmid identity, %linear plasmid, residual genomic DNA, residual RNA, residual protein, bacterial endotoxin and bioburden.

The final filtered bulk long-term storage condition for the linearized plasmid is -25°C to -15°C, with a formal shelf life of three years.

A shelf life of 3 years at -25°C to -15°C is requested for the linearized plasmid based on the prototype vaccine and supported by limited data collected in an on-going stability study. Considering that no changes are included in the manufacturing process of the DNA template as compared to the original variant, the shelf-life is considered sufficiently supported by the original data.

Control of critical steps and intermediates

The process control strategy and methods for critical in-process controls testing for the CX-038839 mRNA manufacturing process are identical to the ones in place for the CX-024414 mRNA (elasomeran).

Process validation and/or evaluation

For mRNA-1273 variant processes that use a manufacturing process and control strategy equivalent (equivalent except for mRNA sequence specific control elements) to the prototype mRNA-1273 process (i.e. the Original CX-024414), one confirmatory PPQ verification lot was performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan . The applicant has successfully completed PPQ verification of the CX-038839 mRNA manufacturing process as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement laboratory-scale studies.

All process trains previously qualified for CX-024414 manufacture are also considered qualified for commercial production of CX-038839.

All discrete process parameters defined were evaluated during PPQ verification for conformance to their target ranges and are summarized. The results of the CPP, PP, critical and non-critical IPC and release

testing of the CX-038839 mRNA PPQ verification batch were within the specifications and the prior defined acceptance criteria. The process performance verification at Moderna TX Norwood and Lonza Visp was completed successfully.

Manufacturing process development

The development of additional mRNA-1273 vaccines was initiated in response to the emergence of SARS-CoV-2 variants of concern. Sequences for mRNA-1273 vaccines are designed upon the prefusion-stabilized two-proline (S-2P) encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made to incorporate the specific mutations of the variant S protein sequence encoded by the sequence of the specific mRNA-1273 RNA. The manufacturing process and process and analytical control strategies established for the CX-024414 mRNA are applied directly to CX-038839 mRNA.

Subsequent process characterization beyond that described for CX-024414 was performed for CX-038839 mRNA (XBB.1.5), with the intent of verifying the applicability of the process description and process control strategy defined. CPPs and the CIPC are consistent between CX-038839 mRNA (XBB.1.5) and CX-024414 mRNA.

A comparability study between CX-024414 to CX-038839 was conducted.

The following three elements were included in the comparability study:

- Evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs).
- Statistical evaluation of comparability of release testing results.
- Statistical evaluation of selected extended characterization results.

The mRNA sequence was the only change represented in this comparability exercise. All CIPC and IPC results met the acceptable ranges. Release results met both specification and comparability acceptance criteria and extended characterization results met the comparability expected ranges. Therefore, the results from the Scale B (75 L IVT scale) PPQ lot of CX-0338839 mRNA manufactured at ModernaTX (Norwood, MA) and from the Scale B (75 L IVT scale) PPQ verification lot of CX-038839 mRNA manufactured at Lonza (Visp, Switzerland) demonstrated that the pre-change and post-change manufacturing processes and quality attributes were comparable. The comparability data clearly indicates that the quality of the CX-038839 mRNA is comparable to the quality of the parental CX-024414 mRNA, as all testing is within the comparability acceptance criteria.

Characterisation

Elucidation of structure and other characteristics

The structure, physicochemical properties of CX-034476 mRNA, were studied using a variety of techniques applicable to mRNAs. The data generated from these analyses confirm the physico-chemical structure and characterize the functional attributes of CX-038839 mRNA. This was studied by techniques applicable to mRNAs, including: determination of UV extinction coefficient, circular dichroism spectrum, reverse transcription followed by Sanger di-deoxynucleotide sequencing, oligonucleotide mapping, N1-methyl-pseudouridine (N1-MeΨU) ID and content, cap identity, Poly A tail length and dispersity, sequence homogeneity of the CX-038839 mRNA coding region, melting profile by Differential Scanning Calorimetry (DSC). Process impurities were evaluated. These included double stranded RNA (dsRNA) and residual protein. The characterization of the new mRNA CX-038839 is considered acceptable.

Impurities

There are no new impurities as compared to parental mRNA.

Control of active substance

The following attributes have been included in the specification for the active substance: appearance, mRNA identity by reverse transcription/Sanger sequencing, total RNA content by UV, purity and product related impurities by RP-IP-HPLC, % 5' capped and Poly A tailed RNA, pH, bacterial endotoxins (Ph. Eur. 2.6.14) and bioburden (Ph. Eur. 2.6.12).

No change in the specification is proposed. The specifications for CX-038839 and CX-024414 are identical, except for the specification for identity by reverse transcription / Sanger sequencing and a product-specific justification for this has been provided.

Analytical methods

The analytical methods used for release testing of CX-038839 and prototype CX-024414 are identical with the exception of the identity method, since this is the only method that is sequence-specific. Confirmation of mRNA Sequence by RT-PCR and Sanger Sequencing has been validated and shown to be suitable for the purpose of determining the mRNA identity of CX-038839.

Batch analysis

Batch results from one batch produced at Moderna Norwood and one batch produced at Lonza Visp are presented and the CoAs are provided. The results show compliance to specifications.

Reference standards of materials

The CX-024414 mRNA reference material is used as a reference standard for measurement of total RNA content of variant mRNA-1273 LNP and DP materials including mRNA-1273.815 LNP and DP. It is also used as a system suitability standard for several release tests.

Assays such as %PolyA tailed variants, use a relative measurement of a specific peak of interest (such as a PolyA tail peak) relative to a total peak area within the same test sample to report results. The measurement of purity and product-related impurities by ion pairing reversed-phase chromatography uses a similar approach, where the purity and impurity peaks are measured in relation to the total peak area within a sample chromatogram. In both cases, a product-specific reference standard is not needed to measure the attributes of interest. To assess the system performance parameters such as peak area or retention time consistency within the run as system suitability, any standard that chromatographs similarly to the analyte of interest can be used, and a product-specific reference standard is not necessarily needed. In the case of the RP IP HPLC purity method, a single mRNA standard (CX-024414) is used to assess system suitability.

The justification that no sequence specific reference material is needed as it is used as system suitability reference material only is acceptable.

Container closure system

The container closure system for CX-038839 mRNA is the same as for the original prototype, CX-024414 mRNA.

Stability

An initial shelf-life of 36 months is proposed as from the time of freezing for CX-038839 mRNA material stored in the commercial container closure system. The CX-038839 mRNA is stored at -60 to -90°C, after an optional interim storage at -15 to -25°C of maximum 3 months.

The properties of CX-038839 mRNA with respect to the attributes that affect product potency have been assessed. These attributes include fidelity of the RNA sequence including cap, tail, and open reading frame, and integrity of the RNA. Direct measurements of those attributes have been established and are included in the routine release panel for CX-038839 mRNA. The product quality attribute expected to change most during the manufacturing and distribution of the product is mRNA purity, which represents the fraction of intact mRNA. The degradation of RNA in the product has been extensively studied by applying a sensitive chromatographic assay to assess the formation of RNA degradants. The principal route of degradation for RNA is hydrolytic chain scission to species that elute prior to the main peak (RNA fragments). mRNA purity correlates with protein levels measured in the *in vitro* relative protein expression assay. Direct measurement of RNA degradation utilizing the RNA purity assay by RP-HPLC is precise, accurate, and the most stability-indicating measure of product activity.

Stability studies have been initiated for CX-038839 mRNA manufactured at ModernaTX, Inc. (Norwood, MA) and at Lonza (Visp, Switzerland). Upon request, the applicant has committed to submit a revised Section 3.2.S.7.2 {CX-038839} by the end of September 2023 to reflect the shelf-life claim, including the optional interim storage at -25°C to -15°C in the annual stability protocol (recommendation 1).

3.3. Finished product intermediate mRNA LNP

CX-038839 mRNA loaded LNP intermediate (referred to by the MAH as mRNA-1273.815 LNP-B)

The process description and in-process controls for the mRNA-1273.815 LNP-B remain identical to the ones previously approved for the mRNA-1273 LNP-B and mRNA-1273.529 LNP-B materials. **Error! Reference source not found.**

Since the same manufacturing process is used; one single Process Verification / Comparability batch was performed to introduce the mRNA-1273.815LNP-B manufacturing on the already approved Moderna Norwood, Lonza Visp and Rovi Granada manufacturing sites.

Raw materials used in the manufacturing process of mRNA-1273.815 LNP-B are the same as those used in the manufacturing process of the other LNPs.

The specifications have not been changed for the newly introduced mRNA-1273.815 LNP-B.

Considering the mRNA LNP stability is sequence agnostic; the same degradation kinetics apply to all mRNA-LNP-B materials and the shelf-life of 12 months when stored at -90°C to -60°C, as previously assigned to the mRNA LNP-B material, is therefore assigned to the mRNA-1273.815 LNP-B material.

Pharmaceutical development

As for the existing formulation, the manufacturing process for the finished product intermediate comprises the manufacture of an mRNA loaded LNP intermediate, i.e. mRNA-1273.815 LNP-B (containing mRNA CX-038839).

*CX- 038839 mRNA loaded LNP intermediate (*referred to by the MAH as *mRNA-1273.815 LNP-B)*

The development of additional mRNA-1273 vaccines was initiated in response to the emergence of SARS-CoV-2 variants of concern. Sequences for mRNA-1273 vaccines are designed based upon the S-2P

encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made to incorporate the specific mutations of the variant S protein sequence encoded by the specific mRNA-1273 RNA sequence. The manufacturing process and process and analytical control strategies established for mRNA-1273 LNP-B are applied directly to mRNA-1273.815 LNP-B.

Subsequent process performance verification beyond that described in Section 3.2.S.2.6 {mRNA-1273 LNP} was performed for mRNA-1273.815 LNP-B (Omicron XBB.1.5), with the intent of verifying the applicability of the process description and process control strategy.

The following three elements were included in the comparability study:

1. Evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs).
2. Statistical evaluation of comparability of release testing results.
3. Statistical evaluation of extended analytical characterization testing results.

Three PPQ batches have been included in the comparability study.

mRNA-1273.815 LNP Lot	Use	Site	Train
5018623001	PPQ Verification Comparability	ModernaTX Norwood, MA	1
5019823001 (Rovi lot 1148100123)	PPQ Verification Comparability	Rovi Granada, Spain	10
5018123001 (Lonza lot 1114001)	PPQ Verification Comparability	Lonza Visp, Switzerland	11

Abbreviations: LNP = lipid nanoparticle; PPQ = process performance qualification

The comparability study was performed using the PPQ batch data from mRNA-1273.815 LNP-B and historical batch data. Historical data from development, clinical, Scale A, preliminary Scale B, and Scale B mRNA-1273 LNP batches were used to define comparability acceptance criteria. Comparability covered data on process performance parameters and in-process controls, results of release testing, and results of extended characterisation. Based on the presented data, mRNA-1273.815 LNP-B is considered comparable to historical batch data.

Manufacture

mRNA loaded LNP intermediate containing mRNA CX-038839 (referred to by the MAH as mRNA-1273. 815 LNP-B)

There are no changes to the currently registered manufacturing and testing sites.

Description of manufacturing process and process controls

mRNA-1273.815 LNP-B is produced in a 200 g nominal batch size, according to the same manufacturing process described for mRNA-1273 LNP-B. There are no change to the registered information for control of critical steps and intermediates

Process validation and/or evaluation

For mRNA-1273.815 LNP-B, the only process change is the change in mRNA sequence. For mRNA-1273.815 LNP-B, manufacturing, including controls remains the same as for mRNA-1273 LNP-B. Therefore, one PPQ batch manufactured per site (Moderna, Lonza Visp, Rovi Granada) has been considered sufficient. Moderna has successfully completed PPQ verification of the mRNA-1273.815 LNP-B manufacturing process as a means of demonstrating that the commercial-scale manufacturing process is

capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement laboratory-scale studies.

The results of the CPP, PP, critical and non-critical IPC and Drug Substance testing of the mRNA-1273.815 LNP - B PPQ batches were within the specifications and the prior defined acceptance criteria. Based on the outcome of the PPQ exercise, the mRNA-1273.815 LNP-B manufacturing process has been successfully validated at the 200 g scale at ModernaTX Norwood, Lonza Visp and Rovi Granada.

The MAH's conclusion that the mRNA-1273.815 LNP-B process at 200 g manufacturing scale was successfully performed and process consistency demonstrated is supported.

Control of finished product

mRNA loaded LNP intermediate containing mRNA CX-038839 (referred to by the MAH as mRNA-1273. 815 LNP-B)

There is no change in specifications.

The following attributes have been included in the specification for mRNA-1273.815 LNP-B: appearance, mRNA identity by reverse transcription/Sanger sequencing, total RNA content by anion exchange chromatography, purity and product-related impurities by RP-IP-HPLC, % RNA encapsulation by absorbance assay, mean particle size and polydispersity by DLS, lipid identity and content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000- DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), in vitro translation by methionine labelling, pH, osmolality, bacterial endotoxins (Ph. Eur. 2.6.14, kinetic chromogenic method) and bioburden (Ph. Eur. 2.6.12). This specification differs from the specification for mRNA-1273 LNP-B only with respect to the identity test.

Method description and validation data for the identity test with Reverse transcription/Sanger sequencing is included. This test method can unambiguously distinguish prototype and variant mRNAs used in the manufacture of monovalent and bivalent mRNA-1273 drug products. All other analytical methods remain unchanged. The presented information for control of mRNA-1273.815 LNP–B is considered sufficient.

The applicant's conclusion that product- and process impurities of mRNA-1273.815 LNP-B are the same as for the other variants, is endorsed. The study results indicate that product-related impurities like RNA fragments and RNA-lipid adducts occur similarly in all variants (mRNA-1273 DP, mRNA-1273.045 DP and mRNA-1273.815 DP). In addition, the applicant has shown that the most abundant lipid-adducted nucleoside species occur in all variants.

Comparison of the current and the former purity method confirms the previous observation that the new method leads to higher purity values - most probably due to poly A variants that are now included in the main peak. This is acceptable since the purity specification has been increased accordingly. The suitability of the new assay as stability-indicating method is confirmed by showing that for heat-degraded samples, the RNA degradation rates obtained from the two methods are highly comparable.

Analytical procedure

The analytical methods used for release testing of mRNA-1273.815 LNP-B and the prototype mRNA-1273 LNPs are identical with the exception of the identity method, since this is the only method that is sequence-specific.

This method has been validated and shown to be suitable for the purpose of determining the identity of mRNA-1273.815 LNP-B.

Batch analyses

Batch analysis data is provided for mRNA-1273.815 LNP–B for the PPQ batches manufactured at Moderna TX Norwood, Rovi Granada and Lonza Visp. All results are within the specifications.

Stability

A shelf life of 12 months is proposed for mRNA-1273.815 LNP-B material stored in the commercial container closure system when stored at the recommended long-term storage condition of -60°C to -90°C.

The properties of mRNA-loaded lipid nanoparticles with respect to the attributes that affect product potency include the quantity of mRNA delivered; the fidelity of the mRNA sequence, including cap, tail, and open reading frame; the integrity of the mRNA; and various biophysical attributes of the lipid nanoparticles, particularly including the state of mRNA encapsulation and the size distribution of the particles. Direct measurements of those attributes of greatest significance have been established and include those assays in the routine release panel for mRNA-1273 LNPs and mRNA-1273.815 LNP-B.

