EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2025
EMA/6890/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

mNEXSPIKE

Common name: COVID-19 mRNA Vaccine

Procedure No. EMEA/H/C/006428/0000

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

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List of abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	Analysis of covariance
AR	adverse reaction
bAb	binding antibody(ies)
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMQ	Customized MedDRA queries
CoV	coronavirus
COVID-19	coronavirus disease-2019
CRO	Clinical Research Organization
CSR	clinical study report
DSMB	data and safety monitoring board
ECLIA	Electrochemiluminescence Immunoassay
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOSL	End-of shelf life
EU	European Union
FAS	Full Analysis Set
GM	geometric mean
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GWS	genome-wide selection
HIV	Human Immunodeficiency Virus
HR	hazard ratio
ICS	intracellular cytokine staining assay
IRB	Institutional Review Board
IRT	Interactive Response Technology
IgG	immunoglobulin G
IM	intramuscular(ly)
IP	Investigational Product
LDP	Labelled Drug Product
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MAA	Marketing Authorisation Application
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory syndrome coronavirus
mRNA	messenger ribonucleic acid
nAb	neutralising antibody

Abbreviation	Definition
NOAEL	no observed adverse effect level
NP	nasopharyngeal
NTD	N-Terminal Domain
PCR	polymerase chain reaction
PD	pharmacodynamics
PIP	Paediatric Investigational Plan
PPIS	Per-protocol Immunogenicity Set
PPSE	Per-protocol Set for Efficacy
PsVNA	pseudotyped lentivirus reporter neutralisation assay
PT	preferred term
RBD	receptor-binding domain
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	system organ class
S1	Spike 1
S2	Spike 2
SRR	seroresponse rate
UDP	Unlabelled Drug Product
US	United States
USA	United States of America
VE	vaccine efficacy
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Moderna Biotech Spain S.L. submitted on 21 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for mNEXSPIKE, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication

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

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0365/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0365/2024 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the N-

terminal domain and receptor-binding domain of the viral spike (S) protein of SARS-CoV-2 (XBB.1.5) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
16 January 2023	EMA/SA/0000121008	*Mair Powell*

The Scientific Advice pertained to the following clinical, non-clinical aspects:

- Non-clinical plan to support Phase 3 and submission of a Marketing Authorisation Application for mRNA-1283.222 vaccine
- Dose selection
- Design of the P301 study, as a pivotal safety and immunogenicity trial to support licensure of mRNA-1283.222

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Daniela Philadelphy

The application was received by the EMA on	21 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 March 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to	04 September 2025

CHMP during the meeting on	
The Emergency Task Force (ETF) agreed on the Assessment Overview during their meeting on	12 September 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	26 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to mNEXSPIKE on	11 December 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	11 December 2025

The (Co-) rapporteurs assessment reports have been discussed and supported by the Emergency Task Force (ETF) in the context of its public health preparedness activities.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The first cases of SARS-CoV-2 were detected in 2019 in Wuhan, Hubei Province, China in December 2019, and has since spread globally. Widespread community transmission was subsequently reported in all WHO regions and the WHO declared COVID-19 a pandemic on 11 March 2020. On 5 May 2023, more than three years into the pandemic, given that the disease was well established and ongoing, WHO considered that COVID-19 no longer met the definition of a Public Health Emergency of International Concern. COVID-19 is no longer a pandemic, but the virus is still present.

2.1.2. Epidemiology and risk factors

As of 2 November 2025, 778,900,250 COVID-19 cases and more than 7.1 million deaths had been reported globally. In Europe, as of 2 November 2025, 281,593,874 COVID-19 cases and 2,281,733 deaths had been reported.

The seasonality pattern is yet to be established for COVID-19, but global and regional (US and Europe) infection and hospitalisation rates during the 2023/2024 season suggest a bimodal distribution with peaks observed in both late summer-to-fall and winter months. Globally in 2023, COVID-19 cases peaked in August (702,000 new cases the week of 06 August 2024) with another peak in December (382,000 new cases the week of 17 December 2024). COVID-19 cases rose again in the Summer of 2024, with 57,300 new weekly cases detected in late July 2024. In Europe in 2023, COVID-19 cases reached a peak in September, followed by a second peak in December, and started to rise again in

summer 2024 (ERVISS 2024a). In the US, during the 2023/2024 season, COVID-19 associated hospitalisations peaked in the fall (4.6 per 100,000 population per week in September 2023) and winter (7.8 per 100,000 population per week in December 2023) and are projected to peak again in late summer-fall 2024, with the most recent hospitalisations reported at 4.4 per 100,000 population for the week ending 03 August 2024.

The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

COVID-19 vaccines based on the spike protein of SARS-CoV-2 have shown high efficacy against symptomatic COVID-19. At present, a large percentage of the global population (70% approximately) is estimated to have been vaccinated against COVID-19, and there is a high seroprevalence globally from natural SARS-CoV-2 infection.

Nevertheless, COVID-19 remains a global health threat, it still places a burden on healthcare systems, and due to new birth cohorts, waning immunity and antigenic evolution of the virus, there is a recognised need for periodic COVID-19 vaccination. Also, there is a recognised need for development of next-generation COVID-19 vaccines providing protection also against transmission, providing greater breadth of protection against viral variants, and longer duration of immunity.

2.1.3. Biologic features, aetiology and pathogenesis

COVID-19 is caused by SARS-CoV-2 (betacoronavirus genus, sarbecovirus sub-genus). SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The pathogenesis of SARS-CoV-2 involves binding of the spike protein (surface-exposed part of virions) to the human receptor (ACE2), followed by internalisation to the cytosol (facilitated by cleavage of the spike protein by the membrane-bound TMPRRS2 protease), where intracellular viral replication takes place, leading to budding/release of progeny virions from the target cell, and typically ultimately death of target cells.

