EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 October 2022
EMA/884918/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Spikevax

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005791/II/0084/G

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

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2022. Reproduction is authorised provided the source is acknowledged.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	26 Sep 2022	26 Sep 2022
☐	First request for supplementary information		04 Oct 2022
☐	CHMP Rapporteur Assessment Report	11 Oct 2022	11 Oct 2022
☐	Second request for supplementary information		11 Oct 2022
☐	CHMP members comments	17 Oct 2022	17 Oct 2022
☐	Updated CHMP Rapporteur Assessment Report	17 Oct 2022	17 Oct 2022
☒	Opinion	19 Oct 2022	19 Oct 2022

Procedure resources	
Rapporteur	Jan Mueller-Berghaus

Table of contents

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 23 September 2022 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, II, 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	I, IIIA and IIIB
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	I, IIIA and IIIB

B.I.a.6.a (Type II): Addition of a new strain (Omicron BA.4-5) resulting in a new Spikevax bivalent Original/Omicron BA.4-5 (50 µg elasomeran/50 µg davesomeran)/mL 0.1 mg/mL dispersion for injection presentation (2.5 mL multidose vial containing 5 doses). The Annex A, the SmPC, the Annex II, the labelling and the Package Leaflet are updated accordingly. The variation also includes a number of quality scopes.

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

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

COVID-19 is the respiratory disease caused by the coronavirus SARS-CoV2. The virus first emerged as a human pathogen in Wuhan province in China and has spread world-wide causing a pandemic. The WHO declared the COVID-19 outbreak as a pandemic in March 2020. The virus infects the airways and

causes a broad spectrum of respiratory infection from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS).

The SARS-CoV-2 virus has repeatedly evolved and appeared in several variants causing new waves of infection. The variants have so far shown cross-reactivity with the original strain, which was the base for the currently approved vaccines. However, there is a concern that presently circulating virus variants are less cross-reactive with the original strain. The variant causing the latest waves of disease at the time of this application has been the Omicron variant, with several subvariants beginning with BA.1. Currently BA.5 is dominating in the EU.

Claimed therapeutic indication

Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

This is the same indication as that recently approved for the Spikevax bivalent Original/Omicron BA.1 variant vaccine.

Biologic features

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development and is the main antigen in all currently developed vaccines against COVID-19.

While the efficacy of available vaccines, emulating the Wuhan strain, against severe disease appears largely retained, efficacy against symptomatic disease due to omicron variants is obviously reduced. Moreover, the duration of protection with the original may be reduced given that the emerging variant is less sensitive than the original target.

It is generally considered that protection may be optimised by a vaccine with a sequence that is as close to the circulating variant as possible. To optimise the broadness of the immune response to Sars-Cov-2 in the present situation, regulatory bodies (ICMRA) and WHO have suggested that a bivalent vaccine including both original as well as an omicron variant may be desirable.

2.1.2. About the product

Spikevax (also referred to as COVID-19 Vaccine Moderna or mRNA-1273) is a vaccine developed for prevention of COVID-19 caused by SARS-CoV-2. It is based on nucleoside-modified mRNA encoding for the full-length SARS-CoV-2 spike (S) protein of the prototype wild-type virus isolate. The SARS-CoV-2 S-protein is modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. The mRNA is encapsulated in lipid nanoparticles (LNP). Spikevax has received conditional marketing authorisation in the EU according to Art. 14 (7) EU-Regulation 726/2004. Following Emergency Use Authorization of mRNA-1273, the phase 3 trial protocol (COronavirus Vaccine Efficacy [COVE]; mRNA-1273-P301) was amended (23 December 2020) from the observer-blind part of the study to an open-label part that is ongoing.

<u>Spikevax Original:</u>

Spikevax is currently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older (conditional marketing authorisation on 06-01-2021).

Spikevax is administered as a course of two 100 µg doses to individuals 12 years of age and older and to children 6 through 11 years of age as a course of two 50 µg doses, which is half of the primary dose for individuals 12 years and older. A third dose of Spikevax may be given at least 28 days after the second dose to individuals 12 years of age and older (100 µg) and children 6 through 11 years (50 µg) who are severely immunocompromised.

A booster dose of Spikevax at a dose of 50 µg mRNA-1273 given at least 3 months after completion of the primary series has been approved for adults 18 years of age and older and for adolescents aged 12 to <18 years.

Spikevax bivalent Original/ Omicron BA.1:

Spikevax bivalent Original/Omicron BA.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

The development programme/compliance with CHMP guidance/scientific advice

The MAH did seek advice on the quality aspects related to the introduction of variant vaccines (Spikevax -Moderna COVID-19 vaccine (EMA/SA/95846)) in July 2022.

2.2. Quality aspects

2.2.1. Introduction

The bivalent finished product is presented as a dispersion for injection containing 50 micrograms/mL of elasomeran and 50 micrograms/mL of davesomeran as active substance, embedded in lipid nanoparticles.

The bivalent vaccine finished product Original (elasomeran)/ Omicron BA.4-5 (davesomeran) is a white to off-white sterile dispersion for injection in a preservative-free buffer at pH 7.5 for intramuscular administration.

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

Davesomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

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 one presentation with fill volume of 3.2 mL (2.5 mL nominal volume) in a type 1 glass/type 1 equivalent glass or cyclic olefin polymer with inner barrier coated, multidose vial with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal), containing 5 doses. Pack size: 10 vials.

2.2.2. Active substance: elasomeran

The active substance elasomeran (also known as CX-024414) is already approved in the existing Spikevax conditional marketing authorisation. No changes were introduced for the manufacturing of the mRNA-024414 (elasomeran).

2.2.3. Active substance: davesomeran

General information

To introduce the bivalent vaccine, the MAH submitted data to support implementation of the omicron variant BA.4-5 mRNA (CX-034476) manufacture.

CX-034476 (INN: davesomeran) active substance, is the mRNA that encodes for the pre-fusion stabilised Spike protein of 2019-novel Coronavirus (SARS-CoV-2) BA.4-5 Omicron sub-variants.

The BA.4 and BA.5 variants are sub-variants of the Omicron variant and were first detected in South Africa in February of 2022. As of July 2022, the BA.4 and BA.5 sub-lineages make up the majority of cases in the US according to the CDC. BA.4 and BA.5 have multiple mutations in the S-protein including several that increase the likelihood of transmissibility and cause a reduction in susceptibility to neutralisation. The mutations in the S protein of the BA.4/BA.5 sub-variants share a number of the same mutations as the Omicron BA.1 variant with several unique mutations as follows:

T19I L24- P25- P26- A27S H69- V70- G142D **V213G** G339D **S371F*** S373P S375F **T376A D405N R408S** K417N N440K **L452R** S477N T478K E484A *R493Q* **F486V** Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K

• bold text indicates mutations unique to BA.4/BA.5

• normal text indicates mutations shared with Omicron BA.1

• italicised text indicates mutation only relative to BA.1, not to Wuhan. BA.1 had Q493R relative to Wuhan. In BA.4/BA.5, this site has reverted back to the Wuhan sequence (R493Q),

•asterisk (*) denotes same mutation as BA.1 but involves different amino acids)

> CX-034476 mRNA is chemically identical to naturally occurring mammalian mRNA with the exception that the uridine nucleoside which is 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-034476 mRNA in place of the normal uridine base to minimise the indiscriminate recognition of CX-034476 mRNA by pathogen-associated molecular pattern (PAMP) receptors (e.g., Toll-like receptors). The molecular sequence of CX-034476 is provided.

The information provided is considered adequate.

Manufacture

Manufacturer(s)

The facilities and responsibilities for the manufacture and quality control testing of CX-034476 were provided.

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

Description of manufacturing process and process controls

The nominal manufacturing batch size for CX-034476 mRNA at ModernaTX (Norwood, United States) is 75 L (Scale B) in vitro transcription (IVT) reaction volume. The manufacturing process for CX-034476 is identical to the manufacturing process presented for CX-024414 at the 75 L scale at ModernaTX Norwood.

Control of materials

The host cell line used for manufacture of PL-030872 for CX-034476 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-030872 is manufactured for CX-034476 mRNA using the same procedure as described for CX-024414 mRNA. The same approach to characterisation testing and kanamycin risk assessment described for CX- 024414 mRNA was taken for CX-034476 mRNA.

The specification for the linearised 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 linearised plasmid is -20°C ± 5°C, with a formal shelf life of three years. This is 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-034476 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 excepting for mRNA sequence specific control elements) to the prototype mRNA-1273 process (CX-024414), one confirmatory PPQ verification lot is performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan. The MAH has

completed PPQ verification of the CX-034476 mRNA manufacturing process. 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 release testing of the CX-034476 mRNA PPQ verification batch were within the specifications and the prior defined acceptance criteria. The MAH did however provide a dT resin reuse report, without providing further information. This reuse of resins across different mRNA constructs had not already been implemented in the dossier (section 3.2.S.2.5). This was raised as a Major Objection (MO) and the MAH was asked to provide further information.

The MAH subsequently clarified that the shared resin used is implemented at the Moderna Norwood site only for CX-024414 and CX-034476, which will be formulated together in one FP later on, dedicating resin to a single finished product. Furthermore, the MAH stated that degradation experiments showed that no detectable full-length RNA persisted after 30 minutes of exposure, which equals the cleaning cycle hold time. In summary the justification to share the resin was found acceptable since it is only for mRNA sequences that will later be formulated into the same finished product. Section 3.2.S.2.5.6 has been updated to better reflect the justification for shared resin use between RNA sequences.

The process verification including 1 batch for the Moderna Norwood site produced in train 1 was successfully conducted. Therefore, the manufacturing of CX-034476 at Moderna Norwood is considered acceptable.

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-stabilised two-proline (S-2P) encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made only 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-034476 mRNA (Omicron BA.4/BA.5).

Subsequent process characterisation beyond that described for CX-024414 was performed for CX-034476 mRNA (Omicron BA.4-5), with the intent of verifying the applicability of the process description and process control strategy defined to all mRNA-1273 RNAs.

CPPs and the CIPC are consistent between CX-034476 mRNA (Omicron BA.4/BA.5) and CX-024414 mRNA. A comparability study between CX-024414 to CX-034476 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 characterisation 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 characterisation results met the comparability expected ranges established from development, clinical, Scale A, preliminary Scale B, and Scale B CX-024414 data. Therefore, the results from the commercial Scale B (75 L in vitro transcription -IVT- scale) PPQ lot of CX-034476

manufactured at ModernaTX Norwood demonstrated that the manufacturing processes and quality attributes are comparable.

Although the comparability data indicates that the quality of the CX-034476 mRNA is comparable to the quality of the parental CX-024414 mRNA, the MAH introduced the IDR in the 3'UTR and this change was not included or discussed/justified in the manufacturing development documents. Furthermore, in the pre-submission meeting it was discussed that the MAH would submit supportive data from influenza mRNA vaccine to support the claim that there exists substantial flexibility to modify the 3´UTR sequence without impacting protein expression or functional mRNA half-life. This was therefore raised as an MO. The MAH subsequently provided supportive data from an influenza mRNA vaccine showing that changes in the 3'UTR have no influence on in vivo potency. This information is now included in Section 3.2.S.2.6.4. The MO was resolved.

Characterisation

The structure and physicochemical properties of CX-034476 mRNA were studied using a variety of techniques applicable to mRNAs. This was studied by a variety of 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-034476 mRNA coding region, melting profile by Differential Scanning Calorimetry (DSC).

Process impurities were evaluated. There are no new impurities as compared to parental mRNA. These included double stranded RNA (dsRNA) and residual protein. The characterisation of the new mRNA CX-034476 is considered acceptable.

Control of active substance

Testing of CX-034476 is performed in accordance with the specification as provided by the applicant.

The following attributes have been included in the specification for CX 034476: appearance, mRNA identity by reverse transcription/Sanger sequencing, total RNA content by UV, purity and product-related impurities by RP-HPLC, pH, osmolality, bacterial endotoxins (Ph. Eur. 2.6.14, kinetic chromogenic method) and bioburden (Ph. Eur. 2.6.12).

The specifications are identical with the specifications for imelasomeran (Omicron BA.1) although for product related impurities in section 3.2 S.4.1 of CX-024414, the specification referring to the same SOP number also included "Report % post-main peak area". The MAH was asked to justify the difference. This was confirmed to be an error and updated documents for this and for an error regarding the purity assay (obsolete documents needed to be deleted) were provided.

For the CX-034476 RNA, the sequence targeted for RNase H digestion to confirm identity is the non-coding region at the 3' end of the mRNA. Therefore, the primer selected for Sanger sequencing is chosen to cover an additional portion of the 3' non-coding region used for finished product identity testing, in addition to 100% of the coding region. As a result of the evolving nature of the identity testing, the specification criterion for identity has been modified to "sequence matches description" for CX-034476 mRNA.

Analytical methods

The analytical methods used for release testing of CX-034476 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-034476. The validation characteristic evaluated was specificity and intermediate precision.

The identity test should be able to distinguish between all licensed mRNA.1273 constructs. Therefore, the MAH was asked to include also CX-031302 in the specificity testing of the identity test or not manufacture CX-031302 in the same facility. The MAH subsequently justified the multi-variant use of the manufacturing site with a control strategy that has been established to appropriately segregate individual RNA products within their intended areas and eliminate the risk of cross-contamination. Furthermore, the MAH has committed to provide a study report demonstrating the capability of the Sanger method (identity testing DS) to detect even minor differences between target sequences and thus the specificity of the identity method, by 30 November 2022 (Recommendation (REC) 1). The MAH was also asked to justify why intermediate precision was not included in the method validation as done for the identity method validation of CX-031302. A justification was provided and this point was suitably addressed.

Batch analysis

Batch results from one batch produced at Moderna Norwood is presented and the CoA is provided. Minor points for clarification were addressed regarding the RP-HPLC method used for batch analysis.

Reference standards of materials

The CX-024414 reference material is used as a system suitability standard for several release tests and as a reference standard for measurement of total RNA content of CX-034476, related variant mRNA-1273 LNP and FP materials.

Sanger sequencing test methods are used to confirm identity for both mRNA-1273 RNA and LNP. These test methods can experimentally measure the nucleotide sequence of specific regions of the RNA. Test results are compared against the theoretical mRNA sequence to confirm identity of the test sample. Since the data reporting is using a theoretical mRNA sequence and not compared against the reference material sequence, a product-specific reference standard is not utilised for these test methods. In this case, the mRNA reference material is used as a positive control for the test method and serves as a system suitability standard. Similarly, no reference material is used in the calculation of total RNA content. Assays such as %PolyA tailed variants and measurement of purity and product-related impurities by ion pairing reversed-phase chromatography use a similar approach, where a product-specific reference standard is not needed to measure the attributes of interest. 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-034476 mRNA is the same as for the original prototype, CX-024414 mRNA (elasomeran).

Stability

An initial shelf-life of 36 months is proposed for CX-034476 mRNA material stored in the commercial container closure system (gamma irradiated, single-use storage bags), when stored at the recommended long-term storage condition of -60°C to -90°C.

The CX-034476 registration stability program was executed according to ICH Q1A (R2), Stability Testing of new Drug Substances and Products, and ICH Q5C, Stability Testing of Biotechnological/Biological Products.

The CX-034476 mRNA is stored at -60 to -90°C, after an optional interim storage at -15 to -25°C of maximum 3 months. An initial shelf-life of 36 months is proposed as from the time of freezing for CX-034476 mRNA 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 CX-034476 mRNA with respect to the attributes that affect product potency have been systematically and thoroughly 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-034476 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 utilising the RNA purity assay by RP-HPLC is precise, accurate and the most stability-indicating measure of product activity.

Stability studies for the proposed long term storage condition for CX-034476 mRNAs at -60°C to -90°C are included. Limited data are provided thus far for two lots.

Upon request, the MAH has committed to provide a stability study protocol by December 2022 that reflects the actual shelf life claim of 3 month at -15 to -25°C before transfer to -60 to -90°C (as already requested in variation II/75/G) (REC 2). The MAH also committed to providing updated stability data by February 2023, when the 3 months timepoint will be available (REC 3). Minor updates were also made to the tabulated data in 3.2.S.7.3 upon request.

2.2.4. Finished product

Description and composition of the finished product

The bivalent vaccine finished product Original/ Omicron BA.4-5 is a white to off-white sterile dispersion for injection in a preservative-free buffer at pH 7.5 for intramuscular administration.

The mRNA-1273.222 (50 mcg/ 50 mcg)/ mL bivalent vaccine comprises two mRNA sequences (equal mass) encoding for the pre-fusion stabilised Spike glycoprotein of:

• The prototype Wuhan-Hu-1 2019-novel Coronavirus (SARS-CoV-2) (as mRNA CX-024414), and

• The BA.4/BA.5 (Omicron) sub-Variants (as mRNA CX-034476)

Both mRNA-1273 LNP-B (CX-024414) and mRNA-1273.045 LNP-B (CX-034476), each contain 0.60 – 1.00 mg/mL of RNA content encapsulated in LNPs in Tris, acetate, sucrose. The LNP is composed of four lipids (SM-102, cholesterol, DSPC [1,2-distearoyl-snglycero-3-phosphocholine], and PEG2000-DMG [1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000]) which act as protectants and carriers of the mRNA.

Other than the new BA.4/BA.5 (Omicron) specific mRNA, there are no other changes in the composition compared to the previous bivalent Spikevax mRNA-1273.214 FP. All the excipients and

lipids (SM-102, Cholesterol, DSPC and PEG2000-DMG) used for the manufacture of the mRNA-1273.222 FP are the same as the ones used in the prior mRNA- 1273 FP – 0.10 mg/mL product. All excipients except the lipid excipients SM-102, DSPC and PEG2000-DMG and trometamol-HCl comply to Ph. Eur. grade.

The qualitative and quantitative composition of the product, including amounts per vial, function and quality standard applicable to each component, is presented. Each 0.50 mL dose of the vaccine contains 25 micrograms of each active substance. The mRNA-1273.222 finished product is supplied as a preservative-free multiple-dose liquid ready to-use solution at 0.10 mg/mL for intramuscular administration in 10R multiple-dose vials with rubber serum stopper and an aluminium seal with flip-off plastic cap.

Pharmaceutical development

Briefly, the bivalent Original/ Omicron BA.4-5 finished product is manufactured by pooling mRNA-1273 LNP-B (containing mRNA CX-024414) and mRNA-1273.045 LNP-B (containing mRNA CX-034476), followed by a dilution with a dilution buffer containing 20 mM Tris and 87 mg/mL sucrose, pH 7.5.