The product quality attribute expected to change most during the manufacturing and distribution of the product is mRNA integrity as assessed by mRNA purity with RP-IP-HPLC. The principal routes of degradation are hydrolytic chain scission, which is measured by the species which elute prior to the main peak (RNA fragments); and the formation of covalent adducts between the RNA and degradants of the cationic lipid, which are relatively hydrophobic and elute after the main peak (RNA-lipid adduct). There is a quantitative correlation between RNA degradation as measured directly and protein expression. The degradation rates can be determined from the purity analysis over different stability timepoints. Based on the stochastic nature of the degradation mechanism, there is a dependence of the rate of degradation on RNA size (length). Since CX-024414 and CX-038839 mRNA have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected for mRNA-1273 LNP and mRNA-1273.815 LNP-B.

No stability data for mRNA-1273.815 LNP-B stored at -70°C±10°C are currently available. The first testing point is 3 months. Data for one month at the storage conditions 5°C for all four batches and at 25°C ± 5°C for one batch included in the stability programme have been provided. As expected OOS results for purity have been observed at 25°C ± 5°C. For batch 5018623001 manufactured at ModernaTX Norwood, OOS results occurred for main peak and RNA lipid adduct; the results were in trend and expected based on OOT limits after 2 weeks at 5°C storage.

A minimum of one mRNA-1273.815 LNP-B Lipid Nanoparticle (LNP) batch per year will be placed on stability. The stability protocol is provided.

In summary, the proposed initial shelf-life of 12 months is acceptable taking into account the supportive data from other mRNA-1273 LNP-B Lipid Nanoparticle (LNP) variants.

3.4. Finished product

The current submission contains the process performance verification data for the mRNA-1273.815 (0.10mg/mL) labelled XBB.1.5 drug product (LDP) in the multidose 10R vial (MDV), single-dose 2R vial (SDV) and pre-filled syringe (PFS).

Stability data for all presentations and sites will be submitted post-approval.

This application includes the following CMC changes:

- Introduction of new variant sequence for Omicron XBB.1.5 and update to identity test method (Type II)

- Addition of Microsynth AG to perform identity testing of the mRNA-1273.815 DP in MDV (Type IB)
- Addition of % encapsulation test on labeled XBB.1.5 DP samples (LDP) for continued process monitoring purpose with an action limit ≥ 85%, when DP process alternative 2 is used (Type IB)

mRNA-127.815 MDV

Description and composition of the finished product

The description of the finished product mRNA-1273.815 multidose vial (MDV) is shown in **Table 1**. The mRNA-1273.815 Drug Product (DP) is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains the mRNA (CX-038839) that encodes for the pre-fusion stabilized Spike glycoprotein of XBB 1.5 (Omicron) sub-variant of the 2019-novel Coronavirus (SARS-CoV-2) and four lipids which act as protectants and carriers of the mRNA. The four lipids are: SM-102 (a custom-manufactured, ionizable lipid), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and 1, 2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG). There is no change in the finished product excipients compared to existing presentations. The mRNA-1273.815 Finished Product is supplied as a preservative-free multidose ready-to-use solution at 0.10 mg/mL for intramuscular administration in 10R vial with rubber stopper and an aluminium seal with flip-off plastic cap. The product is available in a pack size of 10 vials.

Table 1: Description of the finished product mRNA 1273.815 MDV

Component		Grade	Function
Total RNA (CX-038839)		Custom	mRNA that encodes for the prefusion stabilized Spike glycoprotein of XBB 1.5 Omicron variant of 2019-novel Coronavirus (SARS-CoV-2)
Lipids	SM-102	Custom	Lipid components of the Finished Product
	Cholesterol	USP, Ph. Eur., JP	
	DSPC	Non-compendial	
	PEG2000-DMG	Non-compendial	
Trometamol (Tris)		USP, Ph. Eur., JPC	Buffer components in Tris buffer [(a)]
Trometamol-HCl (Tris-HCl)		Non-compendial	
Acetic acid (Glacial)		USP/NF, Ph. Eur., BP, JP	Buffer components for Sodium Acetate buffer in LNP
Sodium acetate trihydrate		USP, Ph. Eur., JP, BP	
Sucrose		USP/NF, Ph. Eur., JP	Cryoprotection
Water for injection		USP, Ph. Eur.	Diluent

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; LNP = lipid nanoparticle; q.s. = quantum sufficit

[a] Target pH 7.5

[b] Comprises 0.017 mg sodium

The quantity of Total RNA (CX-038839) in the finished product mRNA 1273.815 MDV is 0.32 mg/vial (3.2 mL fill) and 0.050 mg/dose (0.5 mL dose).

Pharmaceutical development

Formulation development activities for mRNA-1273 Drug Product leveraged historical knowledge from similar products to develop a suitable formulation for intramuscular injection. The mRNA-1273.815 DP shares the same compositional platform as the prior mRNA-1273 Drug Products. Therefore, all aspects of mRNA-1273 DP development can be extrapolated to mRNA- 1273.815 DP.

Developmental stability studies have been conducted with mRNA-1273 DP prototype as well as multiple monovalent and multivalent variant vaccine DPs. The mRNA-1273 DP sequences are highly similar. The CX-038839 mRNA sequence differs relative to the CX-024414 mRNA prototype sequence, only in the

parts required to incorporate the specific mutations of the variant S protein. A statistical assessment has been performed on the data from various mRNA-1273 and associated variant DP development studies and GMP stability studies. The conclusions from are applicable to the mRNA-1273.815 DP.

Data regarding Rovi SSRR, Dara 1 and Marchesini filling lines has been provided. Data for Catalent (US) will be submitted post-approval.

Comparability of mRNA-1273.815 versus mRNA-1273 LNPs.

The following two elements were included in the comparability study:

1. Evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs).

2. Statistical evaluation of comparability of release testing results.

Extended analytical characterization and forced degradation testing was not performed for mRNA-1273.815 DP as part of comparability studies since the mRNA-1273 DPs characteristics are the same as the mRNA-1273 LNPs, and the extended characterization results for mRNA-1273 LNPs are thus considered representative of mRNA-1273 DPs. Extended characterization testing results for mRNA-1273 LNPs conform to the comparability expected ranges as applicable and are presented in the dossier.

The comparability approach was considered acceptable, however only results for a dummy labelled drug product LDP manufactured according to process alternative 1 (continued processing) were included. Dummy LDP refers to a small amount of UDP which is labelled with a pseudo artwork to simulate the labelling process where the final labels are not yet available.

Manufacture

Sites responsible for manufacturing and testing of the finished product (from mRNA-loaded LNP intermediate to finished product) have been described and valid EU GMP certificates have been provided.

Manufacturers responsible for batch release are:

-Rovi Pharma Industrial Services, S.A., Paseo de Europa 50, 28703 San Sebastián de los Reyes

Madrid, Spain

-Moderna Biotech Spain S.L., Calle del Príncipe de Vergara 132 Plt 12, Madrid 28002, Spain

Description of manufacturing process and process controls of mRNA-1273.815

Representative batch size, composition, and compounding formula for the manufacture of mRNA-1273.815 DP – 0.10 mg/mL MDV are provided. The mRNA-1273.815 specific CPPs and associated PARs, and CIPCs and their associated acceptance criteria are provided in the submission. There are no changes to the approved manufacturing processes at the Rovi SSRR and Catalent sites. The control strategy is also the same with the exception of the mRNA-1273.214 specific CIPC "Weight ratio of LNPs" that does not apply for a monovalent DP. Two alternative manufacturing process flows have been designed for the 0.10 mg/mL drug product and each unit operation along with tables of the associated process parameters are described. In summary, alternative process 1 represents the process with continuous forward processing to finished product. In alternative process 2, filled drug product vials are stored at (-50°C to -15°C) until required for label and pack operations for up to 6 months. The vials are then thawed and labelled. In both process alternatives, a conditioning freeze step then occurs before the vials are transferred to the long term storage condition of -50°C to -15°C. The DP processing duration parameters at 2-8 °C are defined as the completion of LNP thaw (start of DP manufacture) to the beginning of the conditioning freeze step. This duration is monitored as the cumulative process duration (CPD) and process parameters to control time out of refrigeration are also set. These two durations are cumulative

over the course of the process.

The mRNA-1273.815 Drug Product (DP) – 0.10 mg/mL is produced at the Rovi SSRR and Catalent manufacturing sites at a defined scale, according to the same manufacturing process as described for mRNA-1273 DP - 0.10 mg/mL.

Process validation

Since the sites are already registered for mRNA-1273.222, it is acceptable that only one verification batch has been manufactured per site and batch data has been submitted for Rovi, SSRR, Marchesini line, and the Catalent (US) site. Results of CIPCs, CPPs, IPCs, PP and release testing confirm consistent production of the variant vaccine at Rovi, SSRR, Dara 1 and Marchesini lines and Catalent (US).

However, the situation for unlabelled drug product (UDP)/ labelled drug product (LDP) was confusingly described in the dossier and this was corrected upon request. Furthermore, a worst-case scenario LDP was manufactured with processing times higher than the given times for the batch LDP. The applicant satisfactorily explained the worst-case samples and updated section 3.2.P.3.5 with the corrected information referring to the batch.

For Rovi SSRR and Patheon Monza sites (site withdrawn), one palette of dummy LDP (small amount of UDP labelled with a pseudo artwork to simulate the labelling process) was manufactured from unfrozen UDP to obtain results for cumulative (manufacturing) process duration (CPD) and LDP purity. Therefore, process alternative 2 is not represented by these results, because the freeze/thaw step is not included. As a consequence, only process alternative 1 is considered validated.

The applicant was asked to confirm that only vaccine manufactured according to process 1 is released to the EU market or verification and release results and stability programs for process alternative 2 should be submitted. The applicant subsequently responded that for the Rovi, SSRR site, the UDP was indeed frozen before the labelling was conducted therefore representing process alternative 2. Process 2 represents worst case therefore both processes 1 and 2 can be considered validated.

It is also confirmed in the validation report for Patheon Monza, that only option 1 is covered by the interim verification report. The registration of the Patheon Monza site has been withdrawn from the submission as investigations around the % encapsulation results for the mRNA-1273.815 DP verification batch are on-going and the dossier will be updated accordingly within the closing sequence.

For the Catalent site, only batches produced with process 1 will be released to the European market until process validation data for process 2 has been submitted and assessed (recommendation 2).

For all sites, PPQ and comparability data has been submitted with the initial submission or during the procedure.

Control of finished product

The release specifications for mRNA-1273.815 FP are provided. The proposed finished product release specification includes tests for appearance (visual), total RNA content by anion exchange chromatography, mRNA identity by reverse transcription/Sanger, purity and product-related impurities by RP-IP-HPLC, % RNA encapsulation by absorbance assay, in vitro translation (methionine labelling), lipid identity and content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000- DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), mean particle size and polydispersity by DLS, pH, osmolality, particulate matter, container content (USP, Ph. Eur. 2.6.17), bacterial endotoxin (Ph. Eur. 2.6.14, kinetic chromogenic method) and sterility (Ph. Eur. 2.6.1) and container closure integrity.

There is no change in the specification except for the introduction of identity specification (included in the

Type II variation), as approved for prototype mRNA-1273 (0.10mg/mL), and the addition of LDP % encapsulation testing with an action limit for XBB.1.5 presentations (Type IB grouped application).

Note that the application to introduce an action limit of ⩾ 85% '% RNA Encapsulation' on labelled drug product (LDP) as a requirement for release, when Process Alternative 2 is used is agreed. This had been requested as a commitment for all presentations and sites during finalisation of procedure II-100-G (finalised 31 August 2023). This action limit will be in place until more data are available and the need of setting a specification can be evaluated.

Analytical methods

There are no changes in analytical methods except for the update of identity test by SOP-1337 (new primers) which has been validated and (is being) transferred to QC sites. Method transfer protocols for Monza and Eurofins have been provided.

Batch analysis

Batch analysis data have been collected on mRNA-1273.815 Drug Product PPQ verification batches from Rovi, Dara 1 and Marchesini line, Catalent and Patheon Monza (this site was subsequently withdrawn). Batch release results are available for the dummy LDPs (small amount of UDP labelled with a pseudo artwork to simulate the labelling process) manufactured according to process alternative 1. The Certificates of Analyses are provided. The batch data also includes the %encapsulation data from LDP. For Catalent, as mentioned before, the verification batch was produced following process 1 (no process 2 data available) and therefore batches from process 2 should not be brought on the European market before the respective data are submitted.

The impurity profile of mRNA-1273.815 Drug Product is the same as that of the mRNA-1273 LNP. No additional impurities are anticipated to form or be introduced during mRNA- 1273.815 DP manufacturing. The impurities present in the mRNA-1273.815 DP are consistent with the mRNA-1273 prototype.

Reference standards

There is no change to the currently registered information for other presentations.

Container closure system

There is no change to the currently registered information for other presentations. To note, the vials are composed of either glass or cyclic olefin polymer.

Stability

The proposed shelf life is 9 months at the intended storage condition of -50°C to -15°C which includes up to 30 days at 2°C to 8°C, or 12 months at -50°C to -15°C which includes up to 14 days at 2°C to 8°C, and 24 hours at 8°C to 25°C as for the previous Spikevax variants.

mRNA-1273 associated variant vaccine sequences include only the changes relative to the CX-024414 mRNA sequence required to incorporate the specific mutations of the variant S protein sequence. The RNA length is highly conserved between the mRNA-1273 vaccine and mRNA 1273 associated variant vaccines. These minor differences in sequence and sequence length have negligible impact on the stability profile of the product.

The extensive data available in the stability program and shelf-life assessment for the prototype mRNA-1273 vaccine is directly applicable to mRNA-1273 associated variant vaccines. Supportive studies are provided in section 3.2.P.2.3.

The dummy LDP batches placed on stability have been manufactured according to manufacturing process 2. Only release data are currently available. Stability data will be provided post-approval. When Process

Alternative 2 is used, Process Performance Qualification (PPQ) and annual stability samples representative of the LDP will be selected.

A minimum of one mRNA-1273.815 Drug Product (DP) – 0.10 mg/mL Multiple-dose vial batch per year will be placed on stability. Stability testing will be conducted to the specifications provided. Samples representative of the LDP will be placed on stability at -25℃ to -15℃. During assessment, it was raised that the post-approval annual stability program should cover the worst-case storage conditions: maximum interim storage time of 6 months (if process alternative 2 is used) plus 9 months -20°C including 30 days 2-8°C followed by 24 h 25°C. The applicant should commit to update the annual stability program to reflect the long-term storage conditions of 9 months at -20°C including 30 days at 2-8°C followed by 24h at 25°C, in an end-to-end stability annual program, for all sites. The applicant does not wish to include the maximum interim storage of 6 month at UDP level. The applicant should, with the future response to the commitment, provide a detailed justification why the inclusion of the full interim storage is not considered needed, to supplement the high-level information already provided (recommendation 3).

The proposed shelf-life is acceptable, since it has been shown that RNA degradation rate is comparable to previous variants.

mRNA-1273.815 SDV

Description and composition of the finished product

The composition is identical to the MDV presentation except this is a single not multidose presentation. The same container closure system as existing SDV presentations is used. The product is available in pack sizes of 1 and 10 vials.