Disease manifestations reflect the typical route of infection (airborne transmission) and tissue distribution of the ACE2 receptor and TMPRRS2 protease (airways, endothelium, heart muscle, gastrointestinal epithelium). The virus has continually adapted to the new human host since the start of the pandemic, which is considered to have been associated with increased transmissibility but attenuated pathogenicity. However, the actual pathogenicity of currently circulating variants compared to the original index strain is difficult to estimate, due to the high level of population immunity, and even the current variants are considered to present a significant threat for at-risk populations. The aetiology and pathogenesis of the main acute COVID-19 disease manifestations (i.e., pneumonia, myocarditis) are well understood. COVID-19 is also associated with a heterogenous group of post-acute, persistent symptoms and sequelae (currently described as long COVID), for which aetiology and pathogenesis are less well understood

2.1.4. Clinical presentation, diagnosis

The ECDC provides the following description of the clinical presentation of COVID-19 at the current post-pandemic stage:

- Symptoms may vary, both in frequency and severity, depending on the SARS-CoV-2 variant causing the disease episode.
- Most cases of COVID-19 are mild or moderate and do not require hospitalisation or advanced medical care.
- Severe disease usually manifests as pneumonia with shortness of breath and pulmonary infiltrates on chest imaging. Pneumonia can be complicated by respiratory failure requiring oxygen supplementation and mechanical ventilation. Other severe complications include thromboembolism (such as pulmonary embolism and stroke), circulatory shock, myocardial damage, arrhythmias, and encephalopathy. Severe illness usually develops approximately one week after the onset of symptoms.
- Children usually experience mild symptoms (mainly fever and cough), if any, and have a very low risk of hospitalisation or death. However, some children may develop severe disease after infection with COVID-19, defined as multi-system inflammatory syndrome in children (MIS-C).
- Some patients may experience long-term symptoms with unclear aetiology (collectively referred to as post-COVID-19 condition and long COVID). The presentation is heterogenous, often episodic, and affects multiple organ systems [respiratory, cardiovascular, neuropsychiatric/cognitive symptoms, such as chronic fatigue (most commonly), headaches and loss of smell, difficulty concentrating, sleep disturbances, and depression].

Diagnosis is by detection of viral nucleic acid and viral nucleocapsid antigen, typically in nasopharyngeal swab material (RT-PCR and rapid lateral-flow antigen tests).

2.1.5. Management

The most effective way to prevent COVID-19 is vaccination. There are currently 5 vaccines authorised in the EU (i.e., Comirnaty, Spikevax, Nuvaxovid, Bimervax, Kostaive). COVID-19 vaccines have been shown to be effective in reducing the risk of disease and severe disease from SARS-CoV-2 infection.

The main treatment for most patients with severe disease is supportive care, which is often highly effective, antiviral medication (monoclonal antibodies and/or available antiviral drugs) where appropriate, and immune modulators.

2.2. About the product

The nucleoside-modified mRNA is formulated in lipid particles, which encodes the membrane-bound, linked RBD and NTD of the Spike glycoprotein from SARS-CoV-2 strains, which contain the immunodominant epitopes for protective immune responses.

The vaccine elicits an immune response to the RBD and NTD of the Spike antigen, which protects against COVID-19.

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

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

Each single-dose pre-filled syringe contains one dose of 0.2 mL.

One dose (0.2 mL) contains 10 micrograms of SARS-CoV-2 mRNA.

2.3. Quality aspects

2.3.1. Introduction

The finished product (mRNA-1283) is presented as single dose prefilled syringe containing 10 µg RNA-101-B815 per 0.2 ml dose as active substance.

The nucleoside-modified mRNA is formulated in lipid particles, which encodes the membrane-bound, linked Receptor binding domain (RBD) and N-terminal domain (NTD) of the Spike glycoprotein from SARS-CoV-2 strains, which contain the immunodominant epitopes for protective immune responses.

Other ingredients are: Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102), Cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), Trometamol, Trometamol hydrochloride, Sucrose, WFI.

The product is available in a pre-filled syringe (polymeric barrel) with plunger stopper and a rubber tip cap (without needle).

2.3.2. Active Substance

2.3.2.1. General Information

The active substance (AS) RNA-101-B815 (mRNA sequence CX-038869) encodes the linked N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein of the SARS-CoV-2 Omicron XBB.1.5 subvariant. In general, the sequence elements (5′ cap, the 5′ untranslated region (UTR), the Open Reading Frame (ORF), the 3′ UTR, and the 3′ PolyA tail) are described in sufficient detail.

2.3.2.2. Manufacture, process controls and characterisation

RNA-101-B815 is manufactured and tested at the ModernaTX Norwood site.

All sites involved in manufacturing of the RNA active substance comply with GMP requirements.

Manufacturing process:

The manufacturing process of the RNA-101-B815 comprises an in-vitro transcription reaction leading to 5′ capped full-length RNA with a polyadenylated (PolyA) tail. A tangential flow filtration (TFF) to exchange the buffer and adjust the mRNA concentration is performed before the mRNA is captured by Chromatography to reduce process-related impurities. After elution a final TFF is performed to concentrate the RNA and exchange buffer to the final storage buffer and a bioburden reduction clarification step is conducted. The mRNA is then dispensed in containers and actively frozen for long-term storage. The manufacturing process is described in detail and the individual process steps are controlled with numerous process parameters.

The plasmid codes for the molecular elements of mRNA including the 5′ untranslated region (UTR), the coding region (open reading frame), the 3′ UTR, and the PolyA tail. Linearised plasmid manufacture

and testing are performed in accordance with GMP. The purification process and specifications for plasmid are satisfactorily described.

Control of starting and raw materials:

Raw Materials used in the production of RNA manufacturing process are categorized as compendial or non-compendial. Appropriate supplier qualified and testing for conformity with Certificates of Analysis has been provided. No materials of animal or human origin are used in the product of raw materials.

The manufacture of the master cell bank (MCB) and working cell bank (WCB) of the plasmid as well as the release testing and the qualification protocol of new MCB/WCB is described sufficiently according to relevant guidelines. The linearized plasmid that is considered as one of the starting materials is thoroughly tested. In-process controls applied during linearized plasmid DNA manufacture are acceptable.

Control of critical steps and intermediates:

The control of critical steps and intermediates is sufficiently outlined in the dossier. In line with ICH Q8, critical process parameters (CPPs) were initially identified by risk assessment based on their potential to impact critical quality attributes and further evaluated in process characterization studies and process validation studies. In-process hold-times are sufficiently justified by process characterization and validation studies.

Process validation:

Process validation was performed at the intended commercial site ModernaTX Norwood. All PPQ release testing and critical in-process controls (C)IPCs results met the predefined acceptance criteria. Step and Cycle yields were monitored for chromatography, final TFF, clarification and overall process (i.e. total yield) and demonstrated robust process performance. All critical process parameters (C)PPs conformed to their target ranges. The process validation data provided is considered acceptable. The process hold times as well as the shipping are properly validated and justified. Commercial scale qualification of resin lifetime for the RNA process is being performed concurrently to confirm resin. Appropriate shipping validation has been performed.