Since the mRNA-1273.222 FP shares the same compositional platform as the authorised 0.1 mg/mL formulation ((EU/1/20/1507/002-003) and the bivalent Original/ Omicron BA.1 (EU/1/20/1507/004, EU/1/20/1507/005 and EU/1/20/1507/007), all aspects of Spikevax 0.1 mg/mL development can be extrapolated to the bivalent mRNA-1273.222 FP.

The Quality Target Product Profile (QTPP) of Spikevax, which is generally applicable to all strengths of the finished product is presented by the applicant.

No changes have been made compared to the QTPP for the original vaccine. According to the MAH, no change in physicochemical properties, processability and stability is expected for the bivalent vaccine compared to the 0.1 mg/mL formulation. This is agreed to. In accordance with ICH Q9, a systematic assessment of the potential risk to mRNA-1273.222 finished product quality was performed with respect to the manufacturing process.

CX- 034476 mRNA loaded LNP intermediate (referred to by the MAH as mRNA-1273.045 LNP-B)

The manufacturing process and process and analytical control strategies established for mRNA-1273 LNP-B are applied directly to mRNA-1273.045 LNP-B. Subsequent process characterisation beyond that described in Section 3.2.S.2.6 {mRNA-1273 LNP - Process Characterisation} was performed for multiple mRNA-1273 LNPs, including mRNA-1273.045 LNP-B (Omicron BA.4/BA.5), with the intent of verifying the applicability of the process description and process control strategy.

Since the same manufacturing process is used; one single Process Verification was performed to introduce the mRNA-1273.045 LNP-B manufacturing on the already approved ModernaTX, Norwood, manufacturing site.

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 characterisation testing results.

One PPQ batch (kit 8: 5014122001) has been included in the comparability study. The comparability study was performed using this PPQ batch data from mRNA-1273.045 LNP-B (Kit 8) and historical batch data from mRNA-1273 LNP-B. Historical data of mRNA-1273 LNP-B 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-1273.045 LNP-B is considered comparable to historical mRNA-1273 LNP-B batches.

The specifications proposed for the newly introduced mRNA-1273.045 LNP-B are identical to the specifications applied to the prototype mRNA-1273 LNP-B and only the analytical method used for identity testing is newly developed to unequivocally identify the mRNA-1273.045 LNP-B variant.

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-1273.045 LNP-B material.

Finished product (referred to by the MAH as mRNA-1273.222)

The updated bivalent mRNA-1273.222 finished product utilises the same manufacturing process and control strategy as mRNA-1273.214 FP. The critical process parameters and critical in-process tests are consistent between mRNA-1273.214 and mRNA-1273.222. As the change in sequence in mRNA-1273.045 LNP-B to target Omicron BA.4/BA.5 does not impact the process control strategy for mRNA-1273.222 FP, all relevant process characterisation data and failure mode analysis described for mRNA-1273.214 FP (BA.1 bivalent product) is applicable to mRNA-1273.222 FP. Information regarding the microbiological attributes and compatibility refers to Section 3.2.P.2.6 {mRNA-1273 FP}.

Performed to introduce the mRNA-1273.222 FP manufacturing on the already approved Catalent manufacturing site. Due to a deviation occurred during the validation exercise, a second verification batch was added to the validation package for completeness.

A set of supportive data is already available in section 3.2.P.2.3 Manufacturing Process Development {mRNA-1273.214}. Additional data issued from mRNA-1273.222 batches (Development and Clinical) are provided in the dossier.

Comparability of mRNA-1273.222 versus mRNA-1273 FP (prototype vaccine).

The manufacturing process for FP mRNA.1273.222 is identical to the manufacturing process already approved for the mRNA-1273.214 bivalent BA.1 vaccine. Therefore, only 1 single verification batch was planned and accepted in agreement with the CHMP SA from July 2022. Due to a deviation, a second verification batch was manufactured. The overall comparability strategy is described. The comparability acceptance criteria have been updated to incorporate commercial manufacturing experience.

The following two 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.

Extended analytical characterisation and forced degradation testing was not performed for mRNA-1273.222 FP as part of comparability studies since the mRNA-1273 FP characteristics are the same as the mRNA-1273 LNPs and the extended characterisation results for mRNA-1273 LNPs are thus considered representative of mRNA-1273 FPs. Extended characterisation testing results for mRNA-1273 LNPs conform to the comparability expected ranges as applicable and are presented. The complete comparability methodology and statistical analysis are described.

All post-change comparability lots were manufactured with CPPs controlled within the proven acceptable ranges (PARs) provided. IPC results were reviewed for consistency. Process hold times were evaluated against the established ranges. Microbial control monitoring was performed. Release testing

of mRNA-1273.222 FP was performed in accordance with the specification listed.

In conclusion, two PPQ batches have been included in a comparability study that has demonstrated comparable process performance parameters and analytical results. All CIPC and IPC results met the acceptable ranges with the exception of clarification/bioburden reduction and sterile filtration pressures for batch 6028222002 (Catalent lot 055F22). The filtration pressure results were evaluated in the context of the full control strategy and determined not to impact the comparability assessment. Release results met both specification and comparability acceptance criteria established from development, clinical, Scale A, and Scale B mRNA-1273 FP data. Therefore, the results from the Scale B PPQ lots of mRNA-1273.222 FP manufactured at Catalent (Bloomington, IN) on the Vial Line 3 filling line demonstrated that the pre-change and post-change manufacturing processes and quality attributes were comparable. As requested in earlier variations, for the purity test, the comparability acceptance criteria have been adjusted to the new purity test that results in higher values. A comparability report has been provided (DS-IND-0155). The MAH also resolved some other concerns in connection with these data.

Manufacture

The manufacturing process consists of preparation of mRNA loaded-LNP finished product intermediates, dilution buffer preparation, LNP thawing, LNP pooling, dilution, clarification/bioburden reduction filtration, sterile filtration, aseptic filling, stoppering and capping.

mRNA loaded LNP intermediate containing mRNA CX-024414 (referred to by the MAH as mRNA-1273 LNP-B)

The manufacturing process is identical to the one used for the 0.1 mg/mL strength.

mRNA loaded LNP intermediate containing mRNA CX-034476 (referred to by the MAH as mRNA-1273. 045 LNP-B)

Manufacturer(s) of mRNA-1273. 045 LNP-B

There are no changes to the currently registered sites and all possess the appropriate GMP authorisations.

Description of manufacturing process and process controls of mRNA-1273. 045 LNP-B

mRNA-1273.045 LNP-B is produced in a 200 g nominal batch size, according to the same manufacturing process described for mRNA-1273 LNP-B. The control strategy applied to the mRNA-1273.045 LNP-B material is identical to the control strategy applied to the mRNA-1273.529 LNP-B (mRNA loaded LNP intermediate containing mRNA CX-031302 BA.1).

mRNA-1273.045 LNP-B manufacturing including controls at ModernaTX, Norwood remain the same as for mRNA-1273 LNP-B and mRNA-1273.529 LNP-B. The MAH argues that only one PPQ batch is necessary and needs to be included in the comparability study. This is accepted. However, data for a second PPQ batch are available in the validation report attached to section S.2.5. The PPQ verification has generated data at commercial scale to support and complement concurrent laboratory-scale studies.

The results of the CPP, PP, critical and non-critical IPC and Active Substance testing of the mRNA-1273.045 LNP - B PPQ batch were within the specifications and the prior defined acceptance criteria. Based on the outcome of the PPQ exercise, the mRNA-1273.045 LNP-B manufacturing process has been successfully validated at the 200 g scale at ModernaTX Norwood. The original validation report is provided.

Finished product (referred to by the MAH as mRNA-1273.222)

Manufacturer of mRNA-1273.222

All manufacturers involved in FP manufacturing, testing and batch release are given in the dossier. As agreed prior to submission, the current variation only concerns the manufacturing in Catalent, USA. Therefore, only sites associated with Catalent manufacturing and release are included in this submission. The MAH requested two release testing exemptions until July 31, 2023: Sterility testing will be performed by Catalent Indiana, LLC, USA and bacterial endotoxin testing will be performed by Associates of Cape Cod, Inc., USA. The exemption is requested due to the complexities involved in meeting EU supply needs and also associated with international shipping and testing of samples, the duration that these samples may be held in frozen storage conditions prior to analysis and the lead time associated with the testing (particularly sterility, USP <71>, Ph. Eur. 2.6.1.) within the MAH's testing network. The MAH further states that the proposed approach will enable an expedited supply of product into the European market to address the ongoing medical need while maintaining the appropriate quality controls around the product. The proposed end date for this exemption was originally set include an extended period to July 2023 to anticipate any potential risks that could lead to apply again for additional exemption at a later stage. The MAH has however agreed to reduce the exemption coverage period request to a minimum, until 31 March 2023, by which time operations should be stabilised. In the event of further unforeseeable events, should there be a need to extend the requested exemption beyond March 2023, the MAH will contact the EMA in advance. There are no objections regarding this request.

The manufacturers responsible for batch release are Rovi Pharma Industrial Services, S.A. (Madrid, Spain) and Moderna Biotech Spain S.L. (Madrid, Spain).

Description of manufacturing process and process controls of mRNA-1273.222

Representative batch size and manufacturing formula for the manufacture of mRNA-1273.222 FP at Catalent are provided.

The batch composition is provided. The mRNA-1273.222 Finished product (FP) is produced at Scale B, according to the same manufacturing process described for mRNA-1273.214 FP. The controls of critical steps and intermediates at the Catalent manufacturing site are identical for mRNA-1273.214 and mRNA-1273.222.

Process validation of mRNA-1273.222

The MAH has completed process validation of the approved bivalent product mRNA-1273.214 (Section 3.2.P.2.3 {mRNA-1273.214}). The manufacturing process for mRNA-1273.222 finished product is unchanged from that for mRNA-1273.214 except for the substitution of one of the mRNA-LNPs used (substitute mRNA-1273.529 for mRNA-1273.045). The MAH has therefore adopted the strategy of manufacturing a single PPQ verification batch of the mRNA-1273.222 FP as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. PPQ for mRNA-1273.222 FP was performed on Vial Line 3 at Catalent. A total of 2 consecutive lots were completed during process performance verification of the mRNA-1273.222 FP to demonstrate process consistency for Vial Line 3. The second verification batch was manufactured due to a process deviation during the LNP pooling step.

All CQAs, CPPs, and CIPCs met the acceptance criteria defined in the PPQ protocol and the FP Commercial Control Strategy. Microbial attributes and in-process holds were within the limits and ranges defined. All PPQ lot release testing results, encompassing all CQAs, met the predefined acceptance criteria. The CPPs were confirmed to be within target ranges. All CIPCs and IPCs defined were evaluated. Any excursions were evaluated and determined not to impact PPQ outcomes.

Microbial control was appropriately demonstrated during the execution of PPQ. Process Performance Qualification Verification Studies were conducted (dilution mixing and filled vial homogeneity).

The process validation data are considered acceptable. Some clarification points regarding process validation were raised in connection with the total processing duration/ times. The processing times should be described clearly in the dossier (REC 5). A revised FP process validation report, to correct minor errors should also be provided by the end of November 2022 (REC 4).

Control of finished product

mRNA loaded LNP intermediate containing mRNA CX-024414 (referred to by the MAH as mRNA-1273 LNP-B)

This section is unchanged from that approved for the 0.1mg/mL formulation.

mRNA loaded LNP intermediate containing mRNA CX-034476 (referred to by the MAH as mRNA-1273. 045 LNP-B)

An updated specification for mRNA-1273.045 LNP–B has been provided. The following attributes have been included in the specification for mRNA-1273.045 LNP-B: appearance, mRNA identity by reverse transcription/Sanger sequencing, total RNA content by anion exchange chromatography, purity and product-related impurities by RP-HPLC, % RNA encapsulation by absorbance assay, mean particle size and polydispersity by DLS, lipid identity 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), 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.

Reverse transcription Sanger sequencing for the RNA region of interest is applied to distinguish prototype and variant mRNAs. This method has been validated. All other analytical methods remain unchanged.

Batch analysis data is provided for mRNA-1273.045 LNP–B for the PPQ batch manufactured at Moderna TX Norwood (5014122001). All results are within the specifications.

Finished product (referred to by the MAH as mRNA-1273.222)

The release specifications for mRNA-1273.222 FP are provided. The proposed finished product release specification includes tests for appearance (visual), total RNA content by anion exchange chromatography, mRNA identity and mRNA ratio by RP-HPLC, purity and product-related impurities by RP-HPLC, % RNA encapsulation by absorbance assay, in vitro translation (methionine labelling), lipid identity 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), bacterial endotoxin (Ph. Eur. 2.6.14, kinetic chromogenic method) and sterility (Ph. Eur. 2.6.1).

The specifications are acceptable and in line with the approved specifications for mRNA-1273 and mRNA-1273.214. The revised purity specification (due to method change as part of the submission of the bivalent mRNA-1273.214 – 0.10 mg/mL vaccine) has been implemented for the mRNA-1273.222 vaccine. The methods that are specific for mRNA-1273.222 (identity and RNA ratio) have been sufficiently validated.

Batch analysis for the two PPQ lots show no unexpected results. CoAs for theses batches have been provided. All results comply with the specifications.

The impurity profile of mRNA-1273.222 Finished product is the same as that of the mRNA-1273 LNP/mRNA-1273.045 LNP-B. No additional impurities are anticipated to form or be introduced during mRNA-1273.222 Finished product manufacturing. An evaluation of potential extractables and leachables from manufacturing components and container closure systems used in the mRNA-1273 FP manufacturing process at Catalent is provided.

mRNA-1273.222 contain multiple encapsulated mRNA sequences targeting different SARS-CoV-2 variants (CX-024414 and CX-034476). To ensure that the intended content of each individual component is available in a finished product lot, total RNA content and RNA ratio are needed as part of the analytical control on release. Since the total RNA content method measures total RNA and cannot distinguish RNA from different mRNA sequences, a measurement of the ratio of the two RNA components present in the FP is needed to ensure that each component is present at the intended level. Together, control of total RNA content and RNA ratio ensures that each finished product lot contains the intended dose of the individual RNA components comprising the FP and therefore has a direct impact on the efficacy of the product.

Reference standards

The CX-024414 reference material as described in Sections 3.2.S.5 {CX-024414} and 3.2.S.5 {CX-034476} will serve as the reference material for mRNA-1273.222 Finished product testing for the total RNA content method by AEX-HPLC, the % purity method by RP-IP-HPLC (system suitability), ID/Ratio by RP-HPLC, and the in vitro translation assay/methionine labelling assay (positive control). For Total RNA content testing, the CX-24414 mRNA reference material is used as the standard against which samples are compared to obtain the total RNA content values; a sequence specific reference standard is not required for this assay.

Interim reference material lot 8514100101 is a clinical mRNA-1273.222 finished product lot that is used as an interim reference material until a primary and working commercial reference material is qualified. This interim reference material lot has been used for the determination of identity of mRNA-1273.222 FP samples in the RNAse H digestion method. This identity and ratio method was implemented as a release method as part of the commercial analytical control strategy for the mRNA-1273.222 FP.

Future FP Reference Materials will be prepared from commercial mRNA-1273.222 lots. Reference Materials will be qualified against an established Primary and Working Reference Material Qualification Protocol. A certificate of analysis must be generated and approved prior to the Reference Material being used for GMP testing. Acceptance of a Reference Material includes meeting the release criteria outlined in the approved specification. At a minimum, the stability of the Reference Material is re-qualified annually. During assessment, the standard currently in use was queried. The MAH clarified that lot 8514100101 has been used as an interim reference material during the testing of all initial mRNA-1273.222 FP lots on release. Subsequently, a new interim reference material lot 8514100102 has been implemented to support release testing until a primary reference material is qualified. Section 3.2.P.6 has been updated with information on both interim reference material lots.

Container closure system

There has been no change in the container closure systems for all specified intermediates.

The container closure system for the mRNA-1273.222 FP is a type 1 glass or type 1 equivalent glass or

cyclic olefin polymer (with inner barrier coating) multidose vial with a stopper (chlorobutyl rubber) and a blue flip-off plastic cap with seal (aluminium seal). It is the same container closure system as for the prototype vaccine (0.2 mg/mL: EU/1/20/1507/001).

Stability

mRNA loaded LNP intermediate containing mRNA CX-024414 (referred to by the MAH as mRNA-1273 LNP-B)

There is no change from the existing approved presentations. The results support the proposed shelf life of 12 months for the mRNA-1273 LNP in the commercial container closure system, when stored at the recommended long-term storage condition of -60°C to -90°C.

mRNA loaded LNP intermediate containing mRNA CX-034476 (referred to by the MAH as mRNA-1273. 045 LNP-B)

An initial shelf life of 12 months is proposed for the mRNA-1273.045 LNP 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. The product quality attribute expected to change most during the manufacturing and distribution of the product is mRNA integrity as assessed by mRNA purity.

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 strong quantitative correlation between RNA degradation 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-034476 mRNA have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected for mRNA-1273 LNP and mRNA-1273.045 LNP.

No stability data for batch DH-38558.1 (mRNA-1273.045 LNP-B) manufactured in July 2022 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 and 25°C ± 5°C have been provided. As expected, OOS results for purity have been observed at 25°C ± 5°C.

A minimum of one mRNA-1273.045 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.

Finished product (referred to by the MAH as mRNA-1273.222)

The initial shelf life proposed for FP material stored in the commercial container closure system, based on previous data collected for all Spikevax presentations is: 9 months at -50°C to -15°C that can include 30 days of storage at 2°C to 8°C and 24 hours at 8°C to 25°C (in an unpunctured vial to enable administration of the vaccine at the point-of-care site).

The mRNA-1273.222 Finished product (0.10 mg/mL) registration stability program was executed according to ICH Q1A (R2), Stability Testing of new Drug Substances and Products, and ICH Q5C, Stability Testing of Biotechnological/Biological Products.

In addition, storage of 12 months at -50°C to -15°C is also proposed, provided that once thawed and stored at 2°C to 8°C, protected from light, the unopened vial will be used up within a maximum of 14 days (instead of 30 days, when stored at -50ºC to -15ºC for 9 months).

Direct measurements of those attributes of greatest significance have been established and those assays are included in the routine release panel. The product quality attribute demonstrated to be most sensitive during the manufacturing and distribution of the product is mRNA integrity as assessed by mRNA purity. The degradation of mRNA in the product has been extensively studied by applying a sensitive chromatographic assay to assess the formation of RNA degradants. There is a strong quantitative correlation between RNA degradation as measured directly and protein expression levels. Direct measure of mRNA degradation utilising the mRNA purity assay by RP-IP-HPLC is the most stability-indicating measure of product activity.