Table 2: Description of the finished product mRNA 1273.815 SDV

Component		Grade	Function
Total RNA (CX-038839)		Custom	mRNA that encodes for the prefusion stabilized Spike glycoprotein of XBB 1.5 Omicron variant of 2019-novel Coronavirus (SARS-CoV-2)
Lipids	SM-102	Custom	Lipid components of the Finished Product
	Cholesterol	USP, Ph. Eur., JP	
	DSPC	Non-compendial	
	PEG2000-DMG	Non-compendial	
Trometamol (Tris)		USP, Ph. Eur., JPC	Buffer components in Tris buffer [(a)]
Trometamol-HCl (Tris-HCl)		Non-compendial	
Acetic acid (Glacial)		USP/NF, Ph. Eur., BP, JP	Buffer components for Sodium Acetate buffer in LNP
Sodium acetate trihydrate		USP, Ph. Eur., JP, BP	
Sucrose		USP/NF, Ph. Eur., JP	Cryoprotection
Water for injection		USP, Ph. Eur.	Diluent

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; LNP = lipid nanoparticle; q.s. = quantum sufficit

[a] Target pH 7.5

[b] Comprises 0.017 mg sodium

The quantity of Total RNA (CX-038839) in the finished product mRNA 1273.815 SDV is 0.065 mg/vial (0.65 mL fill) and 0.050 mg/dose (0.5 mL dose).

Pharmaceutical development

See section mRNA-1273.815 MDV

Comparability of mRNA-1273.815 versus mRNA-1273 LNPs.:

The following two elements were included in the comparability study of SDV produced at the Patheon, Ferentino site:

1. Evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs).

2. Statistical evaluation of comparability of release testing results.

Extended analytical characterization and forced degradation testing was not performed for mRNA-1273.815 DP as part of comparability studies since the mRNA-1273 DPs characteristics are the same as the mRNA-1273 LNPs, and the extended characterization results for mRNA-1273 LNPs are thus considered representative of mRNA-1273 DPs. Extended characterization testing results for mRNA-1273 LNPs conform to the comparability expected ranges as applicable. CIPC and IPC results were reviewed for consistency as part of the comparability demonstration and all results were within control limits. All release results of the mRNA-1273.815 DP verification lot conformed to both the specification and comparability acceptance criteria. The comparability approach of mRNA-1273.815 SDV produced at the Patheon, Ferentino site versus mRNA-1273 LNPs is in principle acceptable, however only results for LDP manufactured according to process alternative 1 (continued processing) are included (see questions raised regarding process verification). Therefore, only process alternative 1 is considered validated currently.

Manufacture

Sites responsible for manufacturing and testing of the finished product (from mRNA-loaded LNP intermediate to finished product) have been described and valid EU GMP certificates have been provided.

Manufacturers responsible for batch release are:

-Patheon Italia S.p.A., 2 Trav. SX Via Morolense 5, 03013 Ferentino (FR), Italy-Moderna Biotech Spain S.L., Calle del Príncipe de Vergara 132 Plt 12, Madrid 28002, Spain

Description of manufacturing process and process controls of mRNA-1273.815

Representative batch size, composition, and compounding formula for the manufacture of mRNA-1273.815 DP (50 mcg) at Patheon (Ferentino) are provided.

The mRNA-1273.815 Drug Product (DP) in single-dose vial (SDV) is produced at defined scale according to the same manufacturing process described for mRNA-1273.214 DP in SDV (this is the Original/Omicron BA.1 DP). The manufacturing process and process controls described for mRNA-1273.214 SDV are applicable to either monovalent or multivalent mRNA-1273 DP in SDV, with the exception of the weight ratio of pooled LNP in-process control that does not apply for a monovalent DP. The mRNA-1273.815 specific CPPs and associated PARs, and CIPCs and their associated acceptance criteria are provided in the submission. The control strategy is unchanged.

Process validation

Verification was performed at Patheon Ferentino.

Since the sites are already registered for other Spikevax SDV presentations, it is acceptable that only one verification batch has been manufactured. Results of CIPCs, CPPs, IPCs, PP and release testing confirm consistent production of the variant vaccine, although the applicant was asked to clarify the manufacturing process time, indicating that this was indeed representative of the full process. The

relevant documentation was updated.

The Patheon Ferentino verification lot was manufactured from one palette of unfrozen UDP. Therefore, process alternative 2 is not represented by these results because the freeze/thaw step is not included. Therefore, only process alternative 1 is considered validated. The applicant was asked to confirm that only vaccine manufactured according to process 1 is released on the EU market or verification and release results and stability program for process alternative 2 should be submitted. The applicant responded that verification was performed with a batch from process 1 and justified this with the fact that process two is already qualified for mRNA-1273.214 and mRNA-1273.222. Therefore, the applicant stated that because alternative process 2 was successfully validated for mRNA-1273.214 and mRNA-1273.222 at Patheon Ferentino, verification of alternative process 2 process was not repeated for introduction of the new mRNA-1273.815 sequence at this site. This statement is acknowledged however in light of differences in certain parameters between UDP and LDP following alternative process 2 it was clearly stated in pre-submission meetings that verification should be performed with alternative process 2 lots.

Verification results from additional sampling for PA2 will be submitted by 08 September 2023. The Sponsor will not commercialize any PA2 material from Patheon Ferentino to the European market until this commitment is complete (recommendation 4). This means that until the commitment is fulfilled only alternative process one is licensed for the Patheon Ferentino site.

Control of finished product

The release specifications for mRNA-1273.815 FP are provided. The proposed finished product release specification includes tests for appearance (visual), total RNA content by anion exchange chromatography, mRNA identity by reverse transcription/Sanger, purity and product-related impurities by RP-IP-HPLC, % RNA encapsulation by absorbance assay, in vitro translation (methionine labelling), lipid identity and content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000- DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), mean particle size and polydispersity by DLS, pH, osmolality, particulate matter, container content (USP, Ph. Eur. 2.6.17), bacterial endotoxin (Ph. Eur. 2.6.14, kinetic chromogenic method) and sterility (Ph. Eur. 2.6.1) and container closure integrity.

There is no change in specification except for the introduction of identity specification, as approved for prototype mRNA-1273 (0.10mg/mL) (included in the Type II variation) and the addition of LDP % encapsulation testing with an action limit (Type IB).

Note that the application to introduce an action limit of $\geqslant$ 85% '% RNA Encapsulation' on labelled drug product as a requirement for release, when Process Alternative 2 is used is agreed. This had been requested as a commitment for all presentations and sites during finalisation of procedure II-100-G (finalised 31 August 2023). This will be in place until more data are available and the need for setting a specification can be evaluated.

Analytical methods

There are no changes in analytical methods except for the update of identity test by SOP-1337 (new primers) which has been validated and is being transferred to QC sites. A method transfer report from Patheon Ferentino has been provided.

Batch analysis

Batch analysis data have been collected on one mRNA-1273.815 50 mcg single-dose vial Drug Product GMP batch from Patheon Ferentino. Batch release results are available for the dummy LDPs manufactured according to process alternative 1. The impurity profile of mRNA-1273.815 Drug Product (DP) is the same as that of the mRNA-1273 LNP.

Reference standards

There is no change to the currently registered information for other presentations.

Container closure system

There is no change to the currently registered information for other presentations. To note, the single dose vials are composed of glass.

Stability

The proposed shelf life is 9 months at the intended storage condition of -50°C to -15°C which includes up to 30 days at 2°C to 8°C, or 12 months at -50°C to -15°C which includes up to 14 days at 2°C to 8°C, and 24 hours at 8°C to 25°C as for the previous Spikevax variant vaccines.

The dummy LDP batch placed on stability has been manufactured according to process alternative 1. Only release data are currently available. The proposed shelf-life is acceptable, since it has been shown that RNA degradation rate of mRNA-1273.815 Drug Product is comparable to previous variants. Stability data will be provided post-approval. When Process Alternative 2 is used, Process Performance Qualification (PPQ) and annual stability samples representative of the LDP will be selected.

A minimum of one (1) mRNA-1273.815 Drug Product (DP) SDV per year will be placed on stability. The mRNA-1273.815 Drug Product annual post approval stability protocol is provided. Samples representative of the LDP will be placed on stability at -25℃ to -15℃. The applicant commits to update the annual stability program by end of September to reflect the long-term storage conditions of 9 months at -20°C including 30 days at 2-8°C followed by 24h at 25°C, in an end-to-end stability annual program for all sites (recommendation 3).

mRNA-1273.815 PFS

Description and composition of the finished product

The composition is shown in **Table 3** and is the same as described for MDV and SDV in this AR. The pre-filled syringe contains a single dose of 0.5 mL. The same container closure system as existing PFS presentations is used. The product is available in pack sizes of 1 and 10 pre-filles syringes.

Table 3: Description of the finished product mRNA 1273.815 PFS

Component		Grade	Function
Total RNA (CX-038839)		Custom	mRNA that encodes for the prefusion stabilized Spike glycoprotein of XBB 1.5 Omicron variant of 2019-novel Coronavirus (SARS-CoV-2)
Lipids	SM-102	Custom	Lipid components of the Finished Product
	Cholesterol	USP, Ph. Eur., JP	
	DSPC	Non-compendial	
	PEG2000-DMG	Non-compendial	
Trometamol (Tris)		USP, Ph. Eur., JPC	Buffer components in Tris buffer [(a)]
Trometamol-HCl (Tris-HCl)		Non-compendial	
Acetic acid (Glacial)		USP/NF, Ph. Eur., BP, JP	Buffer components for Sodium Acetate buffer in LNP
Sodium acetate trihydrate		USP, Ph. Eur., JP, BP	
Sucrose		USP/NF, Ph. Eur., JP	Cryoprotection
Water for injection		USP, Ph. Eur.	Diluent

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG = polyethylene glycol 2000 dimyristoyl glycerol; LNP = lipid nanoparticle; q.s. = quantum sufficit

[a] Target pH 7.5

[b] Comprises 0.017 mg sodium

The quantity of Total RNA (CX-038839) in the finished product mRNA 1273.815 SDV is 0.050 mg/dose (0.5 mL dose).

Pharmaceutical development (CTD module 3.2.P.2)

See sections -mRNA-1273.815 MDV and SDV.

Comparability of mRNA-1273.815 versus mRNA-1273 LNPs:

The following two elements were included in the comparability study:

1. Evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs).

2. Statistical evaluation of comparability of release testing results.

Extended analytical characterization and forced degradation testing was not performed for mRNA-1273.815 DP as part of comparability studies since the mRNA-1273 DPs characteristics are the same as the mRNA-1273 LNPs, and the extended characterization results for mRNA-1273 LNPs are thus considered representative of mRNA-1273 DPs. Extended characterization testing results for mRNA-1273 LNPs conform to the comparability expected ranges.

mRNA-1273.815 DP – 50 mcg - PFS at Rovi San Sebastian los Reyes (SSRR):

CIPC and IPC results were reviewed for consistency as part of the comparability demonstration and all results were within control limits.

All release results of mRNA-1273.815 DP PFS verification lot conformed to both the specification and comparability acceptance criteria.

mRNA-1273.815 DP – 50 mcg - PFS at Rovi JC:

CIPC and IPC results were reviewed for consistency as part of the comparability demonstration and all results were within control limits.

All release results of mRNA-1273.815 DP PFS verification lot conformed to both the specification and comparability acceptance criteria.

Manufacture

Sites responsible for manufacturing and testing of the finished product (from mRNA-loaded LNP intermediate to finished product) have been described and valid EU GMP certificates have been provided.

Manufacturers responsible for batch release are:

-Rovi Pharma Industrial Services, S.A., Julián Camarillo (Rovi JC), Calle Julián Camarillo 35, 28037 Madrid, Spain

-Rovi Pharma Industrial Services, S.A., San Sebastián de los Reyes (Rovi SSRR), Paseo de Europa 50, 28703. San Sebastián de los Reyes Madrid, Spain

-Moderna Biotech Spain S.L., Calle del Príncipe de Vergara 132 Plt 12, Madrid 28002, Spain

Description of manufacturing process and process controls of mRNA-1273.815

Representative batch size and manufacturing formula for the manufacture of mRNA-1273.815 DP PFS at Rovi JC and Rovi SSRR are provided in the submission. The DP process produces up to 250,000 syringes. Two alternative manufacturing process flows have been designed for the 0.10 mg/mL drug product.

Process Alternative 1 consists of the process with continuous forward processing. Process Alternative 2 consists of the process where a bulk syringe interim frozen state storage step after visual inspection, has been added. There is no change in the control strategy except for the identity and weight ratio of pooled LNP critical IPC that does not apply for a monovalent vaccine. The mRNA-1273.815 specific CPPs and associated PARs, and CIPCs and their associated acceptance criteria are provided in the submission. Since the sites are already registered for other Spikevax PFS presentations, it is acceptable that only one verification batch has been manufactured.

The mRNA-1273.815 Drug Product (DP) in the prefilled syringe (PFS) presentation – 0.10 mg/mL is produced at the Rovi SSRR and Rovi JC manufacturing sites at a defined scale, according to the same manufacturing process as described for mRNA-1273 DP - 0.10 mg/mL in PFS.

Process validation

Rovi SSRR:

PPQ verification was performed on the Dara 3 fill line at Rovi, which is representative of all the manufacturing lines already used at the same manufacturing site (Dara 1 and Marchesini lines).

All CQAs, CPPs, and CIPCs met the acceptance criteria defined in the PPQ verification protocol and the DP Commercial Control Strategy. All IPCs were confirmed to be within target ranges. A dummy LDP batch has been manufactured to obtain results for final CPD and %RNA purity. The applicant clarified that the batch produced at Rovi SSRR was manufactured according to process 2 and updated the respective documents.

Rovi JC:

A process performance qualification (PPQ) verification of the PFS was performed at Rovi JC on the Optima filling line.

All CQAs, CPPs, and CIPCs met the acceptance criteria defined in the PPQ verification protocol and the DP Commercial Control Strategy. All IPCs were confirmed to be within target ranges. The applicant clarified that no dummy LDP was manufactured. Instead, the LDP activities were performed on the entire batch according to process alternative 2. So, both process 1 and process 2 are covered. An updated PPQ report will be provided post-approval (recommendation 5).

Control of finished product

An updated specification for mRNA-1273.815 Drug Product (DP) has been provided. The following attributes have been included in the specification for mRNA-1273.815 Drug Product (DP): appearance, total RNA content by anion exchange chromatography, mRNA identity by reverse transcription/Sanger sequencing, purity and product-related impurities by RP-IP-HPLC, % RNA encapsulation by absorbance assay, in vitro translation by methionine labelling, lipid identity and content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), mean particle size and polydispersity by DLS, pH, osmolality, particulate matter, deliverable volume, bacterial endotoxins (Ph. Eur. 2.6.14), sterility (Ph. Eur. 2.6.1), break loose and gliding force. This specification differs from the specification for mRNA-1273 LNP-B only with respect to the identity test.

Note that the application to introduce an action limit of ⩾ 85% '% RNA Encapsulation' on labelled drug product (LDP) as a requirement for release, when Process Alternative 2 is used is agreed. This had been requested as a commitment for all presentations and sites during finalisation of procedure II-100-G (finalised 31 August 2023). This will be in place until more data are available and the need of setting a specification can be evaluated.