Manufacturing development:

A summary of manufacturing process changes from development through PPQ has been provided. The following processes have been applied: Version A (68 mL IVT; mRNA-1283-P101, mRNA-1283-P201), Version A (96 mL IVT, mRNA-1283-P301, Part 1), Version B (mRNA-1283-P301 Part 1, Part 2, Part 3, mRNA-1283-P301 Japan Study) and commercial scale process. The comparability exercise is robust throughout the whole clinical development and the commercial manufacturing process. Accelerated stability profiles are included in the comparability exercise.

Characterisation:

In general, the applicant provided a detailed package of characterization studies to elucidate the structure and the impurities of RNA-101-B815. The applicant has used orthogonal methods to quantify residual DNA and estimate fragment size, which show reduction of the levels of DNA and size. As both methods are qualitative or semi-quantitative they are not considered suitable for DNA quantification and estimation of residual DNA Fragments. Consequently, other orthogonal methods (e.g. fluorescence-based methods) should be implemented to accurately quantitate DNA levels and size. The Applicant committed to submitting data supporting an orthogonal analytical method to quantitate DNA levels and DNA size as a recommendation (**REC4**).

2.3.2.3. Specification

Specification and analytical methods

In general, the proposed specifications (appearance, identity, total RNA content, purity/product-related impurities, % Total Cap 1, % PolyA tailed RNA/% tailless RNA, pH, bacterial endotoxin and bioburden) are considered acceptable. The analytical methods are described by the applicant and method validation data has been provided. For the testing of residual protein and plasmid DNA, analytical platform data were provided. Batch data of the registration and clinical lots is provided and the justification of the specifications are considered acceptable. The specification for % Total Cap1 by RP-IP HPLC appears wide considering available batch data, however, is additionally supported by an *in vivo* immunogenicity study.

Product-related impurities include molecular variants arising during manufacture or storage with properties potentially different from those of the desired product with respect to activity, efficacy, and safety.

Process-related impurities that may be introduced from the RNA manufacturing process include residual process material and in vitro transcription (IVT) impurities derived from or generated during the manufacturing process.

DNA impurities are considered as critical and the applicant was requested to include residual DNA template as a release test until sufficient data has been collected.

The active substance specification contains appropriate tests for appearance, identification, RNA content and purity, physicochemical and microbiological properties.

The description of the reference standard used for the purity assay is considered acceptable and also details how future reference material will be qualified are included. The reference standard for the commercial production is derived from a registration lot. It was thoroughly tested and characterized and will be followed up by a stability monitoring protocol. The annual requalification protocol has been updated and the reference material used for the clinical lots has been clarified. The description and testing of the container closure system is considered acceptable. Information on the actual size/volume, exact designation of the single-use storage bags used and a CoA have been provided. Suitability of the single-use bags proposed for long-term storage of active substance has been confirmed in a simulated leachables study.

2.3.2.4. Stability

The proposed shelf life claim is sufficiently supported by updated data provided during the procedure. The available data support comparability between clinical and PPQ batches, however, several data points had to be excluded from analysis since atypical chromatography results were found for %poly A tail (for long-term and accelerated conditions). However, this issue is not further pursued here, given that the data from PPQ batches are sufficient to support the proposed shelf-life claim. To support potential future strain updates, the applicant has committed to provide additional accelerated stability data for three additional batches to support comparability stability assessment of PolyA Tailed RNA (**REC1**). The applicant further states that the PolyA Tail method is currently being optimized as part of method lifecycle to enhance the assay robustness and minimize the likelihood of data exclusion caused by a higher-than-expected presence of the early eluting peak. A commitment to validate and implement the respective method has been provided (**REC3**).

The stability data provided are in line with ICH requirements and post-approval stability protocols are largely acceptable, except for the request to add the statement that only one batch in case of a seasonal change is made and no additional batches of the previous season's RNA will be placed on stability from

the dossier. While it is principally agreed that one batch is sufficient to fulfil general GMP requirements, one batch may be insufficient to support the annual strain update. It is however expected to perform stability studies for each new variant AS to build up a vaccine quality database.

2.3.3. Finished Medicinal Product – LNP Intermediate

2 . 3 . 3 . 1 . Description of the product and Pharmaceutical Development

The lipid nanoparticle (LNP) is a finished product intermediate intended for further processing into finished product and is not intended for direct injection. It contains mRNA encoding the N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 virus linked to an influenza haemagglutinin transmembrane domain, which is encapsulated in a lipid mixture (LMX), specifically LMX-100. Except the custom-manufactured lipids SM-102 and PEG2000-DMG and Tris-HCl, all excipients are of compendial quality. No excipients of human or animal origin or novel excipients are used. Except for the specific mRNA, the composition is identical to the composition of LNP intermediate used for manufacture of Spikevax.

Physicochemical, structural, and functional properties of LNP were characterized using a broad panel of orthogonal state-of-the-art analytical methods.

During development, the LNP process was scaled up from an integrated small-scale clinical process (Version A) without separate mRNA and LNP release to large clinical scale process (Version B) and further scaled-up to commercial scale process. The changes and adaptations implemented during development are sufficiently described and justified.

Overall, the information provided on pharmaceutical development is considered acceptable.

2.3.3.2. Manufacture of the product and process controls

The LNP manufacturing process is essentially similar to that of Spikevax and aims to encapsulate the RNA into the lipid mixture. In principle, this process consists of mixing the ingredients, followed by neutralisation, clarification and filling.

The manufacturing sites are in compliance with GMP requirements.

The manufacturing process has been adequately described and information provided on controls of critical steps and intermediates is considered acceptable. The presented PPQ results demonstrate that the commercial manufacturing process is capable of delivering mRNA-1283 LNP of consistent and acceptable quality. The following hold times are proposed for commercial manufacturing. The hold-time validation performed is considered acceptable. Shipping validation results demonstrate that the intended shipping process for LNP from ModernaTX to the FP manufacturer is suitable and under control.