Based on the stochastic nature of this degradation mechanism, there is a dependence of the rate of degradation on RNA size (length). This has been shown through analysis of the rates of purity degradation for multiple products.

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. As an example, the RNAs comprising mRNA-1273.222 finished product are within 9 nucleotides of each other relative to a total length of approximately 4000 nucleotides. The 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.

Stability studies representing similarly formulated lots of mRNA-1273, mRNA-1273.211 and mRNA 1273.351 are available for comparison at study temperatures -70°C, -20°C, 5°C and 25°C.

The product shelf-life claim is established using the degradation rates estimated from stability studies for multiple lots. A minimum of one (1) mRNA-1273.222 Finished product batch per year will be placed on stability.

The testing protocol for two PPQ batches and the post-approval stability protocol is acceptable. No stability data under real time conditions are available yet for the two PPQ lots. Data after 2 weeks at 25°C and 4 weeks at 5°C and 25°C is available for a developmental batch and show no unexpected results.

The MAH refers to platform data and proposes the same shelf life as for mRNA-1273 PFS – 0.10 mg/mL FP and the bivalent mRNA-1273.214 – 0.10 mg/mL FP. This is acceptable. However, since the platform approach should be supported by the accelerated stability data from the developmental batch, the MAH was requested to demonstrate that the degradation rate conforms with the platform data. The MAH subsequently compared the degradation rate of the developmental batch at accelerated temperature with the platform data. The values are in a comparable range. Other minor corrections to the tables in section 3.2.P.8.3 and 3.2.P.8.1 were also corrected upon request.

The storage conditions and expiry limits established for mRNA-1273 FPs (0.20 mg/mL and 0.10 mg/mL) are therefore applied for associated variant vaccines including mRNA-1273.222 FP. Therefore, a FP shelf life of 9 months at -50°C to -15°C that can include 30 days of storage at 2°C to 8°C and 24 hours at 8°C to 25°C (in an unpunctured vial to enable administration of the vaccine at the point-of-care site) is approved.

Storage at 12 months at -50°C to -15°C is also accepted, provided that once thawed and stored at 2°C to 8°C, protected from light, the unopened vial will be used up within a maximum of 14 days (instead of 30 days, when stored at -50ºC to -15ºC for 9 months).

2.2.5. Appendices (CTD module 3.2.A)

A new suite at the currently registered site, Aldevron, North Dakota, is being used and is implemented for the manufacturing of plasmid for all CX sequences currently registered, including the new CX-034476. Appendix 3.2.A.1 is updated accordingly.

2.2.6. Regional information

2.2.7. Discussion on chemical, and pharmaceutical and biological aspects

During the procedure two MOs were raised as follows.

The active substance (CX-034476) process verification including 1 batch for the Moderna Norwood site produced in train 1 was successfully conducted. The MAH did however provide a dT resin reuse report, without providing further information. This reuse of resins across different mRNA constructs had not already been implemented in the dossier (section 3.2.S.2.5). This was raised as a Major Objection (MO) and the MAH was asked to provide further information. The justification to share the resin was found acceptable since it is only for mRNA sequences that will later be formulated into the same finished product. The MO was resolved.

The comparability data clearly indicated that the quality of the CX-034476 mRNA is comparable to the quality of the parental CX-024414 mRNA, as all testing is within the comparability acceptance criteria. However, the MAH introduced the identification and ratio (IDR) sequence in the 3'UTR, this change was not included and or discussed/justified in the manufacturing development documents. This was raised as an MO. The MAH subsequently provided supportive data from an influenza mRNA vaccine showing that changes in the 3'UTR has no influence on in vivo potency. This MO was also resolved.

The MAH requested two release testing exemptions until July 31, 2023: Sterility testing will be performed by Catalent Indiana, LLC, USA and bacterial endotoxin testing will be performed by Associates of Cape Cod, Inc., USA. The exemption is requested due to the complexities involved in meeting EU supply needs and also associated with international shipping and testing of samples, the duration that these samples may be held in frozen storage conditions prior to analysis and the lead time associated with the testing (particularly sterility, USP <71>, Ph. Eur. 2.6.1.) within the MAH's testing network. The MAH further states that the proposed approach will enable an expedited supply of product into the European market to address the ongoing medical need while maintaining the appropriate quality controls around the product. The proposed end date for this exemption was originally set include an extended period to July 2023 to anticipate any potential risks that could lead to apply again for additional exemption at a later stage. The MAH has however agreed to reduce the exemption coverage period request to a minimum, until 31 March 2023, by which time operations should be stabilised. In the event of further unforeseeable events, should there be a need to extend the requested exemption beyond March 2023, the MAH will contact the EMA in advance. There are no objections regarding this request.

After considering the answers to the questions raised, the quality data is deemed sufficient subject to the below recommendations and information to be provided in the closing sequence.

2.2.8. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.9. Recommendations for future quality development

1. The MAH should provide a study report demonstrating the capability of the Sanger method (identity testing AS) to detect even minor differences between target sequences and thus the specificity of the identity method by end of November 2022.
2. The MAH should include the stability protocol of the sequential stability study (3 month at -20°C, then transferred to -70°C for the remaining shelf-life claim of 36 months) in Section 3.2.S.7.1 Stability Summary and Conclusions {CX-034476 mRNA} by December 2022 and provide the stability results in Q1 2026.
3. The MAH should provide updated AS stability data by February 2023, when the 3 months timepoint will be available.
4. The MAH should provide a revised FP process validation report, to correct minor errors, by end of November 2022.
5. The MAH should provide a clear description of the cumulative process durations that are relevant for the Catalent site (504 h maximum process duration and 336 h normal operating range) in all relevant dossier sections by 30/11/2022.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAH submitted new non-clinical data in support of the implementation of the bivalent SARS-CoV-2 vaccine mRNA-1273.222, based on previous authorised monovalent SARS-CoV-2 vaccine mRNA-1273. mRNA-1273.222 consists of mRNA-1273 and mRNA-1273.045 in a 1:1 ratio. mRNA-1273.045 includes a mRNA, which encodes for the BA.4/BA.5 Omicron variant, and mRNA-1273 includes a mRNA, which encodes for the Wuhan variant.

The parental mRNA vaccine mRNA-1273 was shown to be highly immunogenetic and protective against infection with the ancestral Wuhan-Hu-1 SARS-CoV-2 virus in (non-)clinical studies when administering a primary 2-dose regimen. Furthermore, it could be shown that an additional booster dose enhanced the immunogenicity and protective effects of mRNA-1273. However, new emerging virus variants showed increased transmissibility with significant antigenic change and additional antibody neutralisation escape mutations. Currently (2022), the Omicron BA.4 and BA.5 sub-variants are responsible for the majority of cases during the latest wave of COVID-19 infections in Europe. Thus, the MAH developed the bivalent, variant-matched booster vaccine mRNA-1273.222 to provide increased protection against the BA.4/BA.5 variants, as well as broaden neutralisation to previous and emerging virus variants.

For this variation, the MAH presented non-clinical data of the bivalent BA.4/BA.5-matched booster vaccine mRNA-1273.222. An in-vitro and two in-vivo pharmacodynamics non-GLP studies were conducted with mRNA-1273.222.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Study MOD-045EXP: Evaluation of In-Vitro Expression of the BA.4/BA.5 mRNA Contained in the Bivalent mRNA-1273.222 Vaccine

Study design:

Expi293 cells were transfected with two different dose concentrations of mRNA (500 ng/mL and 100 ng/mL) that encodes the SARS-CoV-2 S-2P antigen of the Omicron BA.4/BA.5 sub-variants, contained in the monovalent mRNA-1273.045 and bivalent mRNA-1273.222 vaccines, respectively. As positive control, Expi293 cells were transfected with a mRNA that is included in the monovalent mRNA-1283 vaccine. This mRNA sequence encodes the N-terminal domain (NTD) and receptor-binding domain (RBD) of the Wuhan-Hu-1 spike protein, which are coupled to a hemagglutinin transmembrane domain (NTD-RBD-HATM). Mock mRNA transfected cells were used as negative control. The prepared mRNA were evaluated for expression in Expi293 cells without encapsulation in lipid nanoparticles.

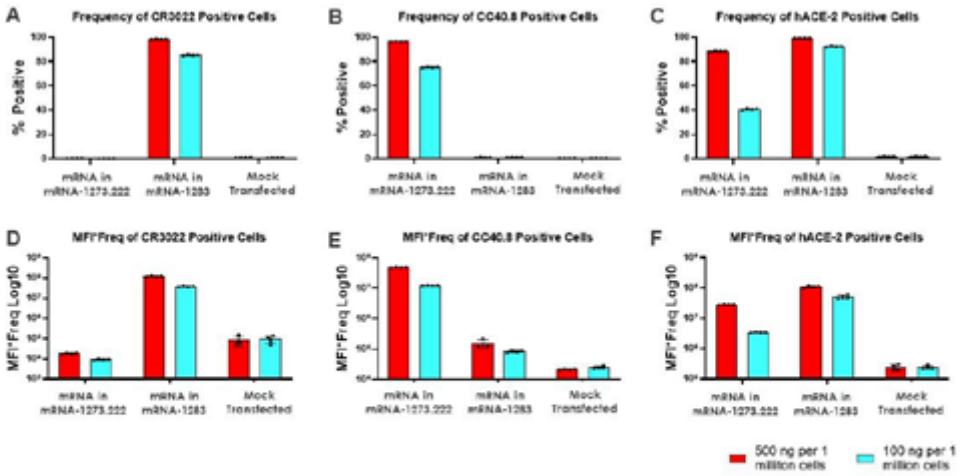
The transfected cells were labelled with the monoclonal antibodies CC40.8 or CR3022 or with recombinant hACE-2, and the surface protein expression was analysed by flow cytometry. The mAb CC40.8 is specific for the NTD of several SARS-CoV-2 Spike protein variants (Wuhan-Hu-1 spike and other VoC) and binds to a conserved region on the S2 subdomain. The mAb CR3022 selectively binds to the original Wuhan-Hu-1 spike protein in the RBD. A recombinant hACE-2 was used to analyse expression of the RBD, as hACE-2 will bind to the receptor-binding motif in the SARS-CoV-2 Spike protein of different virus variants.

Results:

The majority of BA.4/BA.5 mRNA transfected cells were positive for CC40.8, indicating the presence of a conserved region on the RBD S2 subdomain, and could bind to the recombinant hACE-2. Only small amounts of cells could bind unspecifically to CR3022, because the binding epitope was not present on the BA.4/BA.5 spike protein sequence. The positive control mRNA contained in mRNA-1283 was detected by CR3022 and recombinant hACE-2, but not by CC40.8. Thus, CR3022 binds to the Wuhan-Hu-1 spike protein RBD but not to the significantly mutated RBD in the BA.4/5 Omicron variant. CC40.8 did not bind to all positive control mRNA transfected cells, which seems to be unexpected since this monoclonal antibody should bind to a conserved region in the RBD. However, the mean fluorescence intensity was slightly higher in positive control cells than in mock RNA transfected cells.

A small dose effect was observed in BA.4/BA.5 mRNA and positive control mRNA transfected cells with dose-dependent increase of positive cells. Mock-transfected cells showed only low background mean florescence intensities with CC40.8 and hACE-2 labelling. However, CR3022 induced relative high background mean florescence intensity in the mock-transfected cells indicating a reduced specify of the antibody. Moreover, the mean florescence intensity of protein expression was similar to the observed frequency in cells transfected with BA.4/BA.5 mRNA contained in mRNA-1273.222.

Figure 1 In Vitro Cell Surface Expression of the BA.4/BA.5 SARS-CoV-2 S-2P Antigen After Transfection of Expi293 Cells With BA.4/BA.5 mRNA Contained in mRNA-1273.222 or mRNA Contained in mRNA-1283 (Positive Control), Measured by Flow Cytometry at 48 Hours



Abbreviations: hACE-2 = human angiotensin-converting enzyme 2; mAb = monoclonal antibody; MFI = mean fluorescence intensity; MFI*freq = the frequency of positive cells multiplied by the MFI; mRNA = messenger RNA; NTD = N-terminal binding; RBD = receptor binding domain; RBM = receptor binding motif; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Assessor's comment

In this supportive in-vitro study, monoclonal antibody CC40.8 and recombinant hACE-2 could bind to the BA.4/BA.5 mRNA transfected cells. These results indicate that a conserved region within the RBD S2 subdomain and a binding motif for hACE-2 was encodes in the BA.4/5 mRNA sequence. The monoclonal antibody CR3022 did not bind to BA.4/BA.5 mRNA transfected cells, but to the positive control, which shows that the developed BA.4/BA.5 mRNA sequence differ remarkably from the Wuhan-Hu-1 mRNA sequence used for the positive control.

CC40.8 did not bind to the positive control mRNA transfected cells, which seems to be unexpected since this monoclonal antibody should bind to a conserved region in the RBD. However, the data indicates that this RBD region was not present in the positive control mRNA sequence.

Study MOD-5482: Evaluation of Immunogenicity of Primary Series mRNA-1273.222 in BALB/c Mice

Study design:

17-week-old naïve female BALB/c mice (n=8/group) received two intramuscular injections of 1 µg mRNA vaccines or PBS as negative control 3 weeks apart. The used preclinical mRNA vaccines were monovalent mRNA-1273, monovalent mRNA-1273.529 (BA.1-specific), monovalent mRNA-1273.045 (BA.4/BA.5-specific), bivalent mRNA-1273.214 (1:1 bench side mix of mRNA-1273 and mRNA-1273.529) and bivalent mRNA-1273.222 (1:1 bench side mix of mRNA-1273 and mRNA-1273.045).

Blood was collected from all animals on Day 21 (before second dose administered) and Day 35 (2 weeks after second dose). Serum samples were analysed for binding antibody responses via ELISA and neutralising antibody responses via VSV-based and lentivirus-based PSVN assays.

Table 1 Study Design for Study MOD-5482

Group (n = 8/group)	Primary Series (Dose 1 and 2)			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	
1	PBS Control	-	Day 1, 22	**Serum (Day 21)** Antibody responses (ELISA) **Serum (Day 35):** Antibody responses (ELISA and VSV- and lentivirus-based PSVNAs)
2	mRNA-1273	1		
3	mRNA-1273.529	1		
4	mRNA-1273.045	1		
5	mRNA-1273.214	1		
6	mRNA-1273.222	1		

Abbreviations: BA.1 = SARS-CoV-2 Omicron variant (B.1.1.529); BA.4/BA.5 = SARS-CoV-2 Omicron subvariants; bAb = binding antibody; ELISA = enzyme-linked immunosorbent assay; IM = intramuscular; mRNA = messenger RNA; PBS = phosphate-buffered saline; PSVNA = pseudovirus neutralization assay; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VSV = vesicular stomatitis virus.

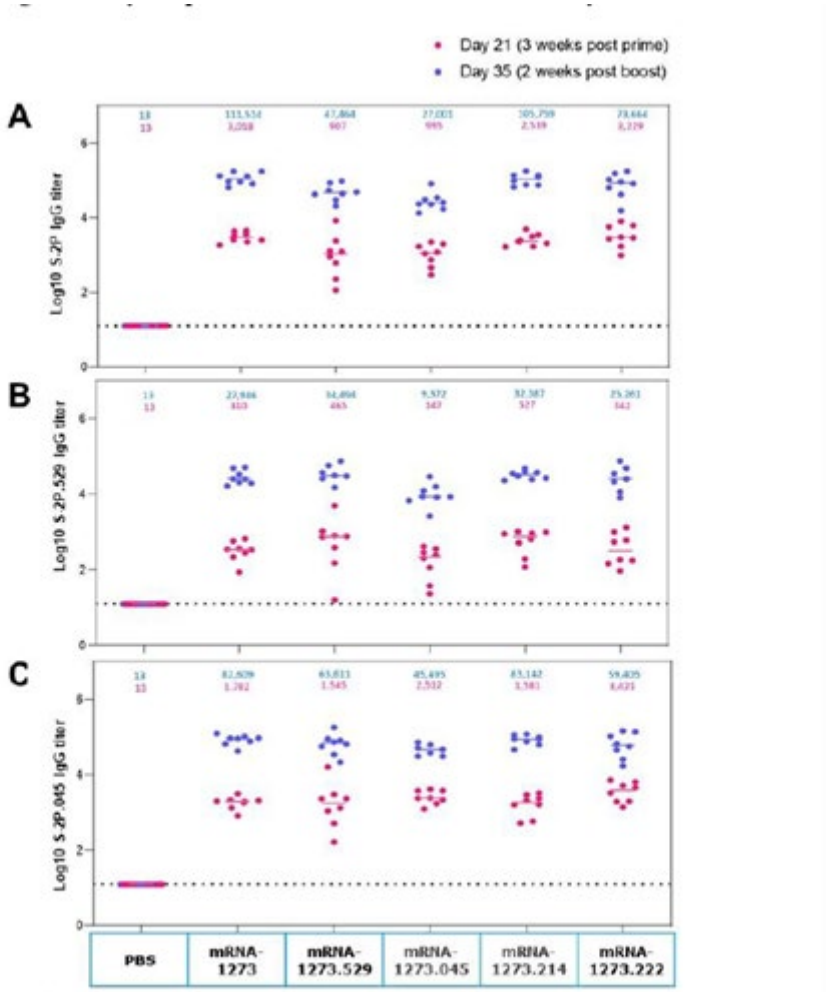
Note: ELISA measured specific bAb titers (S-2P of WA.1, BA.1 and BA.4/BA.5) and lentivirus-based, or VSV-based PSVNAs measured specific nAb titers (WA.1 [lentivirus-based PSVNA], WA.1 + D614G [VSV-based PSVNA] BA.1, and BA.4/BA.5).

Results:

Overall, strong IgG binding antibody titres against Wuhan, BA.1 and BA.4/5 virus variants were observed after a 2-dose primary series with monovalent mRNA-1273, mRNA-1273.529 and mRNA-1273.045 vaccines and bivalent mRNA-1273.214 and mRNA-1273.222 vaccines. Overall, similar high IgG antibody titres were detected after the first dose and titres increased further after the second dose.