Analytical methods

There are no changes in analytical method except for the update of identity test by SOP-1337 (new primers) which has been validated and transferred to QC sites.

Batch analysis

Batch analyses data have been generated for one mRNA-1273.815 DP - 50 mcg - PFS batch according to the approved specifications at both manufacturing sites (Rovi JC and Rovi SSRR). As clarified by the company, batch release results are available for the LDPs manufactured according to process alternative 2.

The impurity profile of mRNA-1273.815 Drug Product (DP) is the same as that of the mRNA-1273 LNP.

Reference standards

There is no change to the currently registered information for other presentations.

Container closure system

There is no change to the currently registered information for other presentations. To note, the pre-filled syringes are composed of cyclic-olefin polymer.

Stability

The proposed shelf life is 9 months at the intended storage condition of -50°C to -15°C which includes up to 30 days at 2°C to 8°C, or 12 months at -50°C to -15°C which includes up to 14 days at 2°C to 8°C, and 24 hours at 8°C to 25°C, as for the previous Spikevax variant vaccines.

The applicant clarified upon request that the provided information was wrong for the stability program for the PPQ lots. The corrected data was provided clarifying that lot from process 2 were used in stability studies and the manufacturing date was for LDP not UDP batches. Stability data will be provided post-approval. When Process Alternative 2 is used, Process Performance Qualification (PPQ) and annual stability samples representative of the LDP will be selected.

Samples representative of the LDP will be placed in stability in accordance with the annual post approval stability protocol for the mRNA-1273 - 0.10 mg/mL PFS. The post-approval annual stability program should cover the worst-case storage conditions: maximum interim storage time of 6 months (if process alternative 2 is used) plus 9 months -20°C including 30 days 2-8°C followed by 24 h 25°C. The applicant commits to update the annual stability program by end of September to reflect the long-term storage conditions of 9 months at -20°C including 30 days at 2-8°C followed by 24h at 25°C, in an end-to-end stability annual program (recommendation 3)

The proposed shelf-life is acceptable, since it has been shown that RNA degradation rate of mRNA-1273.815 Drug Product is comparable to previous variants.

3.5. Discussion on chemical, and pharmaceutical and biological aspects

During this application pertaining to:

- the addition of a new strain (Omicron XBB.1.5, andusomeran) resulting in six new monovalent presentations and
- to use Analytical testing site, Microsynth AG, Balgach Switzerland, as an alternative site responsible for Reverse Transcription Sanger Sequencing (RTSS) batch quality control testing for identity of the finished product,

- to add an action limit of ≥ 85% to the specification '% RNA Encapsulation' on labelled drug product (LDP) as a requirement for release, when Process Alternative 2 is used

no major objections were raised.

Questions were raised during the procedure regarding editorial/ documentation errors and they have been or will be corrected in the closing sequence unless otherwise specified.

The key OC raised on the active substance side was the need to implement an annual stability study that reflects the actual shelf life claim (3 month at -15 to -25°C before transfer to -60 to -90°C) (recommendation 1).

On the FP side, Moderna has established two process alternatives for FP manufacturing: unlabelled drug product (UPD) is directly labelled to become labelled drug product (LDP) or UPD is frozen and can be stored at -20°C for up to 6 months before it is thawed and labelled to become LDP. So far only purity and % encapsulation is tested at LDP with recommendations on-going in different procedures (II-100-G) to re-assess the need to test other parameters at LDP. Confirmation has been sought that LDP from process 2 (considered worst-case) not UDP is used for stability programs. For the purposes of this application, the clarification provided regarding the absence of verification of worst-case process 2 in process validation studies has resulted in several recommendations:

1. Moderna is asked to commit that from the Catalent site and for the Patheon Ferentino site, only FP batches produced with process 1 will be submitted to the European market until process validation data for process 2 has been submitted and assessed (recommendations 2 and 4).
2. Verification results from additional sampling for alternative process 2 at Patheon Ferentino submitted on 08 September 2023 were not deemed sufficient to support the use of process alternative 2 at this site.

The applicant has also committed to provide an updated PPQ report for Rovi JC by end of September 2023 (recommendation 5). For all other sites, PPQ reports have been provided with the initial submission or during the procedure.

Upon request, the applicant has committed to update the annual stability program for DP by end of September to reflect the long-term storage conditions of 9 months at -20°C including 30 days at 2-8°C followed by 24h at 25°C, in an end-to-end stability annual program for all manufacturing sites (recommendation 3)

Finally, during the procedure the Patheon Monza FP site was withdrawn. No further data were provided for mRNA-1273.815 batches manufactured at this site as part of this procedure, as investigations around the % encapsulation results for the mRNA-1273.815 DP verification batch are on-going.

After considering the answers to the questions raised, the quality data is deemed sufficient subject to the below recommendations.

3.6. Conclusions on the chemical, pharmaceutical and biological aspects

The submitted quality data are acceptable subject to the below recommendations.

3.7. Recommendations for future quality development

1. The applicant commits to submit a revised Section 3.2.S.7.2 {CX-038839} by the end of September 2023 to reflect the AS shelf-life claim, including the optional interim storage at -25°C to -15°C in the annual stability protocol.
2. Moderna is asked to commit that from the Catalent site only, FP batches produced with process 1 will be submitted to the European market until process validation data for process 2 has been submitted and assessed.
3. The applicant commits to update the annual stability program for DP by end of September to reflect the long-term storage conditions of 9 months at -20°C including 30 days at 2-8°C followed by 24h at 25°C, in an end-to-end stability annual program for all manufacturing sites. The applicant is asked to commit that with this submission a detailed justification will be provided why the inclusion of the full interim storage is not considered needed to supplement the high-level response already provided.
4. The applicant should commit to not commercialise any PA2 material from Patheon Ferentino to the European market until acceptable process verification data has been submitted and assessed
5. The applicant commits to provide an updated PPQ report for Rovi JC by end of September 2023.

4. Non-clinical aspects

4.1. Introduction

The MAH submitted non-clinical data in support of the authorisation of the monovalent SARS-CoV-2 vaccine mRNA-1273.815, based on previous authorised monovalent SARS-CoV-2 vaccine mRNA-1273. mRNA-1273.815 includes a single mRNA, which encodes for the XBB.1.5 Omicron subvariant.

For this variation, the MAH presented non-clinical data from 3 studies. The non-clinical data comprises of non-GLP immunogenicity studies conducted in young mice.

The new variant vaccines are produced with the same LNP composition than the parental mRNA-1273 vaccine. All mRNAs are formulated into a mixture of the four LNP lipids SM-102, cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and PEG2000-DMG. A sufficient pharmacokinetics and toxicity data package was already provided for the MAA of mRNA-1273.Due to the same vaccine platform, no new pharmacokinetic or toxicity data were provided for the variant vaccines.

4.2. Pharmacology

Primary pharmacodynamic studies

Study MOD-6037: Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice

In this study, the immunogenicity of a primary series of the SARS-CoV-2 XBB.1.5-containing vaccines was evaluated in mice. The test articles were:

- The monovalent mRNA-1273.815; it contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.5/XBB.1.9.1 Omicron subvariant (note: the spike protein of XBB.1.9.1 is identical to that of XBB.1.5)
- The bivalent mRNA-1273.231 vaccine. It is a 1:1 bench side mix of mRNA-1273.045, which

contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the BA.4/BA.5 subvariants of Omicron, and mRNA-1273.815.

- The monovalent mRNA-1273.045
- The bivalent mRNA-1273.222 vaccine, which is a co-formulation of mRNA-1273 (single mRNA encoding the Wuhan-Hu-1 SARS-CoV-2 S-2P antigen) and mRNA-1273.045 vaccines.

The monovalent mRNA-1273.045 and the bivalent mRNA-1273.222 vaccines served as controls. PBS was used as negative control.

Preclinical mRNA-1273, mRNA-1273.045, mRNA-1273.815 and mRNA-1273.222 were prepared with the same method as the Good Manufacturing Practice clinical drug products.

Six- to eight-week-old BALB/c mice (n=8/group) received two intramuscular injections of PBS control article or 1 µg mRNA vaccines as a primary series 3 weeks apart (Day 1 and Day 22). Blood was collected from all animals on Day 21 (three weeks after Dose 1) and Day 36 (two weeks after Dose 2). Serum samples were analysed for Wuhan-Hu-1 spike protein-specific (S-2P) binding IgG antibody responses via ELISA and subvariant-specific neutralising antibody responses via VSV-based PSVNA.

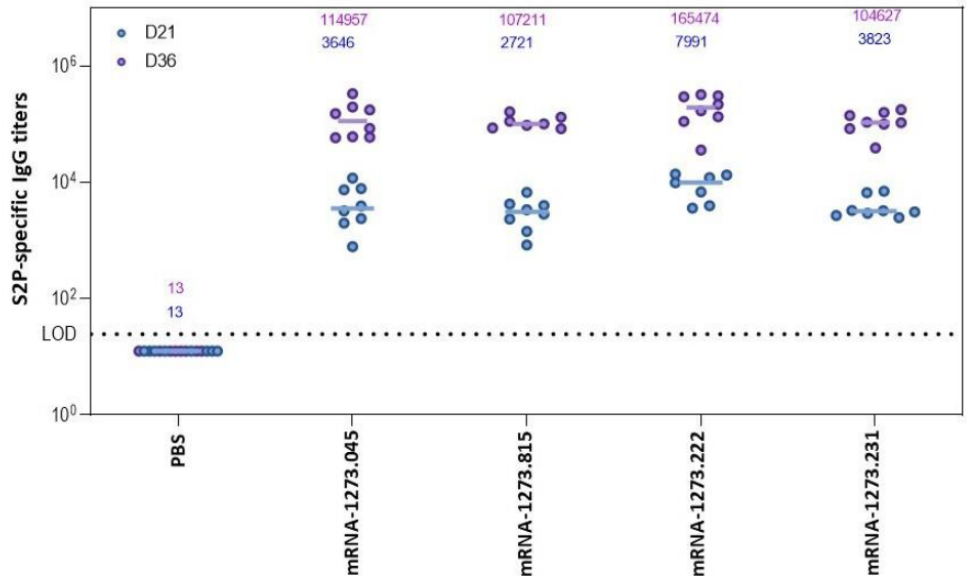
Table 4: Study design for Study MOD-6037

Group (n=8)	Treatment (IM)	Dose Level (µg)	Dose Schedule	Readouts
1	PBS	0	Day 1, Day 22	**Serum (Day 21, Day 36)** bAb response (ELISA) and **Serum (Day 36)** nAb response (VSV-PSVNA)
2	mRNA-1273.045	1 µg		
3	mRNA-1273.815	1 µg		
4	mRNA-1273.222	1 µg		
5	mRNA-1273.231	1 µg		

Abbreviations: bAb=binding antibody; ELISA=enzyme linked immunosorbent assay; IM=intramuscular; nAb=neutralizing antibody; PBS=phosphate-buffered saline; PSVNA=pseudovirus neutralization assay; VSV=vesicular stomatitis virus.

All tested mRNA-1273 vaccine variants showed three weeks after the first vaccine dose a similar high spike protein-specific binding IgG antibody response in serum. Two weeks after the second dose, the binding antibody increased further in all mRNA-1273 variant vaccinated mice. The XBB.1.5-specific vaccines obtained high S-2P binding antibody titres comparable to the binding antibody titres observed in mice administered monovalent mRNA-1273.045 and bivalent mRNA-1273.222.

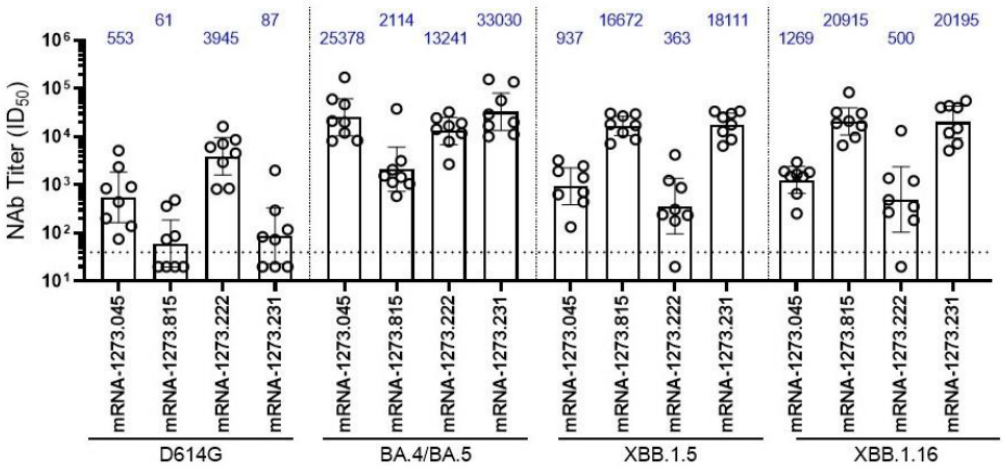
Figure 1: Binding Antibody Responses in BALB/c mice after primary serios vaccination



Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LOD= limit of detection; PBS=phosphate-buffered saline.
Note: GMT values are presented at the top of each figure, with red indicating the GMT for Day 21 (3 weeks after the first dose) and blue indicating the GMT for Day 36 (2 weeks after the second dose). The dotted line indicates LOD of the assay.

On Day 36, mice that received monovalent mRNA-1273.815 or bivalent mRNA-1273.231 had the highest neutralising antibody titres against XBB.1.5 and XBB.1.16. Mice that received mRNA-1273.045 or mRNA-1273.222 had lower serum neutralising antibody titres against XBB.1.5 and XBB.1.16. Neutralising antibody titres against XBB.1.5 and against XBB.1.16 were comparable by treatment groups. Thus, the MAH suggested that these strains are antigenically similar. Among mice that received monovalent mRNA-1273.815 or bivalent mRNA-1273.231, neutralising antibody titres against D614G were very low. mRNA-1273.231 had higher titres against the BA.4/BA.5 strains compared to the mRNA-1273.815 vaccine, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. In the mRNA-1273.045 group, the highest neutralising antibody titres were against BA.4/BA.5, followed by XBB.1.16, XBB.1.5, and D614G. In the mRNA-1273.222 group, the highest neutralising antibody titres were against BA.4/BA.5, followed by D614G, XBB.1.16 and XBB.1.5.

Figure 2: Neutralising Antibody Responses in BALB/c Mice After primary series vaccination



Abbreviations: GMT=geometric mean titer; ID_{50}=inhibitory dilution 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody.
Note: Blue numbers and bars represent GMTs, and whiskers represent 95% confidence interval. The dotted line indicates LLOQ of the assay.

Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice (MOD-5827)

The objective of this study was to evaluate the immunogenicity of a booster dose of monovalent (mRNA-1273.815) and bivalent (mRNA-1273.231) SARS-CoV-2 XBB.1.5-containing vaccines in mice that have received primary series vaccination with mRNA-1273. The monovalent mRNA-1273.045 vaccine and the bivalent mRNA-1273.222 were used as controls. PBS was used as a negative control.