2.3.3.3. LNP Intermediate specification

The proposed specifications for the control of the mRNA-1283 LNP intermediate are considered appropriate to ensure the quality-relevant FP characteristics. LNP Specifications are identical to the approved dossier of mRESVIA (mRNA-1345 LNP) and are considered acceptable. The analytical procedures are described in detail and the validation is deemed sufficient. Batch data and information about product-related impurities have been provided and are acceptable. PPQ lots were performed at ModernaTX Norwood (5027724001/2/3)

The LNP Intermediate specification contains appropriate test for appearance, identification, lipid content and purity, particle size / polydispersity, physicochemical and microbiological properties.

The information provided on reference standards or materials is considered sufficient and acceptable. The container closure system materials are well characterized and controlled and the information provided on container closure system is considered acceptable.

2.3.3.4. Stability of the product

The shelf-life claim is mainly supported by data from PPQ batches as well as additional LNP Clinical/PSB lots.

Freeze/thaw stability of LNP was demonstrated by freeze/thaw studies. A satisfactory post-approval stability protocol for LNP has been filed.

Overall, the shelf-life claim for the LNP intermediate is considered acceptable.

2.3.4. Finished Medicinal Product

2 . 3 . 4 . 1 . Description of the product and Pharmaceutical Development

For manufacturing of mRNA-1283 finished product, mRNA-1283 lipid nanoparticles are formulated with Tris buffer and sucrose at pH 7.5. The final product contains 0.05 mg/ml RNA-101-B815, that is 10 µg RNA per 0.2 ml dose. The final product is presented as a single-dose 1-ml-long cyclic olefin copolymer (COC) syringe. A satisfactory notified body opinion (NoB) for the prefilled syringe has been provided.

The components of the final product have been sufficiently described. It is noticed that acetic acid is not mentioned as a component of the final product as in Spikevax or mRESVIA, instead it is classified as an impurity. The applicant's justification why acetate is not included in the list of excipients as in the SmPCs for Spikevax and mRESVIA, is acceptable. However, it is expected that the list of excipients is consistent across the various approved comparable products and that the list of excipients is aligned. Therefore, the applicant should commit to change the classification of acetate and to exclude it from the list of excipients for Spikevax and mRESVIA **(REC2)**.

Manufacture

The manufacturing process development has been described sufficiently.

Clinical lots have been manufactured according to process version A or B. Version A is an integrated process where product intermediates are placed on hold, in-process without separate release of mRNA and LNPs. Most of version A batches were manufactured at a higher concentration than the commercial concentration of 0.05 mg/ml. Version B is similar to the commercial process with only minor differences, but at a smaller scale with different vessels and with a different container closure system (vial instead of syringe). In early clinical studies mRNA coding for the Wuhan-Hu-1, Beta B.1.351, or Omicron B.1.1.529 variants were used; Phase 3 and commercial (PPQ) product was manufactured using mRNA encoding the Wuhan-Hu-1, Omicron BA.4/BA.5, or Omicron XBB.1.5 variant, respectively.

Comparability between clinical (phase I, II and pivotal phase III lots) and PPQ lots only includes the comparison of the release testing results. No characterisation or stability data are included. This is normally not considered sufficient, however there are only minor process changes between phase III clinical lots and commercial PPQ lots and the FP process is well known from already licensed mRNA vaccines, therefore this is acceptable. Comparable release results are obtained from clinical and commercial finished batches. For the developmental lots, accelerated stability data at 25°C is included

in the comparability assessment. The applicant uses stability data from the developmental lots in PFS for establishment of the shelf-life claim, because the clinical batches have a different container closure system (glass vials). However, the models used to compare all quality attributes between developmental and PPQ lots for stability analyses were not sufficiently well described and do not seem appropriate. Therefore, the shelf-life claim cannot be based on statistical modelling. However, during the procedure, sufficient real-time stability data was available for shelf-life establishment. The general process at ROVI has been sufficiently characterised and takes into account prior knowledge from the authorised mRNA vaccines Spikevax and mRESVIA where appropriate.

All manufacture sites of the intermediates and finished product comply with GMP requirements.

Extractables and leachables assessments have been conducted for finished product (FP) process consumables. A minor question regarding the acceptable limits has been sufficiently answered. A nitrosamine risk assessment has been provided and finds no significant risks in the processes used to manufacture RNA, LNP and final FP. Compatibility with the container closure system components has been shown.

Developmental stability studies have been performed. Photostability studies demonstrate that the FP manufacture under normal room lighting conditions does not impact FP quality although the FP is sensitive to UV-A and visible light. A transport simulation study was performed for the frozen product. Transport at 2°C to 8°C has been removed from the SmPC as no transport simulation data was available at this condition. Overall, the microbiological quality attributes are sufficiently controlled during the manufacturing process and at release.

There are no novel excipients in the product.

2.3.4.2. Manufacture of the product and process controls

All FP manufacturers have been listed. It has been specified in 3.2.P.3.1. which specific tests are performed at the sites responsible for release and stability testing. Endotoxin testing falls into the category of biological testing (not microbiological) and the dossier is revised accordingly.

The batch formula has been provided.

The manufacturing process has been sufficiently described and contains compounding, clarification and sterile filtration steps prior to filling. A flow diagram and a description of the single steps are presented. Two alternative flows are included: Flow 1 with an intermediate storage step of max. 3 months of the unlabelled finished product (UDP) including freeze/thaw before labelling/packaging and Flow 2 for continuous processing leading directly to the final finished product (labelled finished product LDP). Flow 1 will be the main process. In-process controls and process parameters are adequately chosen and are similar to the process of Moderna's already authorised mRNA vaccines. Reprocessing is not allowed at any stage of the FP manufacturing process. The process step considered as the date of manufacture of the finished product, that also represents the start of the shelf-life, is defined. A brief description of the shipping process of finished product is included.

Suitable critical process parameters have been defined and are adequately controlled. Adequate critical in-process controls have been established. A suitable microbial control strategy has been chosen that includes appropriate manufacturing areas, microbial control testing and media fills.

Process validation (PV) has been performed with three UDP batches that are processed to LDP batches (batches without UDP interim storage (PA2), batches with short interim storage time (PA1A) and batches with longer interim storage time (PA1B). The whole batch size range is covered. The PV approach is adequate and the results of release testing, critical and non-critical IPCs and critical and non-critical PPs

confirm that the process is consistently producing FP of the expected quality. The proposed cumulative process duration (CPD) was challenged with a subset of samples during PPQ. A post-clarification hold time has been introduced and is qualified.