3 weeks after the first dose, IgG antibody titres against Wuhan Spike S-2P were similar in all vaccine groups. 2 weeks after the second dose, the titres increased in all vaccinated animals. Mice vaccinated with monovalent mRNA-1273, bivalent mRNA-1273.214 or mRNA-1273.222 achieved slightly higher Wuhan Spike S-2P IgG antibody titres than mice vaccinated with monovalent mRNA-1273.529 or mRNA-1273.045. After the first dose, the BA.1-specific S-2P.529 IgG antibody titres were at a similar level in all vaccine groups but had slightly lower GMT compared to Wuhan Spike S-2P IgG antibody titres. On Day 35, there were no significant differences in BA.1-specific S-2P.529 IgG GMTs across treatment groups, except for mice vaccinated with monovalent mRNA-1273.045, which showed lower S-2P.529 IgG GMTs when compared with other vaccine groups. The BA.4/BA.5-specific S-2P.045 IgG antibody titres were similar in all vaccine groups after the first dose and increased significantly after the second dose

Figure 2 Binding Antibody Responses in BALB/c Mice After Primary Series



Abbreviations: Ab = antibody; BA.1 = SARS-CoV-2 Omicron variant (B.1.1.529); BA.4/BA.5 = SARS-CoV-2 Omicron subvariants; GMT = geometric mean titer; IgG = immunoglobulin G; LLOQ = lower limit of quantification; mRNA = messenger RNA; PBS = phosphate-buffered saline; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; S-2P.045 = BA.4/BA.5 Omicron-specific S-2P; S-2P.529 = BA.1

After the second vaccine dose, the VSV-based PSVN assay showed that mRNA-1273 vaccinated mice have a strong neutralising antibody response against D614G and lower neutralising antibody responses against BA.1 and even lower against BA.4/5 variants. Four mice showed no neutralising antibody response against BA.4/5.

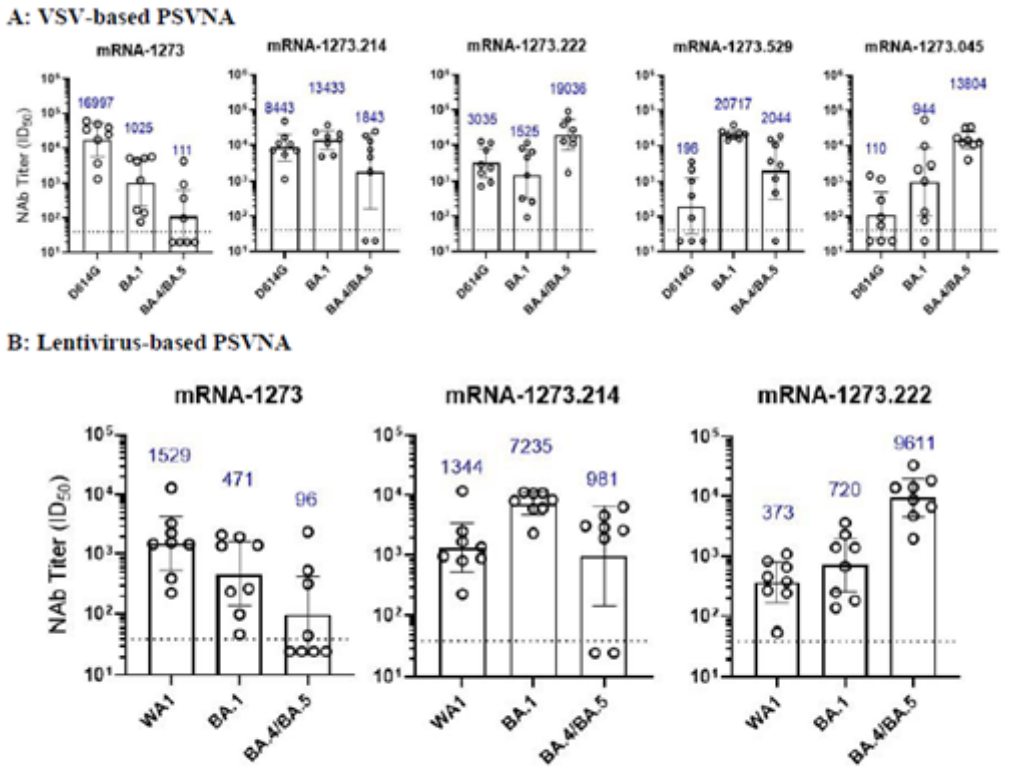
In contrast, the monovalent Omicron-specific vaccines mRNA-1273.529 and mRNA-1273.045 induced only very low D614G-specific neutralising antibody responses and high BA.1 and BA.4/5 responses. Three mice in each vaccine group did not even show neutralising antibody responses against D614G. However, also one mRNA-1273.045 vaccinated mouse showed no neutralising antibody titre against BA.1 and one mRNA-1273.529 vaccinated mouse showed no neutralising antibody titre against BA.4/5.

Furthermore, the bivalent Omicron-variant specific vaccines mRNA-1273.214 and mRNA-1273.222 induced high neutralising antibody responses against all three variants D614G, BA.1 and BA.4/5. However, mRNA-1273.214 showed highest responses against BA.1 and mRNA-1273.222 against BA.4/5, which was expected. However, two mRNA-1273.214 vaccinated mice showed no neutralising antibody response against BA.4/5.

The lentivirus-based PSVN assay showed similar results. 2 weeks after the second dose, mice vaccinated with bivalent mRNA-1273.222 had a high neutralising antibody titre against BA.4/BA.5, while the responses against Wuhan and BA.1 were lower. The monovalent mRNA-1273 vaccine showed

high neutralisation antibody response against Wuhan, but lower neutralising antibody titres against BA.1 and BA.4/BA.5. Four mice did not even show a neutralising antibody response against BA.4/5. The bivalent mRNA-1273.214 vaccine showed high neutralising antibody titres against BA.1 and a lower neutralising antibody response against Wuhan and BA.4/BA.5, with two mice that did not develop a neutralising immune response against BA.4/5. Overall, these results were expected.

Figure 3 Neutralizing Antibody Responses in BALB/c Mice After Primary Series (Day 35)



Abbreviations: Ab = antibody; GMT = geometric mean titer; ID_{50} = inhibitory dilution 50%; LLOQ = lower limit of quantification; mRNA = messenger RNA; nAb = neutralizing antibody; PSVNA = pseudovirus neutralization assay; VSV = vesicular stomatitis virus.

Notes: Blue numbers and bars represent GMTs, and whiskers represent 95% confidence interval. Dotted line indicates LLOQ of the assays. In Figure A (VSV-based PSVNA), D614G = WA.1 + D614G.

Assessor's comment

BALB/c mice were used for this immunogenicity study, which are an acceptable animal model for this purpose. Furthermore, the study design was overall sufficient and the vaccines were administered by the clinical route. Importantly, naïve mice were used and not already SARS-CoV-2 vaccinated mice. However, mRNA-1273.222 is intended to be a booster vaccine for already primed individuals.

In general, 2 intramuscular doses of each tested mRNA vaccine induced robust IgG binding antibody titres against Wuhan-Hu-1, Omicron BA.1 and BA.4/5 in mice. The IgG binding antibody titres against the different virus variants induced by the different vaccines varied only marginally.

Overall, both neutralising antibody response assays showed comparable results. As expected, mRNA-1273.222 induced high neutralising antibody responses against BA.4/5 and remarkably lower titres against Wuhan and BA.1. Importantly to mention, single animals in almost all vaccine group did not induce a neutralising antibody response to Wuhan, BA.1 and/or BA.4/5. However, all mRNA-1273.222 vaccinated mice showed neutralising antibody titres against all tested virus variants above the detection limit.

Study WASHU-K18-89: Evaluation of Immunogenicity and Protection From a Booster Dose of the mRNA-1273.222 Vaccine After Primary Series Vaccination With mRNA-1273 in K18-hACE2 Transgenic Mice

Study design:

31 weeks after a primary series vaccination with two intramuscular doses of 0.25 µg monovalent mRNA-1273 (3 weeks apart), seven-week-old female heterozygous K18-hACE2 C57BL/6 mice (n=8-10/group) were vaccinated intramuscularly in the hind leg with a 0.25 µg booster dose of a monovalent or bivalent mRNA-1273 vaccine variant. The administered dose volume was 0.5 mL. 31 weeks after the primary series with mRNA-1273 vaccine, blood was collected before the mice were boosted and 4 weeks after the booster dose (before the BA.5 challenge) with monovalent mRNA-1273, bivalent mRNA-1273.214, bivalent mRNA-1273.222, non-coding mRNA (UNFIX-01) or PBS control vaccines. All used preclinical vaccine material were prepared with the same method as the GMP mRNA-1273 and mRNA-1273.214 drug products. mRNAs were formulated into a mixture of 4 lipids (SM-102, cholesterol, DSPC and PEG2000-DMG).

The serum neutralising antibody response was analysed by focus reduction neutralisation test (FRNT) assay. 4 weeks after the booster dose, the mice were challenged with 10^4 PFU Omicron-variant BA.5 SARS-CoV-2. Four days later, the animals were sacrificed and viral burden was analysed in nasal wash, nasal turbinates and lung tissue by qRT-PCR.

Table 2 Treatment Regimen for Study WASHU-K18-89

			Primary Series			Boost			Omicron Challenge		
Mouse Strain	Group No.	n	Treatment	Dose Level (µg)	Dose Schedule	Treatment	Dose Level (µg)	Dose Schedule	Variant (10^4 FFU)	Time Point	Collection Time Points
K18-hACE2	1	8-10	UNFIX-01 (control)	0.25	Day 0, Day 21	UNFIX-01	0.25	Day 241	BA.5	Day 269/270	**Serum (Day 239 pre-boost; Day 268 post-boost):** Antibody response (FRNT) **Sacrifice (Day 273/274):** Viral burden (qRT-PCR)
	2		mRNA-1273			PBS					
	3					mRNA-1273					
	4					mRNA-1273.214					
	5					mRNA-1273.222					

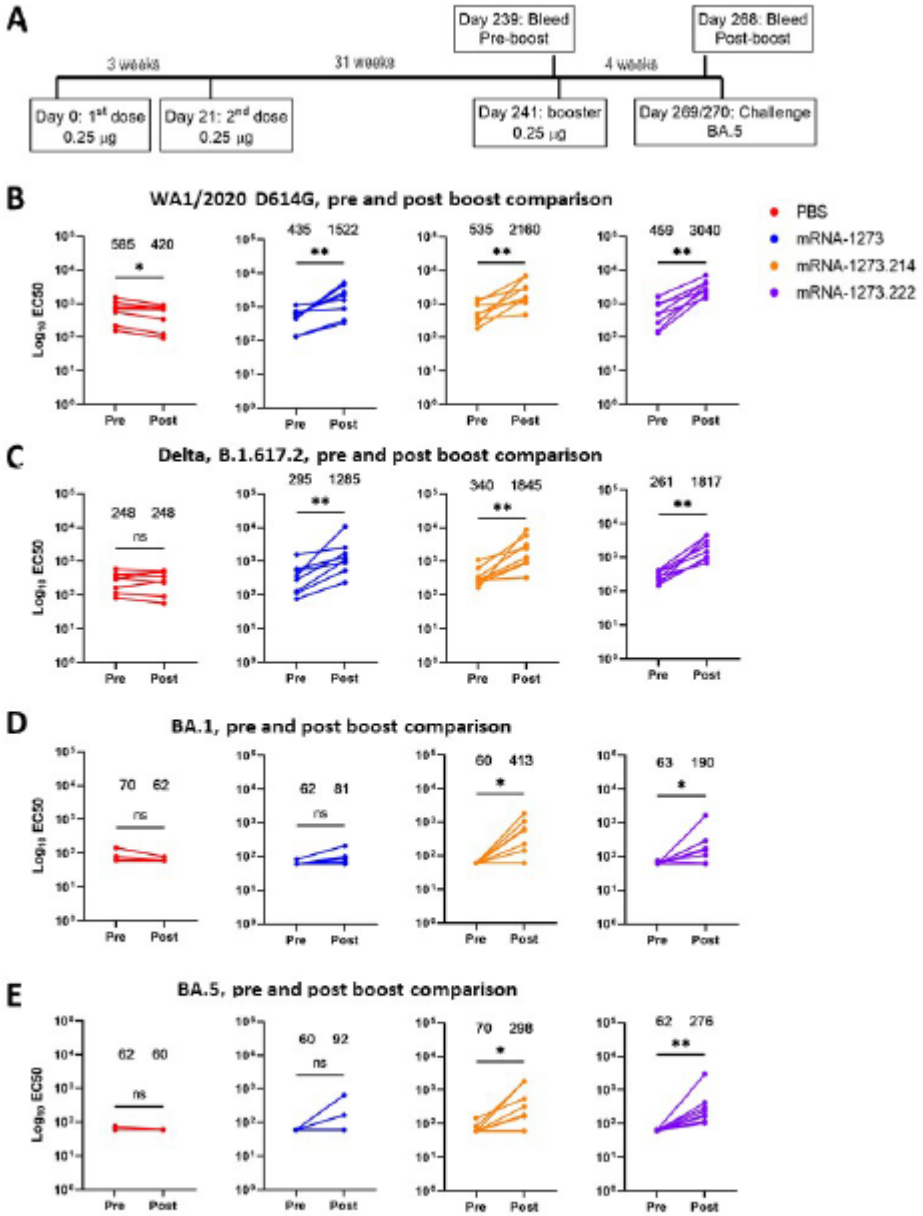
Abbreviations: FFU = focus-forming units; FRNT = focus reduction neutralization test; mRNA = messenger RNA; PBS = phosphate-buffered saline; qRT-PCR = quantitative reverse transcription polymerase chain reaction.

Results:

The pre-boost neutralising antibody titres against SARS-CoV-2 WA.1/2020 D614G and Delta variants had low to moderate titre with levels between ~10^2 to 10^3 EC_{50}. In comparison, the pre-boost neutralising antibody titres against Omicron BA.1 and BA.5 variants were very low in all animals, in general lower than 10^2 EC_{50}.

Four weeks after boosting with the monovalent mRNA-1273 vaccine, the neutralising antibody titres against WA.1/2020 D614G and Delta variants increased about 10-fold. However, only negligible increase of BA.1 and BA.5-specific neutralising antibody titres were observed in those animals. In comparison, boosting with either mRNA-1273.214 or mRNA-1273.222 vaccine induced a statistical significant increase of neutralising antibody titres against SARS-CoV-2 WA.1/2020 D614G, Delta, BA.1 and BA.5. The D614G and Delta-specific neutralising antibody responses reached sufficient high mean values. In contrast, Omicron-specific neutralising antibody titres reached only low to moderate levels. Importantly, the neutralising antibody titres were very heterogeneous within each vaccine group.

Figure 4 Booster Dose of mRNA-1273, mRNA-1273.214, or mRNA-1273.222 Vaccine Enhance Neutralizing Antibody Responses in K18-hACE2 Mice



Abbreviations: BA.1 = SARS-CoV-2 Omicron variant (B.1.1.529); BA.5 = SARS-CoV-2 Omicron subvariant; EC_{50} = half-maximal effective concentration; mRNA = messenger RNA; ns = not significant; PBS = phosphate-buffered saline.

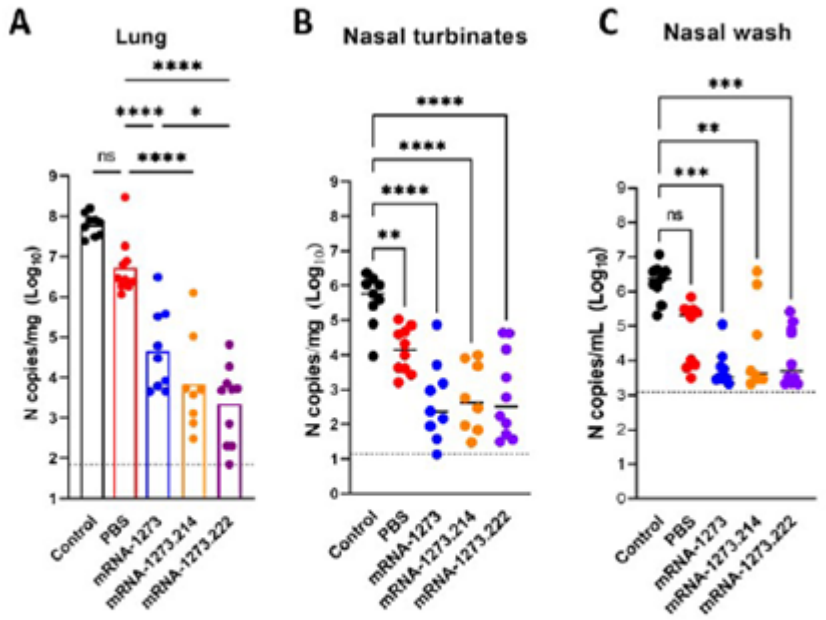
Notes: Statistical analyses were performed using non-parametric Kruskal-Wallis with Dunn's multiple comparison's test; * $p < 0.05$; ** $p < 0.01$.

After BA.5 challenge, the mean viral loads in the analysed tissues of boosted animals were significantly reduced compared to animals treated with non-coding RNA (prime/boost) and in PBS-boosted (mRNA-1273 primed only) mice. Nevertheless, the mice vaccinated only twice with mRNA-1273 (PBS-boosted group) showed still reduced viral loads compared to the mice treated with the non-coding RNA.

The mean viral loads in lung tissue of mRNA-1273.214 and mRNA-1273.222 boosted mice were lower compared to mRNA-1273 boosted mice. The degree of protection against BA.5 infection in lung induced by mRNA-1273.222 booster was the highest followed by mRNA-1273.214 booster and then by mRNA-1273 booster. The mean viral loads in nasal turbinates and nasal wash were similar in all three vaccine groups. Importantly, the viral load values for each vaccinated mice showed a relative high

heterogeneity within each group. The MAH explains this with the relative low vaccine dose. Overall, one booster dose of each mRNA vaccine reduced significantly the viral load in upper and lower respiratory tract 4 days after challenge, but could not induce full protection from BA.5 infection.

Figure 5 Booster Dose of mRNA-1273, mRNA-1273.214, or mRNA-1273.222 Vaccine Enhance Protection Against BA.5 Infection in K18-hACE2 Mice



Abbreviations: ANOVA = analysis of variance; BA.5 = SARS-CoV-2 Omicron subvariant; mRNA = messenger RNA; ns = not significant; PBS = phosphate-buffered saline; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Notes: Statistical analyses were performed using one way ANOVA with Tukey's (A) or Dunnet's (B-C) multiple comparison tests; * $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$.