The parental monovalent mRNA-1273 vaccine was administered as a primary series (Dose 1 and Dose 2). mRNA-1273.815, mRNA-1273.231, mRNA-1273.045, and mRNA-1273.222 were administered as a booster dose (Dose 3). The bivalent mRNA-1273.231 vaccine is a 1:1 bench side mix of mRNA-1273.045 and mRNA-1273.815. Preclinical mRNA-1273, mRNA-1273.045, mRNA-1273.815, and mRNA-1273.222 were prepared with the same method as the Good Manufacturing Practice clinical drug products.

Six- to eight-week-old BALB/c mice (n=8/group) were administered 0.5 µg mRNA-1273 on Day 1 and Day 22. Approximately ten weeks after the second dose (Day 92), these mice were boosted with 1 µg mRNA-1273.045, mRNA-1273.815, mRNA-1273.222, or mRNA-1273.231.

Blood samples were collected on Day 21 (three weeks after Dose 1), on Day 36 (two weeks after Dose 2), on Day 91 (one day before the booster dose), and at Day 106 (two weeks after the booster dose). Samples were analysed for serum Wuhan-Hu-1 spike protein-specific binding IgG antibodies using ELISA and neutralising antibodies using VSV-based PSVNA.

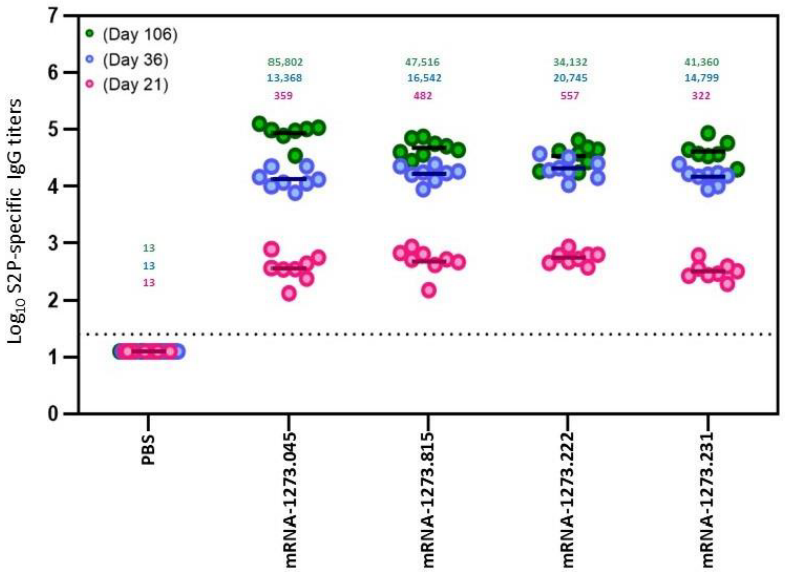
Table 5: Study Design for Study MOD-5827

Group (n=8)	Primary Series			Booster			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	Serum (Day 21, Day 36, Day 106) bAb response (ELISA) Serum (Day 91, Day 106) nAb response (VSV-PSVNA)
1	PBS Control	0	Day 1 Day 22	PBS Control	0	Day 92	
2	mRNA-1273	0.5		mRNA-1273.045	1		
3	mRNA-1273	0.5		mRNA-1273.815	1		
4	mRNA-1273	0.5		mRNA-1273.222	1		
5	mRNA-1273	0.5		mRNA-1273.231	1		

Abbreviations: bAb=binding antibody; ELISA=enzyme-linked immunosorbent assay; IM=intramuscular; nAb=neutralizing antibody; PBS=phosphate-buffered saline; PSVNA=pseudovirus neutralization assay; VSV=vesicular stomatitis virus.

Three weeks after mRNA-1273 Dose 1 (Day 21), the anti-Wuhan S-2P IgG binding antibody titres were low in all vaccinated mice. Two weeks after the second mRNA-1273 dose (Day 36), the binding antibody titres increased significantly in all vaccinated mice, increasing 34- to 46-fold from Day 21. By Day 106, robust binding antibody titres against Wuhan S-2P were observed in all vaccine groups, which only moderately increased compared to Day 36 antibody titre. mRNA-1273.045 induced slightly higher anti-Wuhan S-2P binding antibody response compared to mRNA-1273.815, mRNA-1273.231 and mRNA-1273.222, which elicited comparable anti-Wuhan S2P-binding antibody titres after boosting.

Figure 3: Binding Antibody Responses in BALB/c Mice After Boosting With Third Dose



Abbreviations: IgG=immunoglobulin G; LLOQ=lower limit of quantification; PBS=phosphate-buffered saline; S-2P=spike protein with 2 proline substitutions within the heptad repeat 1 domain.
Note: GMT values are presented at the top of each figure, with pink indicating the GMT for Day 21 (3 weeks after the first dose), blue indicating the GMT for Day 36 (2 weeks after the second dose), and green indicating the GMT for Day 106 (2 weeks after the booster dose). The dotted line indicates LLOQ of the assays.

On Day 91 (pre-boost), robust neutralising antibody titres against D614G were observed in all vaccine groups. Neutralising antibody titres against BA.4/BA.5 at Day 91 were very low in all vaccinated mice. Negligible neutralising antibody titres were observed against XBB.1.5 and XBB.1.16 in all vaccinated mice.

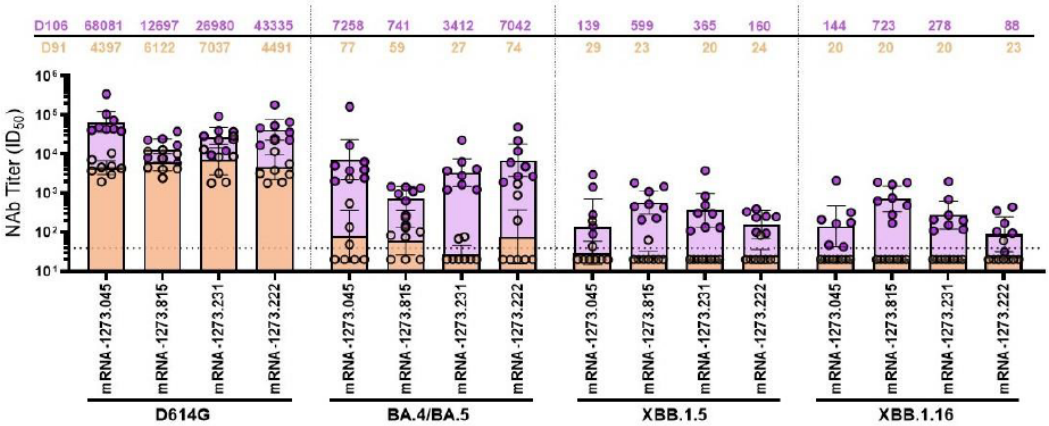
Two weeks after boosting (Day 106), mice that received monovalent mRNA-1273.815 or bivalent mRNA-

1273.231 showed slightly higher serum neutralising antibody titres against XBB.1.5 and XBB.1.16 compared to mice that received mRNA-1273.045 or mRNA-1273.222. Overall, all vaccinated mice showed a significant increase of neutralising antibody titres against XBB.1.5 and XBB.1.16 after the booster dose, but only up to a moderate level.

In addition, all vaccinated mice showed a significant increase of neutralising antibody titres against BA.4/BA.5 after the booster dose. However, the mRNA-1273.815 group showed the lowest neutralising antibody titre at a moderate level, compared to mRNA-1273.045, mRNA-1273.231 or mRNA-1273.222 vaccinated mice, which induced a ~ 5- to 10-fold higher neutralisation titres.

Furthermore, mice that received monovalent mRNA-1273.815 or bivalent mRNA-1273.231 showed a small increase of anti-D614G neutralising antibody titres. In comparison, mRNA-1273.045 and mRNA-1273.222 vaccinated mice developed slightly higher anti-D614G neutralising antibody responses.

Figure 4: Neutralising Antibody Responses in BALB/c Mice After Boosting With Third Dose



Abbreviations: ID_{50}=the inhibitory dilutions 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
Note: GMT values are presented at the top of each figure, with orange indicating the GMT for Day 91 (pre-boost) and purple indicating the GMT for Day 106 (2 weeks after the booster dose). The dotted line indicates LLOQ of the assays.

Study MOD-5972: Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice

In this study, the immunogenicity was evaluated of a booster dose of monovalent and bivalent SARS-CoV-2 XBB.1.16-containing vaccines in mice that have received primary series vaccination with parental mRNA-1273. The study was conducted with the monovalent mRNA-1273.116 vaccine, which contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.16 Omicron subvariant, and the bivalent mRNA-1273.234 vaccine, which is a 1:1 bench side mix of separately formulated mRNA-1273.045 and mRNA-1273.116 vaccines.

mRNA-1273 vaccine was administered as a primary series (Dose 1 and Dose 2). mRNA-1273.116 or mRNA-1273.234 were administered as a booster dose (Dose 3). PBS was used as a negative control.

Preclinical mRNA-1273 and mRNA-1273.045 were prepared with the same method as the Good Manufacturing Practice mRNA-1273 and mRNA-1273.045 clinical drug products. Preclinical material for mRNA-1273.116 was prepared with the representative manufacturing process conditions for mRNA-1273.116, with the exception of the IDR sequence present in the 3′ UTR. However, the MAH included an IDR sequences of up to 25 nucleotides in the 3′ UTR of the final clinical drug substance to facilitate

analytical detection. Because UTR regions are noncoding and therefore will not be translated into proteins, these modifications have no impact on the quality attributes, stability profile, functional activity, or safety of the mRNA product according to the sponsor.

Six- to eight-week-old BALB/c mice (n=8/group) were administered intramuscularly 0.5 µg mRNA-1273 on Day 1 and Day 22 (primary series). On Day 71, mice were boosted with 1 µg of mRNA-1273.116 or mRNA-1273.234. Blood samples were collected on Day 21 (three weeks after Dose 1), on Day 36 (two weeks after Dose 2), on Day 70 (before the booster dose), and on Day 85 (two weeks after the booster dose). Samples were analysed for serum Wuhan-Hu-1 spike protein-specific binding IgG antibodies via ELISA and SARS-CoV-2 variant specific neutralising antibodies using VSV-based PSVNA.

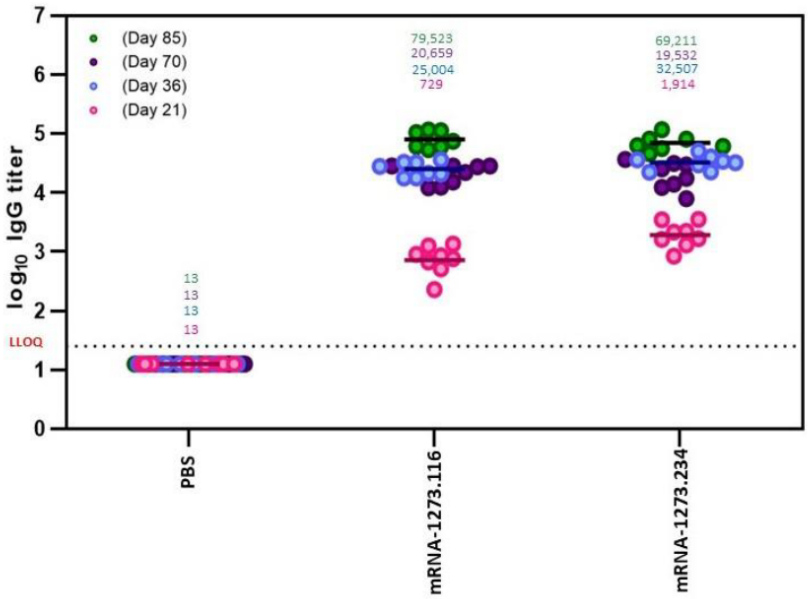
Table 6: Study Design for Study MOD-5972

Group (n=8)	Primary Series			Booster			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	
1	PBS Control	0	Day 1 Day 22	PBS Control	0	Day 71	**Serum (Day 21, Day 36, Day 70, Day 85)** bAb response (ELISA)
2	mRNA-1273	0.5		mRNA-1273.116	1		**Serum (Day 21, Day 70, Day 85)** nAb response (VSV-PSVNA)
3	mRNA-1273	0.5		mRNA-1273.234	1		

Abbreviations: bAb=binding antibody; ELISA=enzyme-linked immunosorbent assay; IM=intramuscular; nAb=neutralizing antibody; PBS=phosphate-buffered saline; PSVNA=pseudovirus neutralization assay; VSV=vesicular stomatitis virus.

Three weeks after the first mRNA-1273 dose, anti-S-2P IgG binding antibody titres were low in all vaccinated mice. Two weeks after the second mRNA-1273 dose, anti-S-2P IgG binding antibody titres increased significantly in vaccinated mice. By Day 70, anti-S-2P IgG binding antibody titres dropped slightly in the vaccinated mice. Two weeks after boosting with the variant vaccines, both vaccines elicited a comparable 4-fold increase in binding IgG antibody titres from Day 70 pre-boost.

Figure 5: Binding Antibody Responses in BALB/c Mice After Boosting (Third Dose)



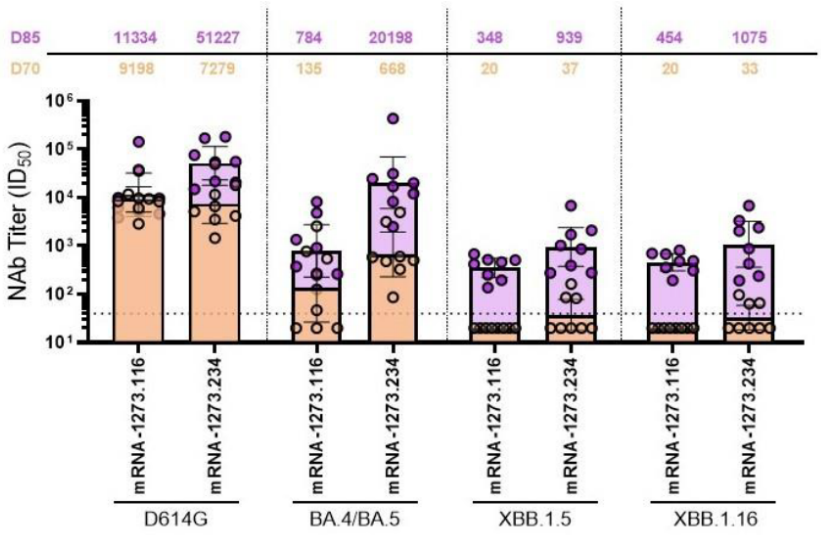
Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LLOQ=lower limit of quantification; PBS=phosphate-buffered saline.
Note: GMT values are presented at the top of each figure, with red indicating the GMT for Day 21 (3 weeks after the first dose) and blue indicating the GMT for Day 36 (2 weeks after the second dose). The dotted line indicates LLOQ of the assay.

On Day 70 (pre-boost), robust neutralising antibody titres against D614G were observed in all vaccinated mice. However, neutralising antibody titres against BA.4/BA.5 were lower compared with those against D614G. Negligible neutralising antibody responses were observed against XBB.1.5 and XBB.1.16 in many mice, indicating substantial immune escape from mRNA-1273 vaccination for these strains.

Two weeks after boosting, mice that received mRNA-1273.116 or mRNA-1273.234 showed increased neutralising antibody titres against XBB.1.5 and XBB.1.16 up to a moderate level. The neutralising antibody titres against XBB.1.5 and XBB.1.16 were slightly higher in mRNA-1273.234 vaccinated mice.