Sufficient information on media fill, cleaning, and sterilising validation has been provided and are considered acceptable. Shipping validation supports transport of the FP.

2.3.4.3. Product specification

The finished product specification contains appropriate tests for appearance, identification, RNA and lipid content and purity, potency, particle size / polydispersity, physicochemical and microbiological properties.

Analytical tests for release and stability have been adequately chosen. The analytical procedures are sufficiently described. The Applicant has agreed to submit supplemental validation data for the mRNA purity/product related impurities method, including additional assessment of samples with lower purity to cover the EOSL specifications, in due time **(REC5)**.

Batch analysis results have been provided for the unlabelled (drug) product (UDP) lots and the resultingLDP PPQ lots. These LDP lots have been manufactured fromUDP lots and cover process alternative 1 with short UDP interim storage, process alternative 1 with longer UDP interim storage and process alternative 2 without interim storage step. All batches show consistent results for all CQAs that comply with the release specifications. All QCAs are tested on LDP level, except for sterility and bacterial endotoxins, which are tested on the unlabelled FP (UDP) level.

During the procedure a Major Objection, MO1 on the release/stability testing limit, has been resolved after further justification for the proposed EOSL limit for RNA purity has been provided. Revision was proposed for specifications for RNA lipid adducts and total lipid impurities and the applicant agreed to the requested tightening of specifications. An EOSL specification for IVRPE assay has been proposed based on a Scientific Advice procedure (in parallel with the MAA). Further tightening of the EOSL specification was accepted by the applicant during the procedure. There are no further impurities expected to be introduced during the FP formulation process. Appropriate specifications were in place during the clinical development.

The specifications of the excipients have been provided. Specifications for TRIS-HCL and DSPC are the same as for the licenced vaccines Spikevax and mRESVIA. The SM-102 manufacturing process has been updated and tests for solvents are not included anymore because the process does no longer include chromatographic purification.

Reference standards are used for mRNA purity determination, RNA content determination, IVRPE assay and lipid content, identity and impurity testing. The information provided is sufficient.

The container closure system is a PFS that consists of a cyclic olefin copolymer (COC) 1-mL long syringe, a 1-mL long halobutyl rubber plunger, and a plunger rod. Components and their specifications were briefly described in the dossier, however, more information on the components, including specifications and suppliers were subsequently provided. Based on further information provided (i.e. same device parts as used for Spikevax and mRESVIA) it is agreed that the Notified Body report sufficiently covers the device parts used for mRNA-1283 PFS.

Satisfactory information has been provided for container extractables and leachables and elemental impurities in product components.

2.3.4.4. Stability of the product

The applicant proposes a shelf life of 12 months at -15°C including up to 30 days at 2-8°C and 24 h at 25°C.

Stability data from process alternative 1 (with interim storage) PPQ lots is available for 9 months at -15°C and for 1 month at 5°C, and 25°C. In addition, stability data from PSB (primary stability batches) has been submitted. However, the applicant was not able to sufficiently demonstrate comparability of the PSB and PPQ/commercial lots in the responses to MO2 raised during the procedure. Therefore, these lots cannot be used for shelf-life determination. The available real-time stability data sufficiently supports the proposed shelf life of 12 months at -15°C including up to 30 days at 2-8°C and 24 h at 25°C.

The stability protocols in line with ICH requirements for the PPQ, clinical and PSB batches have been provided. They are in principle acceptable. Furthermore, an end-to-end stability study will be performed to demonstrate the shelf life of the finished product from the intended long-term frozen storage (11 months) through refrigerated (1 month) and room temperature (24 hours) storage.

The staggered post-approval stability approach is supported. CQAs and time points have been adequately chosen.

The final accepted shelf life is: 12 months stored below -15°C, including up to 30 days at 2-8°C, protected from light. Prefilled syringes may be stored for 24 h at 25°C after removal from refrigerated conditions.

2.3.4.5. Adventitious agents

Adventitious agents' safety for RNA-100-AR02, LNP-100-AR02 and FP is assured through the design and control of the manufacturing process, i.e., controlled selection and appropriate specifications for raw materials and consumables, in-process controls, and release testing for the active substance (AS) and the finished product (FP).

2.3.5. Discussion on chemical, pharmaceutical and biological aspects

Active substance:

The active substance of mNEXSPIKE is a mRNA encoding the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 Omicron XBB.1.5 subvariant (RNA-101-B815). The manufacturing process and the process validation of RNA-101-B815 are described appropriately. The shelf-life claim is now acceptable as additional data was provided. mRNA RNA-101-B815 contained within mNEXSPIKE is to be qualified as a new active substance in itself. A number of recommendations have been raised for further active substance development.

Finished Product Intermediate: The mRNA-1283 LNP intermediate consists of four lipid components (SM-102, Cholesterol, DSPC und PEG2000-DMG) and contains the mRNA (RNA-101-B815) that encodes the linked N- terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein of the SARS-CoV-2 virus. The manufacturing process of mRNA-1283 LNP is similar the process of the applicant's authorised vaccines Spikevax and mRESVIA. The shelf-life claim of mRNA-LNP is acceptable based on the data provided.

Final Finished Product: For manufacture of mRNA-1283 finished product, mRNA-1283 lipid nanoparticles are formulated with Tris buffer and sucrose at pH 7.5. The final product contains 0.05 mg/ml RNA-101-B815 that is 10 µg RNA per 0.2 ml dose. The final product is presented as single-dose 1-ml-long cyclic olefin copolymer (COC) syringe. The final FP manufacturing process is very similar to the applicant's

authorised vaccines Spikevax and mRESVIA. Therefore, the manufacturing process and controls are in principle supported. MOs raised on the RNA purity EOSL specification and the shelf life claim have been resolved during the procedure, with sufficient data. In addition, it was accepted that the container closure components are covered by the provided Notified Body Opinion. Questions regarding the purity assay validation, and the specifications for in vitro relative protein expression, total lipid impurities and RNA lipid adducts have been resolved.