Assessor's comment

In this immunogenicity and challenge study, K18-hACE2 mice were chosen because they are known to be susceptible to infection after intranasal inoculation by many SARS-CoV-2 variants. Overall, the study design was acceptable. Sufficient numbers of animals per group were used and the vaccines were administered via the clinical route (intramuscular). However, a low dose (0.25 µg mRNA) was used for the primary series immunisation and for the booster dose. According to the MAH, this low dose was used to allow for the possibility of breakthrough infection and to measure different levels of protection in mice with the different vaccines. Probably due to the low dose, high heterogeneity in neutralising antibody titres and viral load in lung and upper respiratory tract tissues after BA.5 challenge were determined. Thus, the informative value of this study is reduced regarding the neutralising immunogenicity and protection against Omicron virus variants. Overall, this study showed that one booster dose of the bivalent mRNA-1273.214 and mRNA-1273.222 vaccines induced comparable and slightly higher neutralising antibody responses against Wuhan D614G, Delta, Omicron BA.1 and BA.5 SARS-CoV-2 variants than a booster dose of mRNA-1273. However, mRNA-1273.214 and mRNA-1273.222 induced neutralising antibody titres against BA.1 and BA.5 were still very low and clearly reduced compared to Wuhan D614G and Delta variants. In addition, one booster dose of mRNA-1273, mRNA-1273.214 or mRNA-1273.222 could reduce significantly the viral load in lower and upper respiratory tract compared to not boosted or negative control animals. However, a full protection against BA.5 was not reached and some vaccinated animals showed still a high viral load in analysed tissue samples, which is probably due to the low vaccine dose.

Due to the limitation of this study, it is not clear if a higher vaccine dose would have induced higher neutralising antibody responses and protection against BA.5 infection. However, a second booster dose might be more beneficial to reach higher immunogenicity and protection. Overall, one booster dose of 0.25 µg mRNA-1273.214 or mRNA-1273.222 seems to have a slight benefit over one booster dose of mRNA-1273 regarding BA.5 Omicron virus variant in K18-hACE2 mice.

2.3.3. Discussion on non-clinical aspects

mRNA-1273.222 could induce robust neutralising antibody titre against Wuhan, BA.1 and BA.4/BA.5 in naïve mice after two primary dose vaccinations. However, one lower booster dose of mRNA-1273.222 induced only moderate neutralising antibody titre against Wuhan and Delta, but little titres against BA.1 and BA.5. Thus, the dose level of mRNA-1273.222 and the number of doses seems to be crucial for sufficient neutralising activity against Omicron virus variants. In addition, two dose of primary vaccination with mRNA-1273.222 could also induce high IgG binding antibody titres against Wuhan, Delta, BA.1 and BA.4/BA.5 in naïve mice. However, the measured IgG binding antibody titres did not remarkably differ from titres in other tested monovalent or bivalent mRNA-1273 vaccine variants. Furthermore, a booster dose of mRNA-1273.222, but also mRNA-1273 and mRNA-1273.214, reduced significantly the viral load in the upper and lower respiratory tract after BA.5 challenge compared to not boosted or negative control animals. Nevertheless, a full protection from BA.5 infection was not observed in the K18-hACE2 mice and a high heterogeneity of viral load in all vaccinated mice were measured, probably due to the low amount of the booster dose.

Additionally, an in-vitro study was conducted to prove that a conserved region within the RBD S2 subdomain and a binding motif for hACE-2 was encodes in the BA.4/BA.5 mRNA sequence included in mRNA-1273.045 vaccine, the BA.4/BA.5-matched vaccine included in the bivalent mRNA-1273.222 vaccine.

Additional toxicity or pharmacokinetic studies were not needed due to the high similarity of mRNA-1273.222 to the original mRNA-1273 vaccine, which are based on the same platform technology. mRNA-1273 and mRNA-1273.222 are based on the same LNP formulation and mRNA length does not differ remarkably from each other. Thus, significant differences in safety and kinetics were not expected for the mRNA-1273.222 vaccine.

2.3.4. Conclusion on the non-clinical aspects

The submitted non-clinical data are acceptable.

2.4. Clinical aspects

2.4.1. Clinical efficacy

The MAH is conducting clinical study P205 for evaluation of the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters against SARS-CoV-2 variants. The study consists of mRNA-1273-P205 part A (1, 2), B, C, D, E, F, G, and H. Part H is investigating a second booster dose of 50 µg mRNA-1273.222 (bivalent Original/Omicron BA.4-5) in participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273. The enrolment status of mRNA-1273-P205 part H is currently unclear. Timelines for completion of enrolment and availability of immunogenicity results is requested from the MAH. (**OC**)

No new clinical study results on efficacy or immunogenicity are provided by the MAH in the current application for approval of mRNA-1273.222 (bivalent Original/Omicron BA.4-5) as a booster vaccine.

Efficacy of mRNA-1273 as a primary series and as a booster vaccination has initially been demonstrated in clinical efficacy studies.

Bivalent Original/Omicron BA.1 mRNA-1273.214 has been approved as a booster vaccination in adolescent and adults from 12 years of age and older based on immunogenicity results that support effectiveness of this bivalent vaccine. Bivalent Original/Omicron BA.1 mRNA-1273.214 could demonstrate superiority as a second booster against SARS-CoV-2 Omicron BA.1 and non-inferiority against the ancestral SARS-CoV-2 strain based on nAB GMTs, compared to booster vaccination with mRNA-1273 (Original).

Non-clinical studies in K18-hACE2 mice demonstrate that nABs against SARS-CoV-2 Omicron BA.4-5 are elicited after booster vaccination with mRNA-1273.222. Based on previous clinical experience and supported by non-clinical studies it is reasonably likely that bivalent Original/Omicron BA.4-5 mRNA-1273.222 will elicit a superior neutralising antibody response against SARS-CoV-2 Omicron BA.4-5 and a non-inferior neutralising antibody response against ancestral SARS-CoV-2 strain. Immunogenicity results from study mRNA-1273-P205 part H to confirm this expectation are requested from the MAH as soon as they become available.

The following measures are considered necessary to address issues related to efficacy:

- The MAH should provide interpretable reactogenicity data from the subjects enrolled in study mRNA-1273-P205 Part H within a month of approval, followed by a summary of the Day 29 interim immunogenicity results by 31 December 2022, and by a final clinical study report by 28 February 2023.
- Results from pharmacovigilance and effectiveness studies on the use of Spikevax bivalent Original/Omicron BA.4-5 should be submitted without delay.

2.4.2. Clinical safety

Introduction

The MAH has submitted a request to expand booster vaccination for individuals 12 years of age and older to permit the use of the variant-modified bivalent mRNA-1273.222 (Original + Omicron BA.4-BA.5) vaccine, 50 µg dose, for the prevention of COVID-19 caused by SARS-CoV-2. The dosing regimen is proposed to be an interval of at least 3 months following a primary series and/or previous booster dose with Spikevax or another authorised/approved COVID-19 vaccine.

There were no clinical safety data submitted for Spikevax bivalent Original/Omicron BA.4-BA.5 (mRNA-1273.222). The safety profile of the mRNA-1273.222 can be supported to a certain degree based on extrapolation from the different variant vaccines that have been studied.

P205 Part H is an open-label clinical study assessing safety and immunogenicity of mRNA-1273.222 as a fourth dose (second booster following primary series and booster with mRNA-1273) using a historical mRNA-1273 fourth dose comparator (P205 Part F, Cohort 2) was initiated on Aug 11, 2022 after FDA review and feedback. According to a submitted Clinical Overview document within a different submission (II/85 G) enrolment of Part H was completed on Aug 23, 2022. In other paragraphs of the same document it is mentioned that recruitment is still ongoing.

However, preliminary data from this ongoing study have not been yet submitted from the MAH.

Study mRNA-1273-P205

Study mRNA-1273-P205 is an ongoing, open-label, Phase 2/3 study that is evaluating the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS-CoV-2 variants including mRNA-1273.211, mRNA-1273 (Spikevax), mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA 1273 222 (Spikevax bivalent Original/Omicron BA.4-5). The study consists of 7 parts: A, (1, 2), B, C, D, E, F, G, and H.

- Part A.1: 50 µg mRNA-1273.211 and 100 µg mRNA-1273.211

- Part A.2: Second booster dose 50 µg mRNA-1273.214: Participants who received mRNA 1273.211 50 µg as a first booster dose in Part A.

- Part B: 100 µg mRNA-1273

- Part C: 50 µg mRNA-1273.617.2 and 100 µg mRNA-1273.617.2

- Part D: 50 µg mRNA-1273.213 and 100 µg mRNA-1273.213

- Part E: 100 µg mRNA-1273.213

- Part F - Cohort 1- 50 µg mRNA-1273.529: Participants who previously received 100 µg mRNA 1273 primary series and have not received a mRNA-1273 booster dose previously.

- Part F - Cohort 2, Second booster dose 50 µg mRNA-1273.529 or 50 µg mRNA-1273 dose: Participants who previously received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273

- Part G – Second booster dose 50 µg mRNA-1273.214: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273

- Part H - Second booster dose 50 µg mRNA-1273.222: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273.

In total, 895 adults were treated with mRNA-1273.211 in Part A of the study including 300 adults treated with 50 µg mRNA-1273.211 and 595 adults treated with 100 µg mRNA-1273.211 up to 2 February 2022. Additional 437 adults were treated with Spikevax bivalent (50 µg elasomeran/imelasomeran) in Part G of the study and 377 adults were treated with Spikevax (50 µg elasomeran) in Part F (Cohort 2), up to 27 April 2022.

Reference for the safety data are made to P205 Part G and Part F, where safety of an Omicron-containing bivalent vaccine mRNA-1273.214 (Original + Omicron) administered as a 4th dose (second booster after mRNA-1273 primary series and booster) was evaluated in comparison to mRNA-1273 booster 50 µg administered as a fourth dose (second booster after mRNA-1273 primary series and booster).

Other supportive safety data refer to P205 Part A, where safety of the Beta-containing bivalent vaccine mRNA-1273.211 (Original + Beta) administered as a booster dose following mRNA-1273 primary series was evaluated in comparison to mRNA-1273 booster 50 µg administered as a first booster dose following mRNA-1273 primary series.

All these safety data have been submitted and evaluated in the *Procedure EMEA/H/C/005791/II/0075/G*, and a summary is presented as following:

P205 Part G (Bivalent Original + Omicron BA.1)

In Part G, there were 437 participants who received the booster dose of mRNA-1273.214 50 µg (Spikevax bivalent Original Omicron BA.1). Of these 197 participants, (45.1) had received the primary

series and the first booster dose of mRNA-1273 and other 240 participants (54.9%) had received the primary series and the first booster dose under the EUA in the United States. The median follow-up time was 43 days.

P205 Part F (Spikevax Original)

In Part F there were 377 participants who received the booster dose of mRNA-1273 50 µg (Spikevax Original Monovalent). Of these, 264 participants (70.0%) had received the primary series and the first booster dose of mRNA-1273 and 113 participants (30.0%) had received the primary series and the first booster dose under the EUA in the United States. The median follow-up time was 57 days.

P205 Part A (Beta-bivalent vaccine)

In Part A there were 300 participants who received the booster dose of RNA-1273.211 50 µg (Beta-bivalent vaccine). The median follow-up time from mRNA-1273.211 50 µg booster dose injection was 245.0 days.

Local and systemic reactogenicity (P205 Part G and Part F)

The incidence of solicited local reactions was comparable between the mRNA-1273.214 50 µg booster dose group (Part G) and the mRNA-1273 50 µg booster dose group (Part F), accordingly 79.4% vs. 79.5%.

However slightly higher reactogenicity was noted in the mRNA-1273.214 50 µg booster dose group (Part G) vs. the mRNA-1273 50 µg booster dose group (Part F). The most common local ARs for both groups: were "any pain" with 77.3% vs. 76.6%, followed by "any axillary swelling or tenderness" with 17.4% vs 15.4%. The highest differences were noted regarding any erythema (redness) reported in 6.9 % participants in the mRNA-1273.214 50 µg booster dose group and in 3.7% participants in the mRNA-1273 50 µg booster dose group.

The majority of solicited local ARs were mild- to- moderate (Grade 1-2) for both groups.

Regarding the Grade 3 local ARs, same frequency has been observed in the two groups with (3.4%), however "erythema" was the most common Grade 3 local AR for P205 Part G with 2.1% versus 0.6% for P205 Part F. The Grade 3 erythema events (n=9) had a duration from 1-5 days. No grade 4 events were reported in both Groups. After the booster injection, the median duration of solicited local ARs was 2 days. The slightly higher rate of erythema after booster vaccination with mRNA-1273.214 is deemed acceptable and does not trigger concerns about the reactogenicity profile of the bivalent vaccine.

The incidence of solicited systemic reactions was slightly higher in the mRNA-1273.214 50 µg booster dose group compared to the mRNA-1273 50 µg booster dose group, accordingly 70.3% and 66.1%. The most common systemic AR after the booster dose for both groups accordingly were: fatigue (54.9% vs 51.4%), followed by headache (43.9% vs 41.1%), myalgia (39.6% vs 38.6%), and arthralgia (31.1% vs 31.7%). The majority of the systemic ARs in both groups were mild-to- moderate (Grade 1 -2) and they were comparable between the two groups. Grade 3 events were in higher frequency in the mRNA-1273.214 50 µg booster dose (5.5%) compared to (4.6%) in the mRNA-1273 50 µg booster dose group, the most common Grade 3 event reported in the Part G was fatigue (3.4 % vs 3.1%) while in Part F was myalgia (3.7% vs 2.3%).

A summary for local and systemic reactions in both Part G and Part F is provided in the table below.

Table 3 Summary of Participants with Solicited Adverse Reactions within 7 Days After the Injection by Grade – 2nd Booster Dose: mRNA-1273.214, mRNA-1273 (Solicited Safety Set), source table 23 clinical overview

	P205 Part G	P205 Part F
	mRNA-1273.214	mRNA-1273
Solicited Adverse Reaction	50 µg	50 µg
Category	(N=437)	(N=351)
Grade	n (%)	n (%)
Solicited adverse reactions - N1	437	351
Any solicited adverse reactions	380 (87.0)	301 (85.8)
95% CI	83.4, 90.0	81.7, 89.2
Grade 1	220 (50.3)	184 (52.4)
Grade 2	125 (28.6)	89 (25.4)
Grade 3	35 (8.0)	28 (8.0)
Grade 4	0	0
Solicited local adverse reactions - N1	437	351
Any solicited local adverse reactions	347 (79.4)	279 (79.5)
95% CI	75.3, 83.1	74.9, 83.6
Grade 1	291 (66.6)	239 (68.1)
Grade 2	41 (9.4)	28 (8.0)
Grade 3	15 (3.4)	12 (3.4)
Grade 4	0	0
Pain - N1	437	351
Any	338 (77.3)	269 (76.6)
Grade 1	303 (69.3)	241 (68.7)
Grade 2	31 (7.1)	24 (6.8)
Grade 3	4 (0.9)	4 (1.1)
Grade 4	0	0
Erythema (redness)[a] - N1	437	351
Any	30 (6.9)	13 (3.7)
Grade 1	15 (3.4)	5 (1.4)
Grade 2	6 (1.4)	6 (1.7)
Grade 3	9 (2.1)	2 (0.6)
Grade 4	0	0
Swelling (hardness)- N1	437	351
Any	30 (6.9)	23 (6.6)
Grade 1	17 (3.9)	13 (3.7)
Grade 2	8 (1.8)	5 (1.4)
Grade 3	5 (1.1)	5 (1.4)
Grade 4	0	0
Axillary swelling or tenderness - N1	437	351
Any	76 (17.4)	54 (15.4)
Grade 1	71 (16.2)	46 (13.1)
Grade 2	4 (0.9)	4 (1.1)
Grade 3	1 (0.2)	4 (1.1)
Grade 4	0	0
Solicited systemic adverse reactions - N1	437	351
Any solicited systemic adverse reactions	307 (70.3)	232 (66.1)
95% CI	65.7, 74.5	60.9, 71.0
Grade 1	167 (38.2)	124 (35.3)
Grade 2	116 (26.5)	92 (26.2)
Grade 3	24 (5.5)	16 (4.6)
Grade 4	0	0
Fever[b] - N1	436	351
Any	19 (4.4)	12 (3.4)
Grade 1	14 (3.2)	9 (2.6)
Grade 2	4 (0.9)	3 (0.9)
Grade 3	1 (0.2)	0
Grade 4	0	0
Headache - N1	437	350
Any	192 (43.9)	144 (41.1)
Grade 1	150 (34.3)	112 (32.0)
Grade 2	37 (8.5)	30 (8.6)
Grade 3	5 (1.1)	2 (0.6)
Grade 4	0	0
Fatigue - N1	437	350
Any	240 (54.9)	180 (51.4)
Grade 1	125 (28.6)	95 (27.1)
Grade 2	100 (22.9)	74 (21.1)
Grade 3	15 (3.4)	11 (3.1)
Grade 4	0	0
Myalgia - N1	437	350
Any	173 (39.6)	135 (38.6)
Grade 1	101 (23.1)	68 (19.4)
Grade 2	62 (14.2)	54 (15.4)
Grade 3	10 (2.3)	13 (3.7)
Arthralgia - N1	437	350
Any	136 (31.1)	111 (31.7)

Grade 1	93 (21.3)	70 (20.0)
Grade 2	39 (8.9)	38 (10.9)
Grade 3	4 (0.9)	3 (0.9)
Grade 4	0	0
Nausea/vomiting - N1	437	350
Any	45 (10.3)	35 (10.0)
Grade 1	39 (8.9)	27 (7.7)
Grade 2	5 (1.1)	8 (2.3)
Grade 3	1 (0.2)	0
Grade 4	0	0
Chills - N1	437	350
Any	104 (23.8)	74 (21.1)
Grade 1	65 (14.9)	46 (13.1)
Grade 2	38 (8.7)	27 (7.7)
Grade 3	1 (0.2)	1 (0.3)
Grade 4	0	0

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

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

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

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

Source: Module 5.3.5.1 Table 14.3.1.1.1.8.

Unsolicited adverse events regardless of the relationship to vaccination up to 28 days after the second booster doses were reported in 18.5% of participants in the mRNA-1273.214 and 20.7% in the m RNA-1273 groups. It is observed that it was slightly lower in the mRNA-1273.214 booster group dose. The incidences of AEs considered related to the study vaccination by the investigator were comparable between the two booster groups, respectively 5.7% in the mRNA-1273.214 group and 5.8% in the mRNA-1273 group.

There were 3 SAEs reported in the mRNA-1273.214 50 µg booster dose group (Part G), respectively one severe traumatic pelvic fracture; a SAE of prostate cancer and a SAE of nephrolithiasis. They were all assessed not to be related with the study intervention by the investigator and it has been agreed upon.

In the mRNA-1273 50 µg booster dose group (Part F), has been reported 1 SAE of lumbar osteoarthritis assessed as not related to the study intervention. No deaths have been reported in the two booster groups.