Neutralising antibody titres against BA.4/BA.5 were remarkably higher in the bivalent mRNA-1273.234 mice compared to mRNA-1273.116 mice, consistent with the inclusion of BA.4/BA.5 in the vaccine. Bivalent mRNA-1273.234 also boosted titres against D614G to a greater extent compared to the monovalent mRNA-1273.116.

Figure 6: Neutralising Antibody Responses in BALB/c Mice After Boosting (Third Dose)



Abbreviations: D-Day; GMT=geometric mean titer; ID_{50}=inhibitory dilution 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody.
Note: Blue numbers and bars represent GMTs, and whiskers represent 95% confidence interval. The dotted line indicates LLOQ of the assay.

4.3. Discussion on non-clinical aspects

To support the approval of the Omicron XBB.1.5 variant vaccine, the MAH showed in two non-clinical pharmacodynamics studies that monovalent mRNA-1273.815 (and bivalent mRNA-1273.231) induced moderate neutralising antibody titres against XBB.1.5 and spike protein-specific binding antibody titres after two dose primary vaccination series in naïve mice and after one booster dose in mRNA-1273-primed mice. XBB.1.5-specific neutralising antibody titres were not detected in mice vaccinated only with parental mRNA-1273, indicating substantial immune escape from mRNA-1273 vaccination for Omicron XBB subvariants. Furthermore, vaccination with monovalent mRNA-1273.815 (or bivalent mRNA-1273.231) increased D614G-specific and BA.4/BA.5-specific neutralising antibody titre in mice.

A third non-clinical study submitted showed that the XBB.1.16-specific vaccines, monovalent mRNA-1273.116 and bivalent mRNA-1273.234, elicited similar immunogenicity responses in mice. The measured neutralising antibody titres against XBB.1.5 were comparable to titres against XBB.1.16 in the conducted non-clinical immunogenicity studies. Thus, XBB.1.5 and XBB.1.16 seems to be antigenically similar.

Additional toxicity or pharmacokinetic studies were not conducted and were not considered necessary due

to the high similarity to the parental mRNA-1273 vaccine, which is based on the same platform. This was acceptable.

4.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that from a non-clinical perspective, mRNA-1273.815 is approvable.

5. Clinical Efficacy aspects

5.1. Methods – analysis of data submitted

Study Design and Objectives

mRNA-1273-P205 is a phase 2/3 open-label study in adults to evaluate the safety and immunogenicity of SARS-CoV-2 variant-containing vaccine candidates against COVID-19. P205 part J evaluates the safety, reactogenicity and immunogenicity of a 50 µg dose of the mRNA-1273.815 vaccine which contains 50 µg mRNA of the Omicron XBB.1.5 spike protein and of the mRNA-1273.231 vaccine which contains equal mRNA amounts of the Omicron XBB.1.5 and Omicron BA.4/BA.5 spike proteins (25 µg XBB.1.5 / 25 µg BA.4/BA.5). The vaccines were administered as a fifth dose to adults who previously received a two-dose primary series and a booster dose of an original COVID-19 vaccine and another booster dose of a bivalent (Original + Omicron BA.4/BA.5) vaccine.

The two groups were randomised 1:1 in an open-label fashion. The P205 part J study endpoints and objectives as per P205 study protocol version 10, are included in the following table.

Table 7: Part J - Booster dose of mRNA-1273.815 (50 µg) or mRNA-1273.231 (50 µg): Participants who previously received a primary series of mRNA vaccine, a first booster dose of a monovalent mRNA vaccine, and a second booster dose of a bivalent mRNA vaccine against SARS-CoV-2

Objectives	Endpoints
Primary	
• To evaluate the immunogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg) against SARS-CoV-2 Omicron BA.4/BA.5, BQ.1.1, and XBB.1.5 subvariants at Day 15 and Day 29	• Antibody response of mRNA-1273.815 (50 µg) and mRNA-1273.231(50 µg) against SARS-CoV-2 Omicron BA.4/BA.5, BQ.1.1, and XBB.1.5 subvariants by GMT, geometric mean fold rise (GMFR), and SRR at Day 15 and Day 29
• To evaluate the safety and reactogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg)	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after injection • Unsolicited AEs during the 28-day follow-up period after injection • SAEs, MAAEs, AEs leading to withdrawal, and AESI from Day 1 to Day 181 (EoS)
Exploratory	
• To evaluate the immunogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg) against SARS-CoV-2 variants at any study timepoint	• Antibody response of mRNA-1273.815 (50 µg) and mRNA-1273.231(50 µg) against SARS-CoV-2 variants by GMT, GMFR, and SRR at any study timepoint
• To assess for symptomatic and asymptomatic SARS-CoV-2 infection	• Laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection will be defined in participants: – Primary case definition per the mRNA-1273-P301 (COVE) study – Secondary case definition based on the CDC criteria: the presence of 1 of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample – Asymptomatic SARS-CoV-2 infection is defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for antinucleocapsid antibody after a negative test at time of enrollment

Only immunogenicity results from Day 15 were provided. All analyses were descriptive; there was no hypothesis testing pre-specified with respect to the immune responses. Lastly, per the study protocol, surveillance for COVID-19 events as an exploratory objective begins 14 days after the booster dose, it is therefore not applicable to the Day 15 interim analysis.

Study population, demographics, and baseline characteristics

P205J participants were enrolled between 25 April 2023 and 27 April 2023. Their baseline characteristics (including age, gender, interval between prior doses and evidence of prior SARS-CoV-2 infection) are shown in the below table.

Table 8: Select demographics and study participants characteristics (Safety Set)

	mRNA-1273.815 N = 50	mRNA-1273.231 N = 51
Mean Age – Years (SD)	51.6 (15.2)	48.4 (15.2)
Median Age – Years (range)	54.5 (21, 84)	48.0 (24, 82)
≥ 65 years, n (%)	11 (22.0%)	7 (13.7%)
Female, n (%)	30 (60.0%)	31 (60.8%)
Non-white, n (%)	5 (10%)	10 (19.6%)
Months between 2nd and 3rd Dose, median (Q1, Q3)	8.2 (7.8, 9.8)	9.2 (7.8, 12.2)
Months between 3rd and 4th Dose, median (Q1, Q3)	9.8 (8.3, 10.3)	9.2 (8.2, 10.3)
Months between 4th and 5th Dose, median (Q1, Q3)	8.2 (8.1, 8.3)	8.3 (8.1, 8.4)
Prior SARS-CoV-2 Infection, n (%)	34 (68.0%)	40 (78.4%)

SD=standard deviation

Source: 14.1.3.1.10

Overall, 101 adult participants were randomised between two arms; 50 participants received mRNA-1273.815 and 51 participants received mRNA-1273.231. The mean age was 51.6 and 48.4 years in the mRNA-1273.815 and mRNA-1273.231 groups, respectively. Eleven of 50 (22%) mRNA-1273.815 and 7 of 51 (13.7%) were above 65 years of age. The interval between the fourth dose (BA.4/BA.5 bivalent vaccine) and the investigational vaccine dose in P205J was a median of 8.2 months and 8.3 months for the mRNA-1273.815 and mRNA-1273.231 groups, respectively. Intervals between prior doses (second and third, third and fourth) were also balanced between the two groups. Lastly, 34 of 50 (68%) and 40 of 51 (78.4%) participants in the mRNA-1273.815 and mRNA-1273.231 groups, respectively, had evidence of SARS-CoV-2 infection (positive SARS-CoV-2 anti-nucleocapsid antibody test or positive baseline SARS-CoV-2 polymerase chain reaction, PCR, test) prior to receiving the investigational vaccine.

5.2. Results

Immunogenicity

There was no pre-specified hypothesis on the immune responses elicited by the mRNA-1273.815 and mRNA-1273.231 vaccines and no statistical testing was performed for an immunogenicity comparison between the two randomised groups; all analyses were descriptive.

The baseline, Day 15 neutralising antibody responses (Geometric Mean Titres, GMT) and the Geometric Mean Fold Rises (GMFRs) after the mRNA-1273.815 and mRNA-1273.231 doses are shown below.

In addition, seroresponse (at least 4-fold rise from baseline) rates (SRR) are provided for BA.4/BA.5 and D614G. SRR are calculated only when the pseudovirus assay has an established lower limit of quantification (LLOQ) in a validated assay (D614G, BA.4/BA.5). The XBB.1.5, XBB.1.16 and BQ.1.1 are qualified assays. All assays were performed at the Duke University laboratories using consistent methods (Chalkias et al, NEJM, 2022).

Table 9: Day 15 Neutralising antibody titres, Pre-protocol immunogenicity set

	mRNA-1273.815 50 µg (N=49)		mRNA-1273.231 50 µg (N=50)	
XBB.1.5	n		n	
Pre-booster, GMT (95% CI)	49	154.7 (106.8, 224.1)	50	158.8 (109.9, 229.3)
Day 15, GMT (95% CI)	49	2579.0 (1809.1, 3676.7)	50	1838.1 (1265.9, 2668.9)
Day 15, GMFR (95% CI)	49	16.7 (12.8, 21.7)	50	11.6 (8.7, 15.4)
XBB.1.16				
Pre-booster, GMT (95% CI)	47	221.0 (153.9, 317.3)	50	193.9 (134.1, 280.3)
Day 15, GMT (95% CI)	49	2262.6 (1570.1, 3260.6)	50	1799.9 (1297.2, 2497.5)
Day 15, GMFR (95% CI)	47	11.4 (8.5, 15.4)	50	9.3 (7.0, 12.3)
BA.4/BA.5				
Pre-booster, GMT (95% CI)	49	1540.7 (1127.2, 2105.8)	50	1878.1 (1350.9, 2611.1)
Day 15, GMT (95% CI)	49	9673.4 (6965.6, 13433.8)	50	9904.8 (7610.8, 12890.1)
Day 15, GMFR (95% CI)	49	6.3 (4.8, 8.2)	50	5.3 (3.9, 7.1)
BQ.1.1				
Pre-booster, GMT (95% CI)	48	347.5 (249.5, 483.9)	50	312.8 (221.4, 441.9)
Day 15, GMT (95% CI)	49	1894.1 (1383.2, 2593.6)	50	1895.4 (1348.2, 2664.7)
Day 15, GMFR (95% CI)	48	5.8 (4.7, 7.3)	50	6.1 (4.6, 7.9)
D614G				
Pre-booster, GMT (95% CI)	49	2780.3 (2146.5, 3601.3)	50	2421.3 (1788.4, 3278.1)
Day 15, GMT (95% CI)	49	7749.7 (5943.7, 10104.3)	49	5860.9 (4558.0, 7536.3)
Day 15, GMFR (95% CI)	49	2.8 (2.2, 3.5)	49	2.3 (1.9, 2.8)

n = number of observations at corresponding timepoint
Antibody values reported as below the lower limit of quantification (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.
Antibody values reported as below the lower limit of detection (LOD) are replaced by 0.5 x LOD.
Source: 14.2.1.10.10

Overall, the XBB.1.5 monovalent mRNA-1273.815 and the XBB.1.5 + BA.4/BA.5 bivalent mRNA-1273.231 elicited potent neutralising responses at Day 15 against all variants evaluated: XBB.1.5, XBB.1.16, BA.4/BA.5, BQ.1.1 and D614G. Results for the sub-groups "without prior SARS-CoV-2 infection" and "with prior SARS-CoV-2 infection" are provided were also provided.

Table 10: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 "overall" (i.e., irrespective of prior SARS-CoV-2 infection).

Overall	n=50	mRNA=1273.815	mRNA-1273.231
XBB.1.5	Pre-booster	154.7	158.8
	Day 15	2579.0	1838.1
XBB.1.16	Pre-booster	221.0	193.9
	Day 15	2262.6	1799.9
BA.4/BA.5	Pre-booster	1540.7	1878.1
	Day 15	9673.4	9904.8
BQ.1.1	Pre-booster	347.5	312.8
	Day 15	1894.1	1895.4
D614G	Pre-booster	2780.3	2421.3
	Day 15	7749.7	5860.9

Table 11: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 in sub-group "without prior SARS-CoV-2 infection"

w/o prior infection	n=16/n=11	mRNA=1273.815	mRNA-1273.231
XBB.1.5	Pre-booster	81.7	65.2
	Day 15	1639.3	1256.9
XBB.1.16	Pre-booster	133.7	71.6
	Day 15	1409.5	1452.8
BA.4/BA.5	Pre-booster	691.3	844.4
	Day 15	6254.4	9269.3
BQ.1.1	Pre-booster	247.7	142.2
	Day 15	1438.3	1376.1
D614G	Pre-booster	2179.9	1772.2
	Day 15	7743.5	6226.5

Table 12: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 in sub-group "with prior SARS-CoV-2 infection"

with prior infection	n=33/n=39	mRNA=1273.815	mRNA-1273.231
XBB.1.5	Pre-booster	210.8	204.1
	Day 15	3212.8	2046.1
XBB.1.16	Pre-booster	273.5	256.9
	Day 15	2846.2	1912.0
BA.4/BA.5	Pre-booster	2272.3	2353.1
	Day 15	11951.0	10091.8
BQ.1.1	Pre-booster	405.3	3907.0
	Day 15	2164.5	2075.6
D614G	Pre-booster	3128.4	2644.0
	Day 15	7752.7	5770.7

Figure 7: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 "overall" (i.e., irrespective of prior SARS-CoV-2 infection)

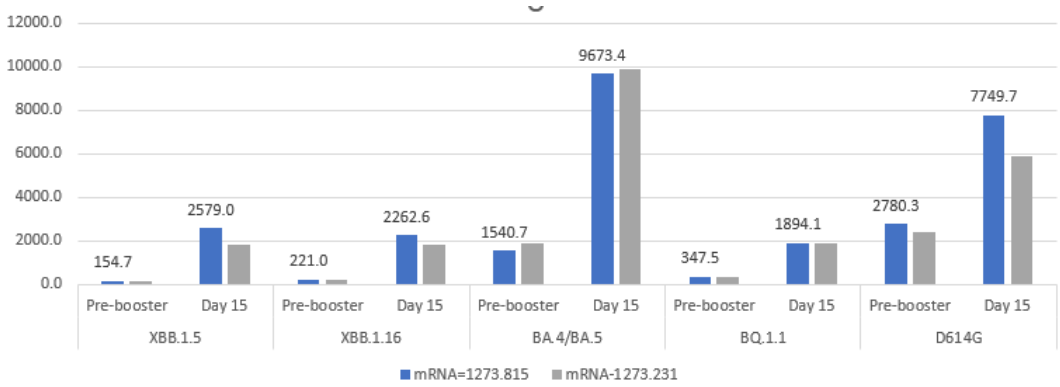


Figure 8: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 in sub-group "without prior SARS-CoV-2 infection"