2.3.6. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.7. Recommendations for future quality development

1. The Applicant commits to providing additional accelerated stability data at 2-8°C for three additional active substance batches to support comparability stability assessment of PolyA Tailed RNA. Data will be provided during the next strain update.
2. The applicant should commit to change the classification of acetate and to exclude it from the list of excipients for Spikevax and mRESVIA via post-approval variation applications in a timely manner.
3. The Applicant commits to validating an optimized method to quantify PolyA tailed RNA. A method validation report, method description, and bridging study summary will be provided by August 2026.
4. The Applicant commits to submitting data supporting an orthogonal analytical method to quantitate DNA levels and DNA size no later than May 2027.
5. The Applicant agrees to submit a supplemental validation for the mRNA purity/product related impurities method, including additional assessment of samples with lower purity to cover the EOSL specifications, by December 2026.

2.4. Non-clinical aspects

2.4.1. Introduction

The applicant submitted a complete non-clinical data package summary in Module 2 and complete study reports in Module 4. The non-clinical data package consists of pharmacodynamics studies with the SARS-CoV-2 mRNA vaccine mRNA-1283, pharmacokinetics studies with data of the applicant's mRNA-based platform, and toxicity data with mRNA-1283 and applicant's mRNA-based platform.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The applicant conducted several pharmacodynamic studies in support of the development mRNA-1283. All pharmacodynamic studies were non-GLP compliant, which is accepted. In these studies, the applicant analysed the expression and immunity derived from mRNA-1283 in comparison to the presently authorised mRNA-1273 vaccine (Spikevax).

The in-vitro expression of NTD and RBD in mRNA-1283 transfected HEK293T cells was evaluated and compared to mRNA-1273 transfected cells in study MOD-4112. The cells were transfected with the mRNA without LNP-encapsulation. Transfection of mRNA-1283 and mRNA-1273 in HEK293T cells showed sustained expression of both NTD and RBD in a dose-dependent manner, with higher expression after transfection with mRNA-1283. In the same study report, the RBD and NTD in vivo expression in spleen and lymph nodes of mRNA-1283 or mRNA-1273 vaccinated mice were analysed at two dose levels: 2 µg or 10 µg. Mice were administered vaccines intramuscularly to both legs and both inguinal draining lymph nodes were collected and pooled for each animal for subsequent analysis. LNP-encapsulated mRNA vaccines were used in this experiment. In the spleen and lymph nodes, in-vivo expression of mRNA-1283 and mRNA-1273 showed no statistically significant differences in the level of antigen expression measured in cDCs or pDCs for either NTD or RBD. Interestingly, in the 10 µg dose groups, mRNA-1273 appeared to have higher expression in the spleen compared to mRNA-1283, while mRNA-1283 was expressed higher in the lymph nodes. However, the individual samples showed a high variability and this experiment showed generally some limitations. The applicant clarified that the flow cytometry assay utilised to assess protein expression was research grade and not qualified nor validated. The lower limit of detection or quantification was not determined.

In a following study (MOD 4079), the immunogenicity was evaluated, and the IgG antibody titre dynamic range of mRNA-1283 (Wuhan) was determined in BALB/c mice after two intramuscular (IM) doses with doses ranging from 0.000305 µg to 20 µg. A dose-dependent increase of IgG binding antibody titre against SARS-CoV-2 S-2P, RBD and NTD was measured after 1st and 2nd dose with increased binding antibody titre after 2nd dose. In general, higher vaccine doses were needed to detect robust NTD-specific IgG antibodies in the mice.

Furthermore, three immunogenicity studies (MOD-3964, MOD-4035 and MOD-4101) were included into one study report. The objectives of study MOD-3964 were to evaluate the immunogenicity of mRNA-1283 (Wuhan) administered as a primary series and to address the theoretical concern of enhanced respiratory diseases (ERD) in BALB/c mice relative to mRNA-1273 at two dose levels: 0.1 µg and 1 µg. This study was repeated for confirmation of dose responses in studies MOD-4035 and MOD-4101 and to allow for the evaluation of additional immune endpoints, including antibody subclasses IgG1 and IgG2a, and T-cell response. S protein-specific IgG binding antibody titres show dose-dependent increase for mRNA-1273 and mRNA-1283. A booster dose showed also increased IgG binding antibody titre demonstrating the enhanced immunogenicity after booster dose. At the 0.1 µg dose level, one single dose was not enough to induce a strong IgG signal. After the 2nd 0.1 µg dose, the antibody titre in the mRNA-1283 group was significantly higher than in the mRNA-1273 group. This difference was only observed in studies MOD-3964 and MOD-4101, but not in study MOD-4035. The S protein antibody titre signal was comparable at 1 µg dose level after 1st and 2nd dose. In all three studies, the results were similar. RBD- and NTD-specific IgG binding antibody titre showed dose-dependent increase with higher titres after 2nd dose. RBD-specific and NTD-specific signals were higher in mRNA-1283 compared to mRNA-1273. The difference for NTD-specific titre was more significant. A 2 dose-regime with 1 µg mRNA showed the highest titre. S protein IgG1:IgG2a ratio was balanced for mRNA-1283 and was slightly Th1-skewed for the higher dose level (1 µg), which was slightly more prominent

than in the mRNA-1273 group after 2-dose of 1 µg. Neutralising antibody titre against S protein was dose-dependent, showing only strong signals with 1 µg vaccine after 2nd dose. Neutralising antibody titres were similar in all three studies. The neutralising antibody titre against S protein was slightly but not statistically significant higher in mRNA-1283 compared to mRNA-1273. In general, similar levels of neutralising antibody titre were observed after two primary IM doses of higher mRNA-1283 or mRNA-1273 dose levels (1 µg/dose) in mice. However, the neutralising antibody titres in the low dose groups (0.1 µg/dose) were generally weak in mRNA-1283 and mRNA-1273 vaccinated mice. No significant differences were observed between mRNA-1283 and mRNA-1273. In splenocytes, IgG levels of S protein and RBD-reactive ASCs were not significantly different between mRNA-1283 and mRNA-1273. Levels of NTD-reactive ASCs in mRNA-1283 mice were similar compared to mRNA-1273 mice, but all mRNA-1283 mice showed detectable IgG levels of NTD-reactive ASCs in contrast to mRNA-1273 mice where only few animals showed detectable levels. Th1 CD4+ T-cell response was very strong in mice vaccinated with two doses of 1 µg mRNA-1283 in study MOD-4101 for the spike S1 peptide pool. However, this signal could not be confirmed in study MOD-4035. In general, for mRNA-1283 and mRNA-1273 at both dose-levels, higher Th1 T-cell responses were measured compared to Th2 T-cell response. These results are consistent to the results collected for RBD- and NTD-specific CD 4+ T-cell responses in studies MOD-4035 and MOD-4101. The data for the CD8+ T-cell responses were not consistent and in general low.