Assessor's comments:

Overall, these data have indicated a trend to slightly higher reactogenicity of the Bivalent Original + Omicron BA.1 compared to Spikevax Original vaccine. However, as concluded in the previous variation these minor differences are not clinically meaningful and are not considered to have a significant impact on the safety profile of mRNA-1273.214 when compared to that of mRNA-1273.

Local and systemic reactogenicity (P205 Part A)

The incidence of solicited local reactions in P205 Part A was 85.2%, with the pain reported as most common (84.9%). The majority of the local solicited ARs were Grade 1 (68.8%) and Grade 2 (13.8%). The Grade 3 events had a frequency of (2.7%) with Pain reported as most common (1.7%).

The incidence of solicited systemic reactions in participants P205 Part A was (75.8%), with fatigue (64.4%) reported as most common. The majority of the events were Grade 1-Grade 2 (35.2%-32.2%). The frequency of the Grade 3 events was (8.4%), with fatigue (6.4%) reported as most common.

A summary for local and systemic reactions in Part A is provided in the table below.

Table 4 Summary of Participants with Solicited Adverse Reactions within 7 Days Table 7 After the Injection by Grade - 1st Booster Dose: mRNA-1273.211 50 µg (Solicited Safety Set), source Table 25 Clinical Overview

Solicited Adverse Reaction Category Grade	P205 Part A mRNA-1273.211 50 µg (N=298) n (%)
Solicited adverse reactions - N1	298
Any solicited adverse reactions	270 (90.6)
95% CI	86.7, 93.7
Grade 1	140 (47.0)
Grade 2	98 (32.9)
Grade 3	32 (10.7)
Grade 4	0
Solicited local adverse reactions - N1	298
Any solicited local adverse reactions	254 (85.2)
95% CI	80.7, 89.1
Grade 1	205 (68.8)
Grade 2	41 (13.8)
Grade 3	8 (2.7)
Grade 4	0
Pain - N1	298
Any	253 (84.9)
Grade 1	211 (70.8)
Grade 2	37 (12.4)
Grade 3	5 (1.7)
Grade 4	0
Erythema (redness)[a] - N1	298
Any	8 (2.7)
Grade 1	5 (1.7)
Grade 2	2 (0.7)
Grade 3	1 (0.3)
Grade 4	0
Swelling (hardness)- N1	298
Any	10 (3.4)
Grade 1	7 (2.3)
Grade 2	2 (0.7)
Grade 3	1 (0.3)
Grade 4	0
Axillary swelling or tenderness - N1	298
Any	74 (24.8)
Grade 1	59 (19.8)
Grade 2	13 (4.4)
Grade 3	2 (0.7)
Grade 4	0
Solicited systemic adverse reactions - N1	298
Any solicited systemic adverse reactions	226 (75.8)
95% CI	70.6, 80.6
Grade 1	105 (35.2)
Grade 2	96 (32.2)
Grade 3	25 (8.4)
Grade 4	0
Fever[b] - N1	298
Any	14 (4.7)
Grade 1	11 (3.7)
Grade 2	3 (1.0)
Grade 3	0
Grade 4	0
Headache - N1	298
Any	151 (50.7)
Grade 1	108 (36.2)
Grade 2	39 (13.1)
Grade 3	4 (1.3)
Grade 4	0
Fatigue - N1	298
Any	192 (64.4)
Grade 1	89 (29.9)
Grade 2	84 (28.2)
Grade 3	19 (6.4)
Grade 4	0
Myalgia - N1	298
Any	146 (49.0)
Grade 1	75 (25.2)
Grade 2	59 (19.8)
Grade 3	12 (4.0)
Grade 4	0

Arthralgia - N1	298
Any	104 (34.9)
Grade 1	59 (19.8)
Grade 2	37 (12.4)
Grade 3	8 (2.7)
Grade 4	0
Nausea/vomiting - N1	298
Any	35 (11.7)
Grade 1	25 (8.4)
Grade 2	10 (3.4)
Grade 3	0
Grade 4	0
Chills - N1	298
Any	63 (21.1)
Grade 1	32 (10.7)
Grade 2	30 (10.1)
Grade 3	1 (0.3)
Grade 4	0

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

N1 = number of exposed participants who submitted any data for the event. Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The 95% CI is calculated using the Clopper-Pearson method. This interim analysis includes Part A participants immunogenicity data up to Day 181 visit. The data cutoff date for safety and SARS-CoV-2 infection is 02 Feb 2022.

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

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

Source: Module 5.3.5.1 Study P205 Part A Interim Analysis Report Table 19.

There were 21% participants who reported unsolicited treatment related adverse events within 28 days after the mRNA-1273.211 50 µg booster dose. The most commonly unsolicited TEAEs were fatigue (3.3%); arthralgia (1.7%); myalgia and injection site lymphadenopathy (1.3%); and rhinovirus infection and headache (1.0%).

In the mRNA-1273.211 50 µg booster dose group (Part A), there were no SAEs up to 28 days while 5 SAEs have been reported in 4 participants after Day 28 and through the data cut-off date. The events included 1 event of dehydration and hypotension concurrently, one event of myocardial infarction (fatal event), 1 SAE as peripheral arterial occlusive disease, and 1 SAE of cholelithiasis. None of the SAEs were considered treatment related by the Investigator or MAH and it is agreed upon. The fatal event of myocardial infarction has been assessed as not to be related with the study intervention by the investigator.

Assessor's comments:

According to the overall incidence of local and systemic adverse events it seems that the reactogenicity of the Beta Bivalent mRNA-1273.211 vaccine given as a 1st booster dose appears similar with the ancestral mRNA-1273 vaccine.

Adverse events of special interest (AESIs)

Up to the data cut-off date, no participants in the mRNA-1273.214 50 µg booster dose group (Part G) had an investigator-assessed AESI.

In the mRNA-1273 50 µg booster dose group (Part F), 1 participant had a moderate non-serious irregular heart rate, assessed as not related to the study investigation by the investigator.

In the mRNA-1273.211 50 µg (P205 Part A), there was one investigator-assessed AESIs beyond 28 days after the mRNA-1273.211 50 µg booster dose, the fatal acute myocardial infarction, assessed to be unrelated to the study intervention.

No events of acute myocarditis or pericarditis were identified in the booster dose groups respectively, in the mRNA-1273.214 50 µg (Part G); mRNA-1273 50 µg (Part F) booster dose groups or in the mRNA-1273.211 50 µg (Part A) booster dose group.

Study mRNA-1273-P201

Study mRNA-1273-P201, a 3-part Phase 2a, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of elasomeran SARS-COV-2 vaccine in adults aged 18 years and older, has been completed.

Part A was a randomised, observer-blind, and placebo-controlled, with adult participants at least 18 years of age. The study included 2 age cohorts: ≥ 18 to < 55 years old and ≥ 55 years old. Eligible participants (approximately 600 planned) received elasomeran or saline placebo control according to a 1:1:1 randomisation ratio, i.e., within each age cohort, 100 participants received elasomeran 50 µg, 100 participants received elasomeran 100 µg, and 100 participants received saline placebo.

Part B was designed to offer participants who received placebo in Part A of the study the option to receive 2 injections of elasomeran (100 µg) and participants who received 1 or 2 doses of 50 µg or 100 µg elasomeran in Part A of this study the option to receive a single booster dose of 50 µg elasomeran. The 50 µg booster dose was selected as the optimal effective dose for boosting in Part B-Booster.

Part C was a proof-of-concept rollover study of 60 participants who were enrolled in the Phase 3 study mRNA-1273-P301, had already been unblinded, and had previously received 2 doses of elasomeran at least 6 months earlier. Upon enrolment into Part C of this study, participants received a single IM injection of mRNA-1273.351 (20 µg or 50 µg) or elasomeran/mRNA-1273.351 mixture (50 µg total) at least 6 months after receiving the second vaccination in study mRNA-1273-P301.

Assessor's comments:
The MAH has provided in this submission a brief clinical overview of the beta monovalent mRNA-1273.351 (20 µg or 50 µg) vaccine administered as a booster dose. Of note a complete vaccine development package has not been submitted and the below safety results are presented only as interpreted by MAH and could not evaluated by the assessors as not data have been submitted.

The mRNA-1273.351 50 µg (Cohort 1, 20 participants), elasomeran/mRNA-1273.351 50 µg (Cohort 2, 20 participants), and mRNA-1273.351 20 µg (Cohort 3, 20 participants) booster vaccines demonstrated acceptable reactogenicity and safety findings that were similar to Part A and Part B.

The frequency, severity, timing, and duration of solicited local and systemic adverse reactions were similar to those reported in Part A and Part B.

Up to 28 days after booster vaccination, at least 1 unsolicited treatment emergent adverse event (TEAE) was reported for 3/20 (15.0%) participants in Cohort 1, 4/20 (20.0%) participants in Cohort 2, and 3/20 (15.0%) participants in Cohort 3. At least 1 medically attended adverse event (MAAE) was reported for 2/20 (10.0%) participants in Cohort 1, 3/20 (15.0%) participants in Cohort 2, and 3/20 (15.0%) participants in Cohort 3. The most frequently reported unsolicited TEAEs up to 28 days after booster vaccination (incidence > 1%) were hypertension (2/20 [10.0%]) and arthralgia, fatigue, and myalgia (1/20 [5.0%] each) in Cohort 1; arthralgia and myalgia (2/20 [10.0%] each) and animal bite, bursitis, extrasystoles, fatigue, headache, lymphadenopathy, and staphylococcal infection (1/20 [5.0%] each) in Cohort 2; and asthma, depression, pharyngitis streptococcal, and sinusitis bacterial (1/20 [5.0%] each) in Cohort 3. All unsolicited TEAEs were mild in severity.

At least 1 TEAE that was considered by the investigator to be related to vaccine was reported up to 28 days after the booster vaccine for 1/20 (5.0%) participants in Cohort 1 and 2/20 (10.0%) in Cohort 2; no participants reported TEAEs considered related to vaccination in Cohort 3. Unsolicited TEAEs considered related to vaccination were arthralgia, fatigue, and myalgia (1/20 [5.0%] each) in Cohort

1; and arthralgia and myalgia (2/20 [10.0%] each), headache and fatigue (1/20 [5.0%] each) in Cohort 2.

Up to End of Study (open label-Day 181), 1/20 (5.0%) participants in Cohort 1 reported 1 SAE of pancreatic carcinoma stage IV, which was considered not related to booster vaccine. No SAEs were reported in Cohorts 2 and 3. At least 1 MAAE was reported for 3/20 (15.0%) participants in Cohort 1, 7/20 (35.0%) participants in Cohort 2, and 7/20 (35.0%) participants in Cohort 3.

Up to End of Study, 1 participant in Cohort 2 reported ongoing MAAEs of arrhythmia, bursitis, extrasystoles, nasal polyps, nasal septum deviation, sinusitis bacterial, and thyroid disorder.

No participants had unsolicited TEAEs leading to study discontinuation. One participant discontinued due to withdrawal of consent after being diagnosed with a severe unrelated SAE of pancreatic carcinoma stage IV. No deaths occurred during Part C. No new safety concerns have been identified.

2.4.2.1. Discussion on clinical safety

The safety profile of the Bivalent Original/Omicron BA.4-BA.5 vaccine can be supported to a certain degree based on extrapolation from the different variant vaccines that have been studied. The scientific question and approach is regarded as different when authorising a variant vaccine with not clinical data compared to the authorisation of variant vaccine with clinical trial data. In the former situation the comparative assessment plays a larger role while in the latter situation the obtained clinical data form the basis of the assessment. Therefore, in order to enable extrapolation of safety profile for the Original/Omicron BA.4-BA.5 the MAH should provide a comparative analysis regarding the reactogenicity of all variant vaccines. This analysis should clearly distinguish trial data obtained as first or second booster and clearly demonstrate the overall safety database. (**OC**)

The MAH is asked to provide the timelines on the submission of preliminary safety data regarding the Bivalent Original/Omicron BA.4-BA.5 vaccine. (**OC**)

Reference for supportive safety data are those from Omicron-containing bivalent vaccine mRNA-1273.214 (Original + Omicron BA.1) administered as a second booster dose and evaluated in comparison to that of the monovalent booster vaccine mRNA-1273 50 µg. Slightly higher incidences of local and systemic adverse events were observed, when comparing these two vaccines given as booster doses. However, these minor differences were not considered clinically meaningful and were not considered to have a significant impact on the safety profile of mRNA-1273.214 when compared to that of mRNA-1273. It is concluded that the reactogenicity of mRNA-1273.214 50 µg as booster dose is covered sufficiently with a short term follow up of more than a month and that no concerns are emerging from the available data set regarding the safety profile of this bivalent vaccine.

Other supportive safety data refer to the Beta-containing bivalent vaccine mRNA-1273.211 (Original + Beta) administered as a booster dose following mRNA-1273 primary series evaluated in comparison to mRNA-1273 booster 50 µg administered as a first booster dose following mRNA-1273 primary series. According to the overall incidence of local and systemic adverse events it seems that the reactogenicity of the bivalent mRNA-1273.211 given as a 1st booster dose appears similar with the ancestral mRNA-1273.

Additional supportive have been provided for the beta monovalent mRNA-1273.351 (20 µg or 50 µg) vaccine administered as a booster dose, however these results have not been submitted and evaluated from the assessors therefore a final conclusion cannot be made at this point.

Overall, all booster vaccines demonstrated no unexpected reactogenicity or new safety results.

2.4.2.2. Conclusions on clinical safety

Overall, from the evaluation of all safety-related data submitted so far for the Spikevax Original and variant vaccines (Beta Bivalent and Omicron Bivalent BA.1) it is concluded that the reactogenicity has been acceptable.

Based on the extrapolation of the safety data, it is not expected that the safety profile of the Spikevax Original/BA.4-5 would be different in this aspect.

But in order to conclude on the expected safety profile for the Original/Omicron BA.4-BA.5 the MAH should provide a comparative analysis regarding the reactogenicity of all variant vaccines and clearly delineate database, clinical situation (1st vs 2nd booster) to underpin his conclusion that a comparable safety is to be expected. (OC)

3. First request for supplementary information

3.1. Major objections

Quality aspects

General question:

1. The MAH introduced the IDR in the 3'UTR, however this change was not included and discussed/justified in the manufacturing development documents. Furthermore, in the pre-submission meeting it was discussed that the MAH will submit supportive data from influenza mRNA vaccine to support the claim that there exists substantial flexibility to modify the 3´UTR sequence without impacting protein expression or functional mRNA half-life. No such data was submitted and should be provided to justify the change.

3.2.S.2.5 Process validation and/or evaluation

2. The MAH provided a dT resin reuse report, without providing further information. This reuse of resins across different mRNA constructs is not implemented in the dossier (section 3.2.S.2.5). If the MAH wants to implement this change the following information need to be provided (as already mentioned in the scientific advice June 2022):
    - For with constructs is this shared resin-use conducted
    - Justification for the specifications of mRNA stated in the resin re-use report
    - The data in the report shows residual mRNA amounts after 48 cycles maximum, however 200 cycles are licensed for the resin currently. It should be clarified whether with this shared use only 48 cycles are conducted with each resin or justified how this data is representative for the 200 cycle usage.
    - "Section 3.2.S.2.5.2 resin reuse study" needs to be adapted, as no shared resin re-use is mentioned currently
    - The identity test used on the mRNA level or mRNA-1273 LNP drug product intermediate can distinguish between all different mRNA variants used and potential cross-contamination by other mRNA variants is detected with a very high sensitivity, so far only specificity is validated

3.2. Other concerns

Quality aspects

Drug substance:

3.2.S.1.2 Structure

3. The MAH is asked to provide more details about the changes in the 3'UTR and the identification and ratio (IDR) sequence itself. Which nucleotides are changed compared to the prototype and the BA.1 3'UTR and the reason for this change? The sentence added in table 2 is not considered adequate.

3.2.S.2.3 Control of material – linearised plasmid

4. The MAH states that the 3'UTR for CX-034476 includes a substitution in an 11 nucleotide region of the prototype 3'UTR of up to 25 nucleotides in length as IDR. The MAH should clearly indicate how long this IDR sequence for CX-034476 is, as it is stated in section 3.2.S.1.2 that a 14 nucleotides substitution is included.

3.2.S.4.1 Specification

5. For product related impurities in section 3.2 S.4.1 of CX-024414 the specification referring to the same SOP number also includes "Report % post-main peak area". The MAH is asked to justify the difference.

6. In the dossier section 3.2 S.4.1 CX-031302 the specification refers document refers to the document in section of the CX-024414, but there are currently two versions. One with the old purity assay, one with the new purity assay. The MAH should clarify with purity test is used for which mRNA and submit/delete the document in the respective sections.

3.2.S.4.3 Validation of analytical procedures

7. The MAH is asked to include also CX-031302 in the specificity testing of the identity test.

8. The MAH is asked to justify why intermediate precision was not included in the method validation as done for the identity method validation of CX-031302.

3.2.S.4.4 Batch analysis

9. In the batch analysis document, the purity test is indicated as a RP-HPLC whereas in the specification it is mentioned that the RP-IP-HPLC method is used. The MAH should clarify if the old (RP-HPLC) or the new (RP-IP-HPLC) purity assay was used and adapt the respective documents accordingly.

3.2.S.7 Stability

10. The MAH is referring to the RP-HPLC method for purity and needs to clarify with purity method is used.

11. The MAH is asked to implement a stability study protocol that reflects the actual shelf life claim with 3 months at -15 to -25°C before transfer to -60 to -90°C as already asked for in the variation II/75/G.

12. The MAH is asked to include the verification lot 4013422002 in table 1 of section stability data stating the available data.

13. The MAH is asked to provide updated stability data if available.

Final product:

3.2.P.2.3 Manufacturing Process Development

13. It is unclear why in Table 13 in section 3.2.P.2.3 Manufacturing Process Development {mRNA-1273.222} and Table 3 in section 3.2.P.3.5 Process Validation and/or Evaluation {Catalent - mRNA-1273.222}, the process durations are given for the unlabelled product, since release testing results include purity results after labelling/packaging so the final process times should already be known.

14. The acceptable range for the CIPC weight ratio pooled LNPs is 0.9-1.1. For one of the batches a result of 0.88 has been measured due to a pooling error. Although identified as deviation, the number 0.9 is given in the tables after rounding of the result. To avoid that results between 0.85 and 0.89 appear as 0.9 (which would be in spec) in the tables, it is recommended to use two decimal places.