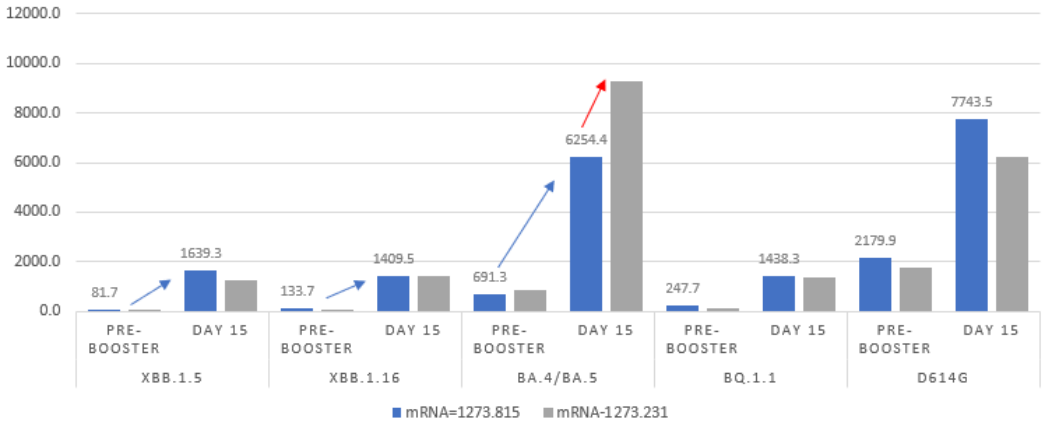
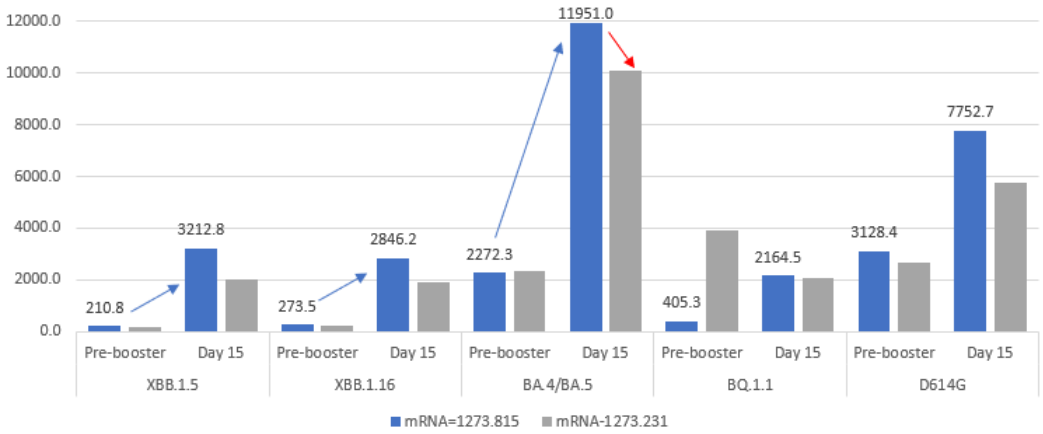


Figure 9: Neutralising Ab GMTs after booster vaccination with Spikevax monovalent SARS-CoV-2 XBB.1.5 or Spikevax bivalent SARS-CoV-2 XBB.1.5+BA.4/BA.5 in sub-group "with prior SARS-CoV-2 infection"



Neutralising Ab values against SARS-CoV-2 variants are shown only for baseline titres and titres 15 days after vaccination with Spikevax XBB.1.5. Booster vaccination with Spikevax XBB.1.5 increases nAb titres against all tested SARS-CoV-2 variants (XBB.1.5, XBB.1.16, BA.4/BA.5, BQ.1.1 and ancestral D614G).

Baseline titres against different variants differ substantially. In the sub-group of previously not SARS-CoV-2 infected participants, baseline titres against D614G (ancestral strain) and BA.4/BA.5 are substantially higher than nAb GMTs against XBB.1.5, XBB.1.16 and BQ.1.1. This is expected as the participants have received prior vaccination against D614G (ancestral strain) as a primary series and a first booster, followed by bivalent booster vaccination against SARS-CoV-2 original+BA.4/BA.5. Expectedly, in the sub-group of participants without prior SARS-CoV-2 infection bivalent Spikevax BA.4/BA.5+XBB.1.5 further increases nAB GMTs against BA.4/BA.5 as compared to booster vaccination with monovalent Spikevax XBB.1.5.

Neutralising Ab GMTs against XBB.1.5, XBB.1.16 and BQ.1.1 after booster vaccination with Spikevax XBB.1.5 are overall expectedly higher in participants with prior SARS-CoV-2 infection but are comparable within each of the particular sub-groups (with or without prior SARS-CoV-2 infection).

Interestingly, in the sub-group of participants with prior SARS-CoV-2 infection booster vaccination with bivalent Spikevax BA.4/BA.5+XBB.1.5 does not elicit higher nAB GMTs against SARS-CoV-2 BA.4/BA.5 as

compared to booster vaccination with monovalent Spikevax XBB.1.5. There is no obvious reason for this finding which needs to remain an observation.

Regarding seroconversion rates, for mRNA-1273.815 and mRNA-1273.231 the Day 15 D614G SRR (95% CI) was 32.7% (19.9%, 47.5%) and 22.4% (11.8%, 36.6%) respectively and the BA.4/BA.5 SRR was 69.4% (54.6%, 81.7%) and 62.0% (47.2%, 75.3%), respectively. It should be noted that for BA.4/BA.5 and D614G the pre-booster titres were numerically higher than the pre-booster titres of other variants (XBB.1.5, XBB.1.16, BQ.1.1) given that all participants had been previously vaccinated with the original and the Original + BA.4/BA.5 bivalent vaccines.

5.3. Discussion

The MAH presented immunogenicity results from study P205 part J on booster vaccination with monovalent Spikevax XBB.1.5 (mRNA-1273.815) and bivalent Spikevax BA.4/BA.5+XBB.1.5 (mRNA-1273.231) day 15 after vaccination.

Results were presented only descriptively, partially due to the limited sample size of about 50 participants per group. Participants in the two groups were overall sufficiently well balanced. Due to the small sample size analyses must be considered with caution, in particular, for sub-group analyses.

It is understood that the participants were followed since the primary vaccination series. Before any of the tested vaccinations, a SARS-CoV-2 anti-nucleocapsid antibody test or PCR test was performed. The resulting group of participants with prior SARS-CoV-2 infection therefore needs to be considered heterogeneous with regards to time since infection and infecting SARS-CoV-2 variant.

Overall, booster vaccination with Spikevax XBB.1.5 increased nAb titres against all tested SARS-CoV-2 variants (XBB.1.5, XBB.1.16, BA.4/BA.5, BQ.1.1 and ancestral D614G). Due to the relatively recent emergence of the SARS-CoV-2 variants XBB.1.5, XBB.1.16 and BQ.1.1, and given the experience with this assay against other SARS-CoV-2 variants, for which the assays were validated, use of qualified assays for this submission as opposed to fully validated assays was considered acceptable.

Baseline titres against different variants differ substantially. In the subgroup of previously not SARS-CoV-2 infected participants, baseline titres against D614G (ancestral strain) and BA.4/BA.5 were substantially higher than nAb GMTs against XBB.1.5, XBB.1.16 and BQ.1.1. This was expected as the participants have received prior vaccination against D614G (ancestral strain) as a primary series and a first booster, followed by bivalent booster vaccination against SARS-CoV-2 original+BA.4/BA.5. Expectedly, in the subgroup of participants without prior SARS-CoV-2 infection, bivalent Spikevax BA.4/BA.5+XBB.1.5 further increased nAB GMTs against BA.4/BA.5 as compared to booster vaccination with monovalent Spikevax XBB.1.5.

Neutralising Ab GMTs against XBB.1.5, XBB.1.16 and BQ.1.1 after booster vaccination with Spikevax XBB.1.5 were overall expectedly higher in participants with prior SARS-CoV-2 infection but were comparable within each of the particular subgroups (with or without prior SARS-CoV-2 infection). Interestingly, in the subgroup of participants with prior SARS-CoV-2 infection booster vaccination with bivalent Spikevax BA.4/BA.5+XBB.1.5 did not elicit higher nAB GMTs against SARS-CoV-2 BA.4/BA.5 as compared to booster vaccination with monovalent Spikevax XBB.1.5. There is no obvious reason for this finding which remains as an observation.

In summary, booster vaccination with Spikevax XBB.1.5 increased nAb GMTs against all tested SARS-CoV-2 variants in both subgroups, with and without prior SARS-CoV-2 infection. Results from both sub-groups are important in the current epidemiological situation as an increase in nAb GMTs after booster vaccination with Spikevax XBB.1.5 in participants without prior SARS-CoV-2 infection provides the impact of the vaccination as such, and an increase in nAb GMTs in participants with prior SARS-CoV-2 infection

(or overall population with or without prior SARS-CoV-2 infection) can be considered a real-world scenario.

According to the WHO, recently the EG.5 and BA.2.86 variants warrant close scrutiny. The MAH has informed on the availability of cross-neutralisation data against the EG.5 and BA.2.86 variants showing that the monovalent XBB.1.5 vaccine induces an immune response consistent with the previous Omicron sub-lineages. Therefore, cross-neutralisation data against these variants should be formally submitted in the variation dossier (**REC**).

5.4. Conclusion on the clinical efficacy aspects

The CHMP is of the opinion that the clinical immunogenicity data provided for Spikevax XBB.1.5 (mRNA-1273.815) is deemed acceptable.

The CHMP considers the following measures necessary to address the clinical efficacy issues:

1. According to the WHO, recently the EG.5 and BA.2.86 variants warrant close scrutiny. The MAH has informed on the availability of cross-neutralisation data against the EG.5 and BA.2.86 variants showing that the monovalent XBB.1.5 vaccine induces an immune response consistent with the previous Omicron sub-lineages. Therefore, cross-neutralisation data against these variants should be formally submitted in the variation dossier.

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

Clinical data have been provided from the clinical study P205 Part J to support this variation.

Study mRNA-1273-P205 is an open label, phase 2/3 study in adults to evaluate the safety and immunogenicity of SARS-CoV-2 variant-containing vaccine candidates against COVID-19. P205 part J evaluates the safety, reactogenicity and immunogenicity of a 50 µg dose of the mRNA 1273.815 vaccine and of the mRNA-1273.231 vaccine. The vaccines were administered as a fifth dose to adults who previously received a two-dose primary series, a booster dose of an original COVID-19 vaccine and a booster dose of a bivalent (Original + Omicron BA.4/BA.5) vaccine. The two groups were randomised 1:1 in an open-label fashion.

The safety objectives included in the protocol of the Study P205 Part J refer to: Primary Objectives: To evaluate the safety and reactogenicity of mRNA-1273.815 (50 µg) and mRNA-1273.231 (50 µg); Exploratory Objectives: To assess for symptomatic and asymptomatic SARS-CoV-2 infection.

The clinical data cut-off date is 16 May 2023.

6.2. Results

Patient exposure

In study P205 Part J were enrolled 101 participants between 25-27 April 2023. The participants were randomised between two arms. 50 participants received monovalent XBB.1.5 (mRNA-1273.815) vaccine and 51 participants received bivalent XBB.1.5+BA.4/5 (mRNA-1273.231) vaccine.

The median follow-up time for both vaccine groups was 20 days (range 20 to 22 days, data cut-off date 16 May 2023).

Demography

The demographics and baseline characteristics of participants in the Safety Set of study P205J are presented in

Table 8. Participants median age was 54.5 and 48.0 years in the monovalent XBB.1.5 and in the bivalent XBB.1.5+BA.4/5 vaccine groups, respectively. Eleven of 50 (22.0%) participants in the MV XBB.1.5 and 7 of 51 (13.7%) participants in the BV XBB.1.5+BA.4/5 vaccine groups were above 65 years of age. Approximately 68% (34/50) participants in the monovalent XBB.1.5 and 78.4% (40/51) participants in the bivalent XBB.1.5+BA.4/5 vaccine groups, had evidence of prior SARS-CoV-2 infection at the time of vaccination.

The interval between the fourth dose (BA.4/BA.5 bivalent vaccine) and the investigational vaccine dose in P205J was a median of 8.2 months and 8.3 months for the monovalent XBB.1.5 (mRNA-1273.815) and the bivalent XBB.1.5+BA.4/5 (mRNA-1273.231) groups, respectively. Intervals between prior doses (second and third, third and fourth) were also balanced between the two groups.

Adverse events

Safety assessment in Study P205 included monitoring of:

- Solicited local and systemic ARs that occurred during the 7 days following each injection, recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following each injection.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
- SAEs, Medically Attended Adverse Events (MAAEs) and AESIs from the first dose on Day 1 through the entire study period.

Solicited Adverse Reactions

At least 1 solicited ARs were reported within 7 days from 38 (76.0%) participants in the monovalent XBB.1.5 (mRNA-1273.815) vaccine group and from 45 (88.2%) participants in the bivalent XBB.1.5+BA.4/5 (mRNA-1273.231) vaccine group. Most of the reported events were Grade 1 and Grade 2. Grade 3 events were reported from 1 (2.0%) in the MV XBB.1.5 and from 6 (11.8%) in the BV XBB.1.5+BA.4/5. No Grade 4 solicited ARs were reported in both vaccine groups.

Any solicited local ARs were reported from 34 (68.0%) participants in the MV XBB.1.5 and from 43 (84.3%) participants in the BV XBB.1.5+BA.4/5 vaccine group. The most reported local solicited ARs were pain (respectively 68.0% and 82.4%) and axillary swelling and tenderness (respectively 16.0% and 27.5%).

Any solicited systemic ARs were reported from 29 (58.0%) participants in the MV XBB.1.5 and from 33 (64.7%) in the BV XBB.1.5+BA.4/5. The most reported systemic solicited ARs were fatigue (respectively 44.0% and 49.0%), myalgia (38.0% and 37.3%) and headache (respectively 34.0% and 45.1%).

Any fever >38 °C was reported by 3 (6.0%) participants in the MV XBB.1.5 and by 1 (2.0%) participant in the BV XBB.1.5+BA.4/5 in the vaccine groups. Detailed information is presented in the table below.