In addition, immunogenicity and challenge data from the scientific paper Stewart-Jones et al (2023) were submitted. Firstly, immunogenicity of an mRNA-1273 or mRNA-1283 primary series (0.1 µg and 1 µg) followed by matched B.1.351 specific mRNA vaccine booster (0.1 µg and 1 µg) was evaluated in BALB/c mice. Neutralising antibody titre were analysed against full-length S protein of Wuhan-Hu-1 variant or B.1.351 variant. The full-length S protein (Wuhan) neutralisation titre was post-prime higher in mice vaccinated with 0.1 µg mRNA-1283 compared to mice vaccinated with 1 µg mRNA-1273. This result is inconsistent with the neutralising antibody result in study MOD-4035 that does not show similar neutralising antibody titre levels comparing 2-dose mRNA-1273 vaccination with a 10-fold lower dose of mRNA-1283. Furthermore, in the cited paper, 1 µg and 0.1 µg were tested for mRNA-1273 and mRNA-1283 for prime doses (1st and 2nd dose), but only the results of the 1 µg dosing groups were shown. The neutralising antibody titre for mRNA-1273 (1.5 fold) and mRNA-1283 (1.9 fold) decrease between D36 and D212 post-prime indicating a slight vanishing effect of neutralising antibody titre. After boosting with a B.1.351-matched vaccine of mRNA-1273 and mRNA-1283, neutralising antibody titre increased for Wuhan and B.1.351 SARS-CoV-2 variants in a dose-dependent manner. The neutralising antibody titre was slightly higher in mRNA-1283 vaccinated animals compared to mRNA-1273 vaccinated animals. Interesting, already at D212 pre-boost variant matched vaccines, B.1.351-specific neutralising antibody response was detected in high-dose groups of mRNA-1273 and mRNA-1283 primed animals indicating cross-protection between Wuhan-specific mRNA vaccines to B.1.351 variant.

In the second part of the publication (Stewart-Jones et al 2023), neutralising antibody titre responses were assessed in mice that were administered in a two-dose primary mRNA-1273 series followed by a booster dose of mRNA-1273, mRNA-1283, or variant-specific monovalent or bivalent mRNA-1273 and mRNA-1283 formulations. The dose level for all administrations was 1 µg/dose. The fold change of neutralising antibodies specific against Wuhan D614G, B.1.351 and B.1.617.2-v2 was for mRNA-1283 type vaccines higher than for mRNA-1273 type vaccines. A positive fold change was observed for all vaccine types after 3rd booster dose. A difference between the variant-matched vaccines within the mRNA-1273 or mRNA-1283 group was not significant due to high variability of individual titres.

In the third part of the publication (Stewart-Jones et al 2023), K18-hACE2 C57BL/6J mice were vaccinated with 2 prime doses (5 µg and 0.1 µg) mRNA-1273 or mRNA-1283 and challenged with D614G or BA.1 on day 56 or 57 via intranasal route. It has to be noted that the data from control

mRNA and mRNA-1273 vaccination groups were not conducted in this study but were used for reference, because these studies were performed concurrently with mRNA-1283 vaccination as part of a larger multi-arm study cohort series. These experiments are time-matched, not historical comparisons. 2 prime-doses of mRNA-1283 (Wuhan) induced high D614G-specific neutralising antibody responses in all animals vaccinated with high dose 5 µg. Significant lower level of D614G-specific neutralising antibody titre were measured for low dose and not in all animals. Cross-protection with BA.1-specific neutralising antibody titre was demonstrated only in the high dose groups. Full protection was observed in lungs of high-dose groups after D614G SARS-CoV-2 challenge and partial protection after BA.1 challenge in high dose group. Low vaccine doses showed partial protection against D614G and no or low protection against BA.1. Similar results have been observed for mRNA-1273 vaccinated animals. Protection against D614G and BA.1 in nasal turbinate was observed in many mRNA-1283 vaccinated animals of the high dose group and only partly in few animals of the low dose group. Similar effects have been observed for mRNA-1273.

In study report MOD-5156.1283, D614G-specific and BA.1-specific binding and neutralisation antibody titres were measured after a 2-dose regime of 1 µg/dose monovalent or bivalent mRNA-1283 and mRNA-1273. The mRNA-1283 variants showed superiority or non-inferiority in binding and neutralising antibody titre against D614G compared to mRNA-1273 variants. BA.1-specific binding and neutralisation antibody titre did not differ significantly between mRNA-1283 variants and mRNA-1273 variants.

In study MOD-5814-1283, the immunogenicity of bivalent mRNA-1283.222 (4 µg) in BALB/c mice was analysed, and the equivalence of two manufacturing versions of the vaccine were compared. mRNA-1283.222 and mRNA-1283.222-v2 contain different UTR sequences and are manufactured using a different mRNA manufacturing process. Analysis certificates of the tested vaccines were submitted upon request with D120 responses. Two doses of mRNA-1283.222 or mRNA-1283.222-v2 induce similar high spike protein IgG binding antibody titre for Wuhan and Omicron BA.4/BA.5 variation. Also, two doses of either vaccine version induce detectable neutralising antibody titre against the whole spike protein of Wuhan or Omicron BA.4/BA.5 variant. However, the BA.4/BA.5-specific neutralising antibody titre was higher after vaccination with mRNA-1283.222 compared to mRNA.1283.222-v2. CD4+ and CD8+ T-cell responses specific for Wuhan and Omicron BA.4/BA.5 were similar for mRNA-1283.222 and mRNA-1283.222-v2. Both vaccines showed also a higher Th1 CD4+ T-cell response. These data are consistent with measured T-cell responses with the mRNA-1283 vaccine (Wuhan-matched), analysed in studies MOD 3964, MOD-4035, and MOD-4101.