3.2.P.3.5 Process Validation

15. All relevant dossier sections, including comparability report and process validation report, should be updated to include final cumulative process duration times.

16. In dossier section 3.2.P.3.5.1.3.4, it is stated that during PPQ, processing durations of no less than the target limit were used to confirm holding times. However, it appears that reported process durations are not at the limit. This should be clarified.

17. In table 11.4 of the process validation report, the clarification filtration pressure exceeded the normal operating rage leading to a deviation. Therefore "Met NOR?" should be reported as No and not as Yes. In addition, the footnote references to REC 577851 instead of REC 577581.

18. Defined Processing time duration for Catalent is 504 hours. Therefore, it is unclear why in the PV report a maximum cumulative process time of 336h is stated in table 11.9 and 11.10. In addition, it should be stated clearly in the PV report that the process times are not the final ones and do not include labelling and packaging times.

3.2.P.6 Reference standards

19. In dossier section 3.2.P.6, the interims standard lot 8514100101 is described. In contrast, a CoA for a standard lot Reference standard 8514100102 is provided. It should be clarified which standard is currently used and the respective information in the dossier should be harmonised.

3.2.P.8 Stability

20. The platform stability approach should be supported by the accelerated stability data from the developmental DP batch. The MAH should demonstrate that the degradation rate for the developmental batch at accelerated conditions is conform with the platform data.

21. In the tables in section 3.2.P.8.3 (stability data), the former purity test (RP-HPLC) is listed instead of the current RP-IP-HPLC test. This should be corrected. The same error is found in the footnote to table 4 in section 3.2.P.8.1.

4. Assessment of the responses to the first request for supplementary information

4.1. Major objections

Quality aspects

Question 1: The MAH introduced the IDR in the 3'UTR, however this change was not included and discussed/justified in the manufacturing development documents. Furthermore, in the pre-submission meeting it was discussed that the MAH will submit supportive data from influenza mRNA vaccine to support the claim that there exists substantial flexibility to modify the 3´UTR sequence without impacting protein expression or functional mRNA half-life. No such data was submitted and should be provided to justify the change.

Summary of the MAH's response: The MAH had submitted the relevant background information supporting the introduction of the IDR sequence into the 3'UTR in the reviewer's guide in Module 1. The relevant information is incorporated into Section 3.2.S.2.6 {CX-034476 mRNA}, including data obtained from previous studies performed on the influenza mRNA vaccine currently included in clinical studies (refer to Section 3.2.S.2.6.4).

Assessment of the MAH's response: The MAH included supportive data from an influenza mRNA vaccine showing that changes in the 3'UTR has no influence on in vivo potency. This information is now included in Section 3.2.S.2.6.4

Conclusion:

Issue solved.

Question 2: The MAH provided a dT resin reuse report, without providing further information. This reuse of resins across different mRNA constructs is not implemented in the dossier (Section 3.2.S.2.5).

If the MAH wants to implement this change the following information need to be provided (as already mentioned in the scientific advice June 2022):

- For with constructs is this shared resin-use conducted

- Justification for the specifications of mRNA stated in the resin re-use report

- The data in the report shows residual mRNA amounts after 48 cycles maximum, however 200 cycles are licensed for the resin currently. It should be clarified whether with this shared use only 48 cycles are conducted with each resin or justified how this data is representative for the 200 cycle usage.

- "Section 3.2.S.2.5.2 resin reuse study" needs to be adapted, as no shared resin re-use is mentioned currently

- The identity test used on the mRNA level or mRNA-1273 LNP drug product intermediate can distinguish between all different mRNA variants used and potential cross-contamination by other mRNA variants is detected with a very high sensitivity, so far only specificity is validated

Summary of the MAH's response: Shared use of Oligo dT Chromatography Resin has been implemented at Moderna's Norwood, MA facility only for CX-024414 and CX-034476, both of which are later formulated together into mRNA-1273.222 drug product. To date, all lots of CX-024414 have been produced starting with virgin resin and continued with dedicated packed resin columns. All lots of CX-

034476 produced at the Norwood facility were manufactured using resin that was previously used for commercial manufacture of CX-024414.

This limitation dedicates resin to a single drug product, while allowing for the use of resin across sequences that are formulated together in the drug product. This limitation also obviates the need for detection of possible cross-contaminating sequences in drug product since resin is dedicated to the intended sequences. The existing identity method for drug product is able to detect the intended sequences, and thus is adequate given this limitation to shared resin use.

This response provides justification for shared use of resin among RNA sequences that are later formulated into the same drug product.

Additionally, an updated version of Section 3.2.S.2.5.6 has been included with this response to better reflect the justification for shared resin use between RNA sequences.

Data supporting shared resin use and resin lifetime can be summarised in these arguments which are explained in more detail below.

1. The chromatography column cleaning solution contains 0.1 M sodium hydroxide, which degrades full length RNA into RNA fragments. Degradation experiments showed that no detectable full-length RNA persisted after 30 minutes of exposure, which equals the cleaning cycle hold time.

2. The RNA carry-over limit used in resin lifetime studies (0.25 µg/mL) is established based on site cleaning validation requirements and provides a safety factor of >7000 compared to the Maximum Allowable Carryover derived from a Permissible Daily Exposure calculation.

3. Measured against the RNA carry-over limit, full-scale and small-scale data show consistent and comparable clearance of RNA across the column lifetime and across sequences. This has been demonstrated at full-scale over 600 cycles for CX-024414 (See 3.2.S.2.5.5.1.5). Similar performance has been demonstrated at small scale over 200 cycles for resin exposed to multiple sequences (PD-REP-1094). Finally, similar cleaning performance was verified at full scale with resin that was used to manufacture CX-024414, and later CX-034476 (See Section 3.2.S.2.5.2 resin reuse study.)

4. In addition to the cleaning effectiveness shown, the risk of exogenous cross contamination within a drug product is eliminated by limiting the cross-sequence use of resin to only those sequences that will eventually be formulated together into the same drug product.

Conclusion on Cross-sequence Resin Use

Data presented above support the use of resin across multiple RNA sequences because RNA carryover between batches has been shown to be consistently below the established limit. Furthermore, low levels of detectable RNA are not expected to contain full-length RNA from one batch to another based on the rapid degradation of RNA in sodium hydroxide solutions.

While the studies summarised above support the cross-sequence resin use, the MAH confirms that currently the cross-sequence resin use is limited to sequences that are co-formulated into the same drug product. Sharing of resin to new sequences introduced for future variants will be supported by adequate data and justification, and submitted in the scope of further variations as appropriate.

Assessment of the MAH's response: The MAH clarifies that the shared resin used is implemented at the Moderna Norwood site only for CX-024414 and CX-034476, which will be formulated together in one DP later on dedicating resin to a single drug product. Furthermore, the MAH states that degradation experiments showed that no detectable full-length RNA persisted after 30 minutes of exposure, which equals the cleaning cycle hold time. In summary the justification to share the resin is

acceptable since it is only for mRNA sequences that will later be formulated into the same drug product.

Conclusion:

Issue solved.

☐Overall conclusion and impact on benefit-risk balance has been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

4.2. Other concerns

Quality aspects

Question 3: The MAH is asked to provide more details about the changes in the 3'UTR and the identification and ratio (IDR) sequence itself. Which nucleotides are changed compared to the prototype and the BA.1 3'UTR and the reason for this change. The sentence added in table 2 is not considered adequate.

Summary of the MAH's response: Please find the updated Section 3.2.S.1.2 Structure {CX-034476 RNA} included in this response.

Assessment of the MAH's response: The MAH provided an updated document including the requested information.

Conclusion:

Issue solved

Question 4: The MAH states that the 3'UTR for CX-034476 includes a substitution in an 11 nucleotide region of the prototype 3'UTR of up to 25 nucleotides in length as IDR. The MAH should clearly indicate how long this IDR sequence for CX-034476 is, as it is stated in section 3.2.S.1.2 that a 14 nucleotides substitution is included.

Summary of the MAH's response: The MAH clarifies that the strategy for IDR incorporation into a 3'UTR for a new variant mRNA sequence can utilise sequences up to a maximum length of 25 nt. In the specific case of CX-034476 mRNA, this IDR sequence is 14 nt. Future variant mRNA-1273 sequences may incorporate longer IDR sequences.

Assessment of the MAH's response: That future variant mRNA-1273 sequences may incorporate longer IDR sequences was understood before however in section 3.2.S.2.3.1.1 Origin of the DNA Sequence it is stated: "In addition to the elements described for the 3'UTR of CX-024414, the 3'UTR for CX-034476 also includes a substitution in an 11 nucleotide region of the prototype 3'UTR for up to 25 nucleotides in length as an Identification and Ration (IDR) sequence." This is not accepted, as CX-034476 has specifically a 14 nucleotides substitution included. This is not about the general approach or platform but about the specific mRNA variant.

Conclusion:

Issue only solved if the MAH provides updated section 3.2.S.2.3.1.1 within the closing

sequence.

Question 5: For product related impurities in section 3.2 S.4.1 of CX-024414 the specification referring to the same SOP number also includes "Report % post-main peak area". The MAH is asked to justify the difference.

Summary of the MAH's response: The MAH acknowledges a typo in Section 3.2.S.4.1 Specification {CX-024414} which incorrectly includes "Report % post-main peak area" which is not a reportable result for SOP-1142. The relevant section is updated with this response.

Assessment of the MAH's response: The MAH submitted the corrected document.

Conclusion:

Issue solved.

Question 6: In the dossier Section 3.2.S.4.1 CX-031302 the specification document refers to the document in section of the CX-024414, but there are currently two versions. One with the old purity assay, one with the new purity assay. The MAH should clarify with purity test is used for which mRNA and submit/delete the document in the respective sections.

Summary of the MAH's response: The MAH clarifies that SOP-1142 is the effective release method for CX-024414 and CX-034476 mRNA, mRNA-1273 LNP-B and mRNA-1273.045 LNP-B and mRNA-1273.222 drug product. However, the mRNA-1273.222 DP lots manufactured to date were manufactured using pre-existing inventory of CX-024414 mRNA and mRNA-1273 LNP-B that were previously released using SOP-0996. The MAH will remove the obsolete Section 3.2.S.4.1.

Assessment of the MAH's response: The MAH commits to remove the obsolete section 3.2.S.4.1.

Conclusion:

Issue solved.

Question 7: The MAH is asked to include also CX-031302 in the specificity testing of the identity test.

Summary of the MAH's response: The Sanger sequencing method used for identity testing of CX-034476 uses primers which expanded the sequence coverage to include 3'UTR in addition to the ORF. Since CX-034476 mRNA has a change in the 3'UTR, in addition to changes in the ORF, the method would be able to distinguish CX-034476 mRNA from other prototype and variant RNAs based on the numerous sequence differences within the coverage range. The reference sequence used for identity testing of RNA includes the full ORF and part of the 3'UTR to include the IDR sequence. This reference sequence for each RNA is unique. The sample sequence is determined independently by Sanger sequencing and is then compared to the reference sequence and assessed for conformity. Any RNA sample that is compared to any incorrect reference sequence will fail conformity; this can be detected at a single base pair mismatch. The use of CX-024414 as the incorrect reference sequence was to demonstrate this, and this applies to any RNA sequence including CX-031302. Per ICH Q2(R2) guidelines for specificity, only components which may be expected need to be assessed. The inclusion of an incorrect reference sequence is an additional assessment as no additional RNA sequence is expected.

Assessment of the MAH's response: The MAH's explanation is agreed with as long as CX-031302 is not produced at the same time in the manufacturing building.

Conclusion:

Issue solved.

Question 8: The MAH is asked to justify why intermediate precision was not included in the method validation as done for the identity method validation of CX-031302.

Summary of the MAH's response: The MAH confirms that the CX-034476 mRNA identity method is used as a qualitative identity test. As such, intermediate precision was not evaluated as this is not a requirement per ICH Q2(R1). Intermediate precision was evaluated in a previous method validation when a new sequencing instrument was implemented in the QC release test lab, as additional supporting information.

Assessment of the MAH's response: The explanation that intermediate precision was only included in the previous validation due to implementing a new sequence instrument is acceptable.

Conclusion:

Issue solved.

Question 9: In the batch analysis document the purity test is indicated as a RP-HPLC whereas in the specification it is mentioned that the RP-IP-HPLC method is used. The MAH should clarify if the old (RP-HPLC) or the new (RP-IP-HPLC) purity assay was used and adapt the respective documents accordingly.

Summary of the MAH's response: The MAH confirms that the new RP-IP-HPLC method was used for the testing of the CX-034476 batch presented in Section 3.2.S.4.4 Batch Analysis {CX-034476} and provides the corrected 3.2.S.4.4 Section with this submission.

Assessment of the MAH's response: The MAH provided the corrected document.

Conclusion:

Issue solved.

Question 10: The MAH is referring to the RP-HPLC method for purity and needs to clarify with purity method is used.

Summary of the MAH's response: The MAH confirms that RP-IP-HPLC method was performed for purity. Please refer to the updated Section 3.2.S.7.1 Stability Summary and Conclusions {CX-034476} attached together with this response.

Assessment of the MAH's response: The MAH provided the corrected document however the footnote of Table 3 needs to be adapted as well.

Conclusion:

Issue only solved, if the footnote of Table 3 will also be adapted when submitting the document within the closing sequence.

Question 11: The MAH is asked to implement a stability study protocol that reflects the actual shelf life claim with 3 months at -15 to -25°C before transfer to -60 to -90°C as already asked for in the variation II/75/G.

Summary of the MAH's response: A stability study with CX-034476 batch stored for 3 months at -20°C, then transferred to -70°C for the remaining shelf-life claim of 36 months, is currently planned and the MAH commits to provide the results as they become available.

The planned study will be completed by Q1 2026. In addition, the MAH commits to include the stability protocol in Section 3.2.S.7.1 Stability Summary and Conclusions {CX-034476 mRNA} by December 2022.

Assessment of the MAH's response: The MAH commits to provide the requested stability protocol by December 2022.

Conclusion:

Issue solved with the commitment to provide the stability protocol December 2022 and the results Q1 2026.

Question 12: The MAH is asked to include the verification lot 4013422002 in Table 1 of section stability data stating the available data.

Summary of the MAH's response: The verification lot 4013422002 has been included in Table 1 of Section 3.2.S.7.3 Stability Data {CX-034476 mRNA} submitted together with this response. The earliest data available (3 months timepoint) will be pulled by January 2023, as such the MAH commits to include the data by February 2023.

Assessment of the MAH's response: The MAH updated Table 1.

Conclusion:

Issue solved.

Question 13: The MAH is asked to provide updated stability data if available.

Summary of the MAH's response: The MAH commits to provide updated stability data by February 2023, when the 3 months timepoint will be available.

Assessment of the MAH's response: The MAH commits to provide updated stability data by February 2023, when the 3 months timepoint will be available.

Conclusion:

Issue solved with the commitment to provide updated stability data by February 2023.

Question 14: The It is unclear why in Table 13 in section 3.2.P.2.3 Manufacturing Process Development {mRNA-1273.222} and Table 3 in section 3.2.P.3.5 Process Validation and/or Evaluation {Catalent -mRNA-1273.222}, the process durations are given for the unlabelled product, since release testing results include purity results after labelling/packaging so the final process times should already be known.

Summary of the MAH's response: Please refer to Table 11.9 of the PPQ summary report (VPPQ-256-105-00002-S). The TOR data presented is for the complete process duration from end of LNP thaw to the start of Label and Pack step at -40oC. Table 13 in Section 3.2.P.2.3 Manufacturing Process Development {mRNA- 1273.222} has been updated to reflect the final durations for the batches through to the Label and Pack step.

Assessment of the MAH's response: The MAH has clarified that the given process durations are the final ones and has corrected table 13 in Section 3.2.P.2.3 Manufacturing Process Development mRNA-1273.222} accordingly.

Conclusion:

Issue solved

Question 15: The acceptable range for the CIPC weight ratio pooled LNPs is 0.9-1.1. For one of the batches a result of 0.88 has been measured due to a pooling error. Although identified as deviation, the number 0.9 is given in the tables after rounding of the result. To avoid that results between 0.85 and 0.89 appear as 0.9 (which would be in spec) in the tables, it is recommended to use two decimal places.

Summary of the MAH's response: Pooling of LNPs is held to a range of 0.9 to 1.1 in the batch record to ensure a robust manufacturing process. The final release RNA ratio (0.80 to 1.20) for each CX is a result of the combination of the weight and LNP concentration. In this specific instance, the calculations were performed on the manufacturing floor to assess the impact of the deviation and should have been reported as 0.9 in the validation report to align with reporting convention in the batch record. The MAH commits to amend the Catalent PPQ report (PV-VAL-RPT-0144) by 30 Nov 2022. The MAH also notes that a second verification batch was manufactured as a consequence of this deviation. Both batches meet the RNA ratio release criteria, demonstrating appropriate control of the manufacturing process.

Assessment of the MAH's response: The MAH was asked to use two decimal places for the presentation of the results for the weight ratio pooled LNPs in table 4 in section 3.2.P.3.5. and in table 14 in 3.2.P.2.3 Manufacturing Process Development and table 5 in the comparability report. Therefore, it is not understood at all why the MAH proposes to do the opposite and report results with only one decimal place also in the validation report. Since this is only a question of data presentation (the result of 0.88 is handled as deviation, although 0.9 is written in the tables) **this is not further pursued due to the limited assessment time.**

Conclusion:

Issue solved

Question 16: All relevant dossier sections, including comparability report and process validation report, should be updated to include final cumulative process duration times.

Summary of the MAH's response: Please refer to the response provided to Item 14: the cumulative process durations included in the process validation report and related 3.2.P.3.5 Process Validation Section correspond to the final cumulative process duration times.

Assessment of the MAH's response: The MAH has clarified that the given process durations are the final ones and has corrected table 13 in Section 3.2.P.2.3 Manufacturing Process Development mRNA-1273.222} accordingly.

Conclusion:

Issue solved

Question 17: In dossier Section 3.2.P.3.5.1.3.4, it is stated that during PPQ, processing durations of no less than the target limit were used to confirm holding times. However, it appears that reported process durations are not at the limit. This should be clarified.

Summary of the MAH's response: The MAH would like to clarify that the hold time qualification study was performed during PPQ campaign for the mRNA-1273.214 DP. The manufacturing process being identical between mRNA-1273.214 and mRNA-1273.222, the results obtained on the mRNA-1273.214 are considered applicable also to the mRNA-1273.222 product, and the maximum cumulative process durations were therefore not challenged during process verification campaign for mRNA-1273.222 DP.