Table 13: Solicited local and systemic Adverse Reactions (Solicited Safety Set)

Solicited Adverse Reaction	mRNA-1273.815	mRNA-1273.231
Category	50 µg	50 µg
Grade	(N=50)	(N=51)
Solicited Adverse Reactions - N1	50	51
Any Solicited Adverse Reactions	38 (76.0)	45 (88.2)
Grade 1	23 (46.0)	28 (54.9)
Grade 2	14 (28.0)	11 (21.6)
Grade 3	1 (2.0)	6 (11.8)
Solicited Local Adverse Reactions - N1	50	51
Any Solicited Local Adverse Reactions	34 (68.0)	43 (84.3)
Grade 1	26 (52.0)	33 (64.7)
Grade 2	8 (16.0)	7 (13.7)
Grade 3	0	3 (5.9)
Pain - N1	50	51
Any	34 (68.0)	42 (82.4)
Grade 1	28 (56.0)	33 (64.7)
Grade 2	6 (12.0)	7 (13.7)
Grade 3	0	2 (3.9)
Erythema (Redness) - N1	50	51
Any	2 (4.0)	1 (2.0)
Grade 1	1 (2.0)	0
Grade 2	1 (2.0)	0
Grade 3	0	1 (2.0)
Swelling (Hardness) - N1	50	51
Any	5 (10.0)	6 (11.8)
Grade 1	2 (4.0)	3 (5.9)
Grade 2	3 (6.0)	2 (3.9)
Grade 3	0	1 (2.0)
Axillary Swelling or Tenderness - N1	50	51
Any	8 (16.0)	14 (27.5)
Grade 1	8 (16.0)	12 (23.5)
Grade 2	0	2 (3.9)
Grade 3	0	0
Solicited Systemic Adverse Reactions - N1	50	51
Any Solicited Systemic Adverse Reactions	29 (58.0)	33 (64.7)
95% CI	43.2, 71.8	50.1, 77.6
Grade 1	16 (32.0)	17 (33.3)
Grade 2	12 (24.0)	12 (23.5)
Grade 3	1 (2.0)	4 (7.8)
Fever - N1	50	51
Any	3 (6.0)	1 (2.0)
Grade 1	1 (2.0)	1 (2.0)
Grade 2	1 (2.0)	0
Grade 3	1 (2.0)	0
Headache - N1	50	51
Any	17 (34.0)	23 (45.1)
Grade 1	14 (28.0)	17 (33.3)
Grade 2	3 (6.0)	5 (9.8)
Grade 3	0	1 (2.0)
Fatigue - N1	50	51
Any	22 (44.0)	25 (49.0)
Grade 1	12 (24.0)	14 (27.5)
Grade 2	10 (20.0)	9 (17.6)
Grade 3	0	2 (3.9)
Myalgia - N1	50	51
Any	19 (38.0)	19 (37.3)
Grade 1	14 (28.0)	11 (21.6)
Grade 2	5 (10.0)	6 (11.8)
Grade 3	0	2 (3.9)
Arthralgia - N1	50	51
Any	14 (28.0)	15 (29.4)
Grade 1	12 (24.0)	8 (15.7)
Grade 2	2 (4.0)	6 (11.8)
Grade 3	0	1 (2.0)
Nausea/Vomiting - N1	50	51
Any	4 (8.0)	5 (9.8)
Grade 1	4 (8.0)	3 (5.9)
Grade 2	0	2 (3.9)
Grade 3	0	0
Chills - N1	50	51
Any	7 (14.0)	12 (23.5)
Grade 1	5 (10.0)	9 (17.6)
Grade 2	2 (4.0)	3 (5.9)
Grade 3	0	0

N1=Number of exposed subjects with data for the event

Source: 14.3.1.1.1.10

Unsolicited Adverse Events

Up to the cutoff date (16 May 2023), unsolicited AEs, regardless to the relationship to study vaccine were reported from 5 (10.0%) participants in the MV XBB.1.5 and from 7 (13.7%) participants in the BV XBB.1.5+BA.4/5 vaccine groups. Unsolicited AEs, related to study vaccine were reported from 1 (2.0%) participant in the MV XBB.1.5 and from 2 (3.9%) participants in the BV XBB.1.5+BA.4/5 vaccine groups. Out of the unsolicited TEAEs, MAAEs were reported respectively by 4 (8.0%) participants and 4 (7.8%) participants.

Unsolicited adverse events were grade 1 or grade 2 in severity; no grade 3 or higher events were reported. Detailed information is presented in the table below.

Table 14: Unsolicited Adverse Events (Safety Set)

	mRNA-1273.815 50 µg (N=50) n(%)	mRNA-1273.231 50 µg (N=51) n(%)
Unsolicited TEAEs Regardless of Relationship to Study Vaccination		
All	5 (10.0)	7 (13.7)
Serious	0	0
Fatal	0	0
Medically-Attended	4 (8.0)	4 (7.8)
Unsolicited TEAEs Related to Study Vaccination		
All	1 (2.0)	2 (3.9)
Serious	0	0
Fatal	0	0
Medically-Attended	1 (2.0)	0

Source: 14.3.1.7.2.10

In the MV XBB.1.5 group, most of the unsolicited AEs were SOC Infections and infestations, reported in 2 (4.0%) participants: 1 event of upper respiratory tract infection (2.0%) and 1 event of viral infection (2.0%).

In the BV XBB.1.5+BA.4/5 group most of the unsolicited AEs were SOC Infections and infestations, reported in 2 participants (3.9%): 1 event reported Bronchitis (2.0%) and 1 event of Rhinovirus infection (2.0%). Also SOC Blood and lymphatic system disorders, reported in 2 participants (3.9%), both of them in Lymphadenopathy (3.9%).

Unsolicited TEAEs related to study vaccination were reported from 1 (2.0%) participants in the MV XBB.1.5 (1273.815) and from 2 (3.9%) participants in the BV XBB.1.5+BA.4/5 (1273.231) vaccine group. Of those, MAAEs were reported in 1 (2.0%) participants in the MV XBB.1.5 (1273.815) and no MAAEs in the BV XBB.1.5+BA.4/5. The unsolicited AEs considered related to the study vaccine in the MV XBB.1.5 (1273.815) group were: one event of pruritic rash (on Study D13 and reported as ongoing at the cut-off date); and one event of pain in the extremity/left arm pain, started on D13 and resolved on D15.

In the BV XBB.1.5+BA.4/5 group were: one event of chills; one event of arthralgia/joint aches in several joints and one event of fatigue; all considered resolved.

Upon request, the MAH conducted another Interim Analysis up to Day 29 (data cut-off date May 25, 2023); the median (min, max) follow-up duration was 29 days (29, 31 days) for both treatment groups. Unsolicited TEAEs regardless to the relationship to study vaccine were reported from 6/50 participants (12.0%) in the MV XBB.1.5 (1273.815) and from 9/51 participants (17.6%) in the BV XBB.1.5+BA.4/5 (1273.231) vaccine group. Unsolicited TEAEs related to study vaccination were reported from 1 (2.0%) participant in the MV XBB.1.5 (1273.815) and from 3 (5.9 %) participants in the BV XBB.1.5+BA.4/5 (1273.231) vaccine group. Of those, MAAEs were reported in 1 (2.0%) participant in the MV XBB.1.5 and

no MAAEs in the BV XBB.1.5+BA.4/5. There were four non-SAE, non-AESI unsolicited AE reported; 3 were considered non-related to the study investigational product (one event of supraventricular tachycardia; one event of upper respiratory tract infection and one event of hypoesthesia) and one event as vaccine related (Rhinovirus infection).

Discontinuation due to adverse events

There were no unsolicited AEs leading to discontinuation from study vaccine or study participation during the study period.

SAEs, AESIs and Deaths

There were no fatal or serious adverse events and no adverse events of special interest reported until Day 29 (data cut-off date May 25, 2023).

6.3. Discussion on clinical safety

Within this submission the MAH requested the approval for use of the new COVID-19 vaccine formulation mRNA-1273.815 (monovalent XBB.1.5). Clinical data have been provided from the clinical study P205 Part J. The XBB.1.5-containing vaccines, MV XBB.1.5 (mRNA-1273.815) and BV XBB.1.5+BA.4/5 (mRNA-1273.231) were administered as a 3rd Booster dose (fifth dose).

Overall it is observed lower frequency of solicited ARs (including local and systemic ARs) in the MV XBB.1.5 (mRNA-1273.815) compare to the BV XBB.1.5+BA.4/5 (mRNA-1273.231), respectively 76.0% and 88.2%.

Up to the 16th May cut-off date, any solicited local ARs were reported by 68.0 % participants in the MV XBB.1.5 and from 84.3% participants in the BV XBB.1.5+BA.4/5 vaccine group. Pain was the most reported local ARs (respectively 68.0% and 82.4%). Grade 3 events were reported by 0 and 3 (5.9%) participants respectively. No grade 4 events were reported.

Any solicited systemic ARs were reported from 58.0% participants in the MV XBB.1.5 and 64.7% in the BV XBB.1.5+BA.4/5 vaccine group. The most reported systemic solicited ARs was fatigue (respectively 44.0% and 49.0%). Grade 3 events were respectively reported by 1 (2.0%) and 4 (7.8%) participants. No grade 4 events were reported.

Any fever >38 ºC was reported by 3 (6.0%) participants in the MV XBB.1.5 and by 1 (2.0%) participants in the BV XBB.1.5+BA.4/5 vaccine groups. Grade 3 event fever was reported in 1 participant (2.0%) in the MV XBB.1.5 vaccine group.

Up to the 25th May data cut-off, unsolicited TEAEs regardless to the relationship to study vaccine were reported from 6/50 participants (12.0%) in the MV XBB.1.5 (1273.815) and from 9/51 participants (17.6%) in the BV XBB.1.5+BA.4/5 (1273.231) vaccine group. Unsolicited TEAEs related to study vaccination were reported from 1 (2.0%) participants in the MV XBB.1.5 (1273.815) and from 3 (5.9 %) participants in the BV XBB.1.5+BA.4/5 (1273.231) vaccine group. Of those, MAAEs were reported in 1 (2.0%) participant in the MV XBB.1.5 and no MAAEs in the BV XBB.1.5+BA.4/5. There were no grade 3 or higher reported events.

There were no events leading to discontinuation from participation in the study. There were no deaths, no SAEs and no AESIs reported.

There were no clinical data on the use of the Spikevax MV XBB.1.5 (mRNA-1273.815) vaccine in adolescents and children and the MAH confirmed that are no ongoing studies administering mRNA-1273.815 in adolescents and young children. The assumption of acceptable reactogenicity and safety data in these age groups can be based on the safety data extrapolation from the use of the Spikevax MV

XBB.1.5 (mRNA-1273.815) vaccine in adults and the large amount of data from Spikevax Original and Spikevax bivalent adapted vaccines from the clinical studies and post marketing settings.

The safety of Spikevax XBB.1.5 have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. No data are available yet regarding the use of MV XBB.1.5 during pregnancy and during breast feeding. This is acceptable for the purpose of this variation.

XBB.1.5-containing vaccines (monovalent 1273.815, bivalent 1273.231) given as a fifth dose were well tolerated. Taken together, in this limited study population of 101 participants the frequency and severity of reported local reactions and systemic events appears to be similar to prior doses of the original mRNA-1273 vaccine and the bivalent BA.4/BA.5 vaccine mRNA-1273.222.

No new safety concern was detected in this small study population with a short follow up time.

6.4. Conclusions on clinical safety

The CHMP is of the opinion that the clinical safety data provided for Spikevax XBB.1.5 (mRNA-1273.815) is deemed acceptable.

7. Changes to the Product Information

As a result of this variation, relevant sections of the SmPC, labelling and package leaflet are being updated to adequately reflect the addition of a new strain (Omicron XBB.1.5, andusomeran).

The MAH is taking the opportunity to include editorial changes into the SmPC, Annex II, labelling and package leaflet.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

8. Overall conclusion and impact on the benefit/risk balance

With this type II variation, the MAH sought the introduction of a monovalent vaccine targeting SARS-CoV-2 Omicron strain XBB.1.5 to assist in the continued management of COVID-19. This is in line with EMA/ECDC statement, where it was recommended that "*the inclusion of a strain belonging to the XBB family of Omicron subvariants is adequate to ensure cross-reactivity against current dominant and emerging strains, and XBB.1.5 is considered as a reasonable choice to increase the breadth of immunity also against XBB descendent lineages*".

The MAH has submitted a full quality data package for Omicron XBB.1.5 active substance and monovalent finished product formulations. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Concerning quality, the provided data are acceptable, however the manufacturing site Patheon Monza was withdrawn during the procedure.

The MAH has provided mouse immunogenicity data comparing the response of the Omicron XBB.1.5 vaccine with that of the bivalent Original/Omicron BA.4-5 and of the investigational bivalent Omicron BA.4-5/Omicron XBB.1.5 vaccine for both primary series and booster. In both cases, the XBB.1.5 containing vaccines provided a superior response to XBB.1.5 strain. The monovalent XBB.1.5 vaccine showed a higher response than the bivalent. These data were acceptable.

The MAH also provided clinical data related to the on-going clinical study P205 Part J, which evaluates safety, reactogenicity and immunogenicity of the monovalent XBB.1.5 (mRNA 1273.815) vaccine and the

bivalent XBB.1.5+BA.4/5 (mRNA-1273.231) vaccine administered as a fifth dose. The use of this vaccine as booster vaccination increased nAb GMTs against all tested SARS-CoV-2 variants (XBB.1.5, XBB.1.16, BA.4/BA.5, BQ.1.1 and ancestral D614G). This is suggestive of an adequate boosting response. The safety data provided for Spikevax MV XBB.1.5 (mRNA-1273.815) was deemed acceptable and no concerns were raised.

The benefit-risk balance of Spikevax, remains positive.

9. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variations requested		**Type**	**Annexes affected**
B.I.a.6.a	B.I.a.6.a - Changes to the active substance of a vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine	Type II	I, IIIA, IIIB and A
B.II.b.2.a	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	Type IB	None
B.II.d.1.z	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	Type IB	None

B.I.a.6.a (Type II): Addition of a new strain (XBB.1.5, andusomeran) resulting in six new monovalent presentations: Spikevax XBB.1.5 0.1 mg/mL dispersion for injection (2.5 mL multidose glass (EU/1/20/1507/011) or cyclic olefin polymer (EU/1/20/1507/012) vials, both in pack sizes of 10 vials), Spikevax XBB.1.5 50 micrograms dispersion for injection (0.5 mL single dose glass vials in pack sizes of 1 (EU/1/20/1507/013) and 10 vials (EU/1/20/1507/014)) and Spikevax XBB.1.5 50 micrograms dispersion for injection in a pre-filled syringe (0.5 mL single dose in pack sizes of 1 (EU/1/20/1507/015) and 10 syringes (EU/1/20/1507/016)). As a result, the SmPC, labelling and package leaflet, and Annex A are updated accordingly.

The finished product mRNA-1273.815 is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-038839 mRNA active substance that encodes for the pre fusion stabilized Spike protein of the SARS-CoV-2 XBB.1.5 variant.

Within this variation, the MAH takes the opportunity:

• To add a sequence-specific Reverse Transcription Sanger Sequencing (RTSS) identity test for analytical release testing of the active substance CX-038839 mRNA (XBB.1.5, andusomeran) for EU/1/20/1507/011- 16. The RTSS method is currently approved for active substance identity quality control testing of all Spikevax presentations (EU/1/20/1507/001- 010).

• To add a sequence-specific RTSS identity test for analytical release testing of mRNA-1273.815 LNP B finished product intermediate and mRNA-1273.815 finished product (for EU/1/20/1507/011- 16). The RTSS method is currently approved for finished product identity quality control testing of Original

monovalent finished product presentations (EU/1/20/1507/001, EU/1/20/1507/002 and EU/1/20/1507/003).

B.II.b.2.a (Type IB): To use Analytical testing site, Microsynth AG, Schützenstrasse 15 9436 Balgach Switzerland, as an alternative site responsible for Reverse Transcription Sanger Sequencing (RTSS) batch quality control testing for identity of the finished product (Spikevax XBB.1.5 -multidose vial (EU/1/20/1507/011, EU/1/20/1507/012 only)). This site is registered for RTSS identity testing of the RNA active substance and finished product intermediate of already authorised presentations.

B.II.d.1.z (Type IB): To add an action limit of ⩾ 85% to the specification '% RNA Encapsulation' on labelled drug product (LDP) as a requirement for release, when Process Alternative 2 is used (for EU/1/20/1507/011-016).

The MAH is taking the opportunity to include editorial changes into the SmPC, Annex II, labelling and package leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II, IIIA, IIIB and A are recommended.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the addition of a new strain, the CHMP is of the opinion that the already existing entry in the EURD list needs to be amended to: "elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5)".

10. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Spikevax-H-C-005791-II-0111-G'