In study MOD-6124, different mRNA-1283 and mRNA-1273 variants were analysed: mRNA-1283.815 (monovalent, XBB.1.5/XBB.1.9.1 matched), mRNA-1283.116 (monovalent, XBB.1.16 matched), mRNA-1283.222 (bivalent, mRNA-1283 + mRNA-1283.045 BA.4/BA.5), mRNA-1273.222 (bivalent, mRNA-1273 + mRNA-1273.045 BA.4/BA.5), and mRNA-1273.116 (monovalent, XBB.1.16). The dose level for all administrations was 1 µg/dose. Whole spike-protein (Wuhan)-specific IgG binding antibody titre was high for all tested vaccine candidates and increased after 2nd dose to a higher level. High neutralising antibody titre against D614G was observed for mRNA-1273.222 and mRNA-1283.222. High neutralising antibody titre against BA.4/BA.5 was observed in all vaccine groups with highest in mRNA-1273.222, mRNA-1283.116 and mRNA-1283.222. High neutralising antibody titre against XBB.1.5 and XBB.1.16 were observed for mRNA-1273.116, mRNA-1283.815 and mRNA-1283.116.

In study MOD-5972.1283, mice were vaccinated with two doses of 0.5 µg/dose mRNA-1273 within 3 weeks and boosted with 1 µg/dose mRNA-1273.116, mRNA-1283.815, mRNA-1283.116 or mRNA-1283.222. Full-length Wuhan S protein binding IgG antibody titre and neutralising antibody titre against S protein (Wuhan, BA.4/BA.5, XBB.1.5, and XBB.1.16) were analysed. All vaccine groups showed high IgG binding antibody titre boosting. The binding antibody titre for mRNA-1273.116 was lower than for the mRNA-1283 variant vaccine candidates. The PBS control group showed also relative

high binding antibody titre, about 6-fold lower than for the vaccine groups indicating that the mice were not SARS-CoV-2 naive. Thus, these study results are not very meaningful in regard to immunogenicity of the vaccines. All vaccine groups showed strong neutralising antibody titre against D614G, which did not increase after the booster dose, except for the mRNA-1283.222 group. All vaccine groups showed low neutralising antibody titre against BA.4/BA.5 after the prime-dosing, which increased after the booster dose. The highest increase was observed in the mRNA-1283.222 group. The other vaccine candidates included other Omicron variants, which showed a higher similarity to BA.4/BA.5 than to Wuhan. For XBB.1.5 and XBB.1.16, the neutralising antibody titre after the prime vaccination was at the lowest detection limit. After the booster doses, all vaccine groups showed a significant increase of neutralising antibody titre. The mRNA-1283.222 group showed the lowest titre for these two variants. The other vaccine candidates included one of either antigen sequences. These two Omicron variants are very similar, thus high cross protection was observed in those 3 vaccine candidates.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies have been conducted.

2.4.2.3. Safety pharmacology programme

No safety pharmacology studies have been conducted.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions have been studied.

2.4.3. Pharmacokinetics

No pharmacokinetic (PK) studies have been conducted with mRNA-1283. In the biodistribution study 2308-582, NPI-Luc mRNA, SM-102 and NPI-Luc protein were analysed in female and male Sprague Dawley (SD) rats after intramuscular administration of single dose 100 µg LNP-encapsulated mRNA. This study report (Report 2308-582 Amendment 1) was already submitted to EMA within the Spikevax regulatory life-cycle. The test product NPI-Luc mRNA was encapsulated in LNPs containing the same lipids as in the drug product mRNA-1283. No sex-dependent exposures in serum and tissues were observed. The distribution of NPI-Luc mRNA and SM-102 were high in injection site, lymph nodes (axillary, inguinal and popliteal) and spleen, and showed generally low exposures and transient distribution in other tissues. NPI-Luc protein tissue concentrations could only be quantified in 3 liver tissue samples and 2 injection sites tissue samples, all in females.

For the biodistribution and PK study 20456513, mRNA-1273 (Spikevax) was used, which is based on the same LNP-platform than mRNA-1283. This study report (20456513 Amendment 1) was already submitted to EMA as Variation for Spikevax (EMA product number EMEA/H/C/005791) and assessed. Male and female SD rats were administered an intramuscular injection of 78 µg mRNA-1273 on Day 1 or on Day 1 and Day 28. The study results delineate PK properties of mRNA after mRNA-1273 IM injection, showing highest distant distribution to peripheral immune tissues of spleen and lymph nodes, followed by liver. Exposures observed in vital organs including the heart and the brain are generally very low and transient. These data were very similar to those generated with similar products of the mRNA SM-102-LNP platform (NPI-Luc, mRNA-1647). The applicant concluded that systemic exposure to mRNA from mRNA-1273 generally appeared to be sex-dependent with females having a higher exposure for serum and tissues than males. This is in contrast to study Report 2308-582 with NPI-Luc

mRNA where the applicant states that PK was sex-independent. According to the study report 20456513 Amendment 1, exposures in serum and tissues tend to be higher in females than males, but with less consistency in lymph node and injection site. The applicant also stated sex-dependent exposures to SM-102, with generally higher in females than males across matrices. However, there was no consistent difference observed for lymph nodes and injection site. Also, no sex-dependent exposures were observed in a similar study 2308-582. Furthermore, the applicant stated sex-dependent exposures to SARS-CoV-2 Spike protein, generally higher in females than in males, for serum and tissues. This does not appear to hold for lymph node tissues, as also evidenced by tissues-to-serum ratios (MTX) data. Overall, no apparent increase or changes were observed in exposure and kinetic of mRNA from mRNA-1273 or SM-102 after the first and the second dose of mRNA-1273. However, it is found that exposures to SARS-CoV-2 S protein across matrices appeared to consistently decrease after the second dose of mRNA-1273 injection such as reported for the inguinal lymph nodes, axillary lymph nodes and the injection sites. In addition, success detection of anti-Spike IgG antibody in each animal demonstrated exposure of animal to mRNA-1273 vaccine. An increase in the anti-S protein IgG antibody titres was observed after the 2nd dose.

A biodistribution study was conducted in male SD rats with mRNA-1647 (Report 5002121 Amendment 2), a mRNA-based CMV vaccine that was formulated in the same SM-102-containing LNPs. The same study was previously used to support the development of Spikevax and mRESVIA (EMA product number EMEA/H/C/006278). The data from this biodistribution study performed with mRNA-1647 indicated that mRNA construct could be distributed to most tissues analysed except for kidney, after single IM administration. The highest mRNA concentrations were observed at the injection site (muscle), followed by the proximal (popliteal) and distal (axillary) lymph nodes, suggesting distribution via the lymphatic system