Assessment of the MAH's response: The MAH has clarified that the maximum cumulative process durations were not challenged during process verification for mRNA-1273.222 DP. The hold time qualification study was performed during PPQ campaign for the mRNA-1273.214 DP. Since both processes are similar, this is acceptable.

Conclusion:

Issue solved

Question 18: In table 11.4 of the process validation report, the clarification filtration pressure exceeded the normal operating rage leading to a deviation. Therefore "Met NOR?" should be reported as No and not as Yes. In addition, the footnote references to REC 577851 instead of REC 577581.

Summary of the MAH's response: The MAH confirms that the correct reference is REC 577581, and that the reference as well as results reported in the Table 11.4 will be corrected on the process validation report. The corrected report will be provided by end of November 2022.

Assessment of the MAH's response: The MAH has committed to correct the table and provide a revised process validation report by end of November 2022.

Conclusion:

Issue solved with the commitment to provide a corrected report by end of November 2022.

Question 19: The Defined Processing time duration for Catalent is 504 hours. Therefore, it is unclear why in the PV report a maximum cumulative process time of 336h is stated in table 11.9. and 11.10. In addition, it should be stated clearly in the PV report that the process times are not the final ones and do not include labelling and packaging times.

Summary of the MAH's response: The MAH confirms that the cumulative process duration of 336 hours corresponds to the normal operating range (NOR) for this parameter for Catalent. Additionally, as included in Item 14 and Item 16, the durations included in the report correspond to the final total inclusive of the Label and Pack step.

Assessment of the MAH's response: The MAH does not clarify why for Catalent a normal operating range (NOR) is defined that differs from the maximum allowed processing time durations. In addition, this is not described clearly in the dossier. However, since the processing time of 504 hours is already approved for Catalent this is acceptable, but the processing times should be described clearly in the dossier.

Conclusion:

Issue solved with recommendation

Question 20: In dossier section 3.2.P.6, the interim standard lot 8514100101 is described. In contrast, a CoA for a standard lot Reference standard 8514100102 is provided. It should be clarified which standard is currently used and the respective information in the dossier should be harmonised.

Summary of the MAH's response: The MAH clarifies that lot 8514100101 has been used as an interim reference material during the testing of all initial mRNA-1273.222 drug product lots on release. Subsequently, a new interim reference material lot 8514100102 has been implemented to support release testing until a primary reference material is qualified. Section 3.2.P.6 has been updated with information on both interim reference material lots and will be included with this response.

Assessment of the MAH's response: The MAH has revised section 3.2.P.6 to include information on both interims reference standards.

Conclusion:

Issue solved

Question 21: The platform stability approach should be supported by the accelerated stability data from the developmental DP batch. The MAH should demonstrate that the degradation rate for the developmental batch at accelerated conditions is conform with the platform data.

Summary of the MAH's response: The degradation rate for developmental batch DHM-99117 at the 25°C accelerated condition conforms with the platform data. The degradation rate estimate for these results is -0.075% purity per hour (95% confidence interval -0.093 to -0.057% per hour). The confidence interval for the estimated rate for this batch includes the estimated degradation rate -0.064% purity per hour based on common slope for all mRNA-1273 drug product stability data obtained using the same purity method SOP-1142 available as of May 25, 2022.

Assessment of the MAH's response: The MAH has only very shortly compared the degradation rate of the developmental batch at accelerated temperature with the platform data. The values are in a comparable range.

Conclusion:

Issue only solved, if the information given in the answer to ITEM21 will be included in dossier section 3.2.P.8. when the closing sequence is submitted.

Question 22: The In the tables in section 3.2.P.8.3 (stability data), the former purity test (RP-HPLC) is listed instead of the current RP-IP-HPLC test. This should be corrected. The same error is found in the footnote to table 4 in section 3.2.P.8.1.

Summary of the MAH's response: Section 3.2.P.8.1 Stability Summary and Conclusions {mRNA-1273.222} and Section 3.2.P.8.3 Stability Data {mRNA-1273.222} have been updated accordingly.

Assessment of the MAH's response: The tables have been corrected.

Conclusion:

Issue solved

5. Second request for supplementary information

5.1. Other concerns

Quality aspects

1. The MAH should provide an updated section 3.2.S.2.3.1.1 within the closing sequence.
2. The MAH should agree not to produce CX-031302 at the same time as CX-024414 and CX-034476 in the manufacturing building (Norwood, USA)
3. The updated document (RP-IP-HPLC details in 3.2.S.7.1) with corrected footnote for Table 3 should be submitted in the closing sequence
4. Information provided in response to Q21 (informal LoQ II/84) should be included in section 3.2.P.8 of the dossier in the closing sequence

Clinical aspects

5. The MAH should provide a comparative analysis regarding the reactogenicity of all variant vaccines. This analysis should clearly distinguish trial data obtained as primary series, first or second booster and clearly demonstrate the overall safety database to underpin his conclusion that a comparable safety is to be expected.
6. The MAH is asked to provide the timelines on the submission of preliminary safety data regarding the Bivalent Original/Omicron BA.4-BA.5 vaccine.
7. The MAH is asked to provide the current status and timelines on availability of immunogenicity results from study mRNA-1273-P205 part H.
8. The MAH is requested to provide results on immunogenicity from study mRNA-1273-P205 part H as soon as they become available.

6. Assessment of the responses to the second request for supplementary information

6.1. Other concerns

Quality aspects

Question 1: The MAH should provide an updated section 3.2.S.2.3.1.1 within the closing sequence.

Summary of the MAH's response: The MAH commits to provide an updated Section 3.2.S.2.3 within the closing sequence.

Assessment of the MAH's response: The MAH will provide the requested document.

Conclusion: Issue solved

Question 2: The MAH should agree not to produce CX-031302 at the same time as CX-024414 and CX-034476 in the manufacturing building (Norwood, USA)

Summary of the MAH's response: The MAH would like to provide the following clarifications, to complement its response to item 7 of the informal list of questions dated 04-Oct 2022.

Moderna Norwood (MTC-S) operates as a multi-product GMP manufacturing facility on a campaign basis, with only one RNA construct (CX-024414, CX-031302, CX-034476 and potential future variants) produced at a time within an individual suite. A comprehensive multi-product control strategy has been established to appropriately segregate individual RNA products within their intended areas and eliminate the risk of cross-contamination. Prior to campaign start, each suite undergoes a fully documented area clearance and product changeover with equipment and facility cleaning. All product specific components (e.g. raw materials) are prescribed within electronic batch records with positive verification enforced prior to batch introduction, minimising the probability of mix-ups. During campaigns, segregation controls are in place to control unintended transfer of product or related materials between suites, and include closed processing whenever feasible, gowning, and prescribed personnel/material/product/waste flow controls, as well as facility HVAC cascade design with active monitoring. Establishment and administration of these controls ensures appropriate product segregation is maintained throughout processing and transport of all RNA batches within Norwood MTC-S.

The MAH is manufacturing RNA for COVID-19 vaccines using this approach. Manufacture of the different RNA products have been performed in parallel, in separate suites, to support production requirements for bivalent vaccines. For a bivalent vaccine, target RNA sequences must be produced simultaneously in order to be combined and generate the bivalent product. Given the multi-product manufacturing capabilities of the Norwood facility, limitation of production for single RNA product manufacture would significantly hinder the MAH's production capabilities for multivalent vaccines and risk robust patient supply.

The Sanger sequencing method used by the MAH for identity testing is highly specific towards the targeted sequence. The primer sequences are designed to enable full sequence coverage of the open reading frame portion of the sequence and for CX-034476 mRNA the 3'UTR with two-fold bidirectional coverage. The Sanger method applies a minimum Q20 (Phred) quality score to every nucleotide base called by the sequencer as a system suitability criterion. This quality score ensures the probability of an incorrect base being called is no greater 1 in 100 (99% base call accuracy). In addition, the resultant sample RNA sequence is a consensus that is derived from minimally four distinct reads (2-fold bi-directionally) covering every nucleotide. The consensus sequence must match the reference sequence with 100% homology. Across the full-length mRNA CX-031302 and CX-034476 sequences are more than 100 nucleotide mismatches; any one mismatch between the consensus sequence and the product-specific reference sequence would be an out-of-specification test result.

The MAH commits to providing a study report by 30-Nov 2022 that demonstrates Sanger method capability in detecting even minor differences between target sequences and thus the specificity of the identity method.

Assessment of the MAH's response: The MAH justifies the multi-variant use of the manufacturing site with a control strategy that has been established to appropriately segregate individual RNA products within their intended areas and eliminate the risk of cross-contamination. Furthermore, the MAH commits to provide a study report demonstrating the capability of the Sanger method (identity testing DS) to detect even minor differences between target sequences and thus the specificity of the identity method by 30. Nov. 2022.

Conclusion: Issue solved with recommendation.

Question 3: The updated document (RP-IP-HPLC details in 3.2.S.7.1) with corrected footnote for Table 3 should be submitted in the closing sequence

Summary of the MAH's response: The MAH commits to provide an updated Section 3.2.S.7.1 within the closing sequence.

Assessment of the MAH's response: The MAH will provide the requested document.

Conclusion: Issue solved

Question 4: Information provided in response to Q21 (informal LoQ II/84) should be included in section 3.2.P.8 of the dossier in the closing sequence

Summary of the MAH's response: The MAH commits to provide an updated Section 3.2.P.8.1 within the closing sequence.

Assessment of the MAH's response: The MAH will provide the requested document.

Conclusion: Issue solved

Clinical aspects

Question 5: The MAH should provide a comparative analysis regarding the reactogenicity of all variant vaccines. This analysis should clearly distinguish trial data obtained as primary series, first or second booster and clearly demonstrate the overall safety database to underpin his conclusion that a comparable safety is to be expected.

Summary of the MAH's response: The MAH provided the requested table.

Assessment of the MAH's response: The table provided by the MAH is satisfactory.

Conclusion: Issue solved

Question 6: The MAH is asked to provide the timelines on the submission of preliminary safety data regarding the Bivalent Original/Omicron BA.4-BA.5 vaccine.

Summary of the MAH's response: The MAH provided the requested information.

Assessment of the MAH's response: The information provided by the MAH is satisfactory.

Conclusion: Issue solved

Question 7: The MAH is asked to provide the current status and timelines on availability of immunogenicity results from study mRNA-1273-P205 part H.

Summary of the MAH's response: The MAH provided the requested information.

Assessment of the MAH's response: The information provided by the MAH is satisfactory.

Conclusion: Issue solved

Question 8: The MAH is requested to provide results on immunogenicity from study mRNA-1273-P205 part H as soon as they become available. (**PAM**)

Summary of the MAH's response: The MAH provided a commitment to provide interpretable reactogenicity data from the subjects enrolled in study mRNA-1273-P205 Part H within a month of approval, followed by a summary of the Day 29 interim immunogenicity results by 31 December 2022, and by a final clinical study report by 28 February 2023. Results from pharmacovigilance and effectiveness studies on the use of Spikevax bivalent Original/Omicron BA.4-5 should be submitted without delay.

Assessment of the MAH's response: The commitment provided by the MAH is acceptable.

Conclusion: Issue solved

7. Risk management plan

No updated RMP version has been submitted regarding this procedure.

Safety concerns

Pharmacovigilance plan

Study protocols for mRNA-1273-P904, mRNA-1273-P905 and mRNA-1273-P910 in the Pharmacovigilance Plan have been updated to include exposure to Spikevax bivalents (both original/omicron BA.1 and BA.4-5) and to stratify the results by Spikevax and Spikevax bivalents (both Original/ Omicron BA.1 and BA.4-5). Progress and eventual updates for these protocols will be provided in the submissions of the interim results.

Along with the positive CHMP opinion received on 15 September 2022 (Procedure number: EMEA/H/C/005791/R/0074) granting the full marketing authorisation for Spikevax, RMP v5.0 was merged with approved v4.2 in order to reclassify category 2 studies (mRNA-1273-P301, mRNA-1273-P203, and mRNA-1273-P204 in category 3.

In addition, study mRNA 1273 P205 was included as a category 3 study in the Pharmacovigilance Plan related to the move from a conditional marketing authorisation to a full marketing authorisation.

8. Update of the Product information

As a result of this group of variation, the SmPC, Labelling and the Package Leaflet have been updated (see Attachment 1).

8.1. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of Article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

Outer and immediate labelling (from start of supply to end of December 2022 (around 171 batches)

All EU Member States have agreed to grant a temporary exemption for the use of the 171 initial PPQ batches with a "temporary labelling" printed at risk. The exemption is granted only until end of December 2022. These exemptions are justified by the necessity to label batches ahead of time.

Outer carton

- Expression of strength: Strength: "0.1 mg/mL' (initially proposed)", instead of "(50 micrograms/50 micrograms)/mL" (agreed during evaluation).
- Invented name qualifier: "BA.4/BA.5" instead of "BA.4-5" (agreed during evaluation).
- INN/common name: "bivalent COVID-19 mRNA Vaccine (nucleoside modified)" (printed at risk), instead of common name "COVID-19 mRNA Vaccine (nucleoside modified)" and INN "elasomeran/davesomeran" (agreed during evaluation).
- Statement of the active substance: "One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran" (agreed during evaluation).

Vial label

- Expression of strength: Strength: "0.1 mg/mL' (initially proposed)", instead of "(50 micrograms/50 micrograms)/mL" (agreed during evaluation).
- Invented name qualifier: "BA.4/BA.5" instead of "BA.4-5" (agreed during evaluation).
- INN/common name: "bivalent COVID-19 mRNA Vaccine" (printed at risk), instead of INN "elasomeran/davesomeran" (agreed during evaluation).
- "Discard time:" (printed at risk), instead of "Discard date/time" (agreed during evaluation).

9. Overall conclusion and impact on the benefit-risk balance

9.1. Therapeutic Context

9.1.1. Disease or condition

After emerging as a human pathogen causing COVID-19, SARS-CoV-2 has continuously evolved and appeared in several variants causing new waves of infection. The strain causing the latest waves of disease has been the Omicron, with several subvariants beginning with BA.1. Currently BA.5 is dominating in the EU.

Sought indication: Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

9.1.2. Available therapies and unmet medical need

While the efficacy of available vaccines emulating the original wild-type strain against severe disease due to Omicron appears largely retained, efficacy against symptomatic disease is obviously reduced. Moreover, the duration of protection with the original vaccine may be reduced given that the emerging variant is less sensitive than the original target.

Bivalent variant mRNA vaccines containing the original strain as well as BA.1. were approved for boosting in the EU beginning of September 2022 (similar indication as the one presently sought). However, Sars-Cov-2 evolution has been rapid, and as stated above the dominating variant at the present time is no longer BA.1 but BA.5.

Established principles of immunology as well as some preclinical immunogenicity data, indicate that a vaccine targeting BA.5 would optimise immunogenicity against BA.5, which might be translated into greater vaccine efficacy. Given the dynamic nature of the pandemic, and that it cannot be predicted what strain will cause the next wave, there is a benefit of having different vaccines available that can be used as booster.

It has been proposed that an adapted bivalent vaccine with the BA.4-5 spike protein sequence substituting for half of the content of the Original vaccine, might be approved based on widely accepted immunological principles, as well as the extrapolation of reactogenicity from the experience of different other variant vaccines.

Main clinical studies

There are no specific clinical trial data available yet to support the authorisation of Spikevax bivalent Original/Omicron BA.4-5.

9.2. Favourable effects

There are no available clinical data on immunogenicity or efficacy of Spikevax bivalent Original/Omicron BA.4-5.

9.3. Uncertainties and limitations about favourable effects

So far, all variant vaccines have been able to elicit an immune response, in the case of Spikevax bivalent Original/Omicron BA.1 it was confirmed by the clinical data that an adapted vaccine induces a superior immune response towards the variant spike protein compared to the original booster. This finding is supported by non-clinical data in various settings. It is therefore reasonably likely that also Spikevax bivalent Original/Omicron BA.4-5 adapted vaccine induces a better adapted immune response.

9.4. Unfavourable effects

There is a large safety database for Spikevax Original, showing an acceptable safety profile.

Acceptable reactogenicity data have been provided when boosting with Beta and Spikevax bivalent Original/Omicron BA.1 vaccines.

9.5. Uncertainties and limitations about unfavourable effects

The frequency of local and systemic reactogenicity events was possibly higher when boosting with the bivalent Original/Omicron BA.1 vaccine even though this difference was not regarded as clinical meaningful.

With the still limited experience of the impact of changes of the antigenic sequence on clinical safety there is some degree of uncertainty. This uncertainty is reduced by the submission by the MAH of a detailed and comparative analysis regarding the reactogenicity of all variant vaccines.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

There is a large safety database for Spikevax Original, showing an acceptable safety profile.

Acceptable reactogenicity data have been provided when boosting with Beta and Spikevax bivalent Original/Omicron BA.1 vaccines.

The safety profile of Spikevax bivalent Original/Omicron BA.4-5 can be supported to a certain degree based on extrapolation from the different variant vaccines that have been studied. The scientific question and approach however is regarded as different when authorising a variant vaccine with no clinical data compared to the authorisation of variant vaccine with clinical trial data. In the former situation the comparative assessment plays a larger role while in the latter situation the obtained clinical data form the basis of the assessment. The MAH provided a satisfactory comparative analysis regarding the reactogenicity of all variant vaccines, distinguishing trial data obtained as primary series, first or second booster and demonstrating the overall safety database underpinning the conclusion that a comparable safety is expected.

9.6.2. Balance of benefits and risks

Given the evolution of Sars-Cov-2, the benefits of an early approval of Spikevax bivalent Original/Omicron BA.4-5 outweighs the uncertainties related to extrapolations on immunogenicity and reactogenicity.

9.7. Conclusions

The benefit-risk balance of Spikevax bivalent Original/Omicron BA.4-5 is considered positive in the applied indication.

10. Recommendations

Outcome

Based on the review of the submitted data, this application regarding the following changes:

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, II, 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	I, IIIA and IIIB
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	I, IIIA and IIIB

B.I.a.6.a (Type II): Addition of a new strain (Omicron BA.4-5) resulting in a new Spikevax bivalent Original/Omicron BA.4-5 (50 µg elasomeran/50 µg davesomeran)/mL 0.1 mg/mL dispersion for injection presentation (2.5 mL multidose vial containing 5 doses). The Annex A, the SmPC, the Annex II, the labelling and the Package Leaflet are updated accordingly. The variation also includes a number of quality scopes.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA, IIIB, II 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 Annex II, Section C of the CHMP Opinion. Please add this product to the current EURD list entry: 10897 and re-name the entry: elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5).

11. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Spikevax-H-C-005791-II-84-G'

12. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 19 October 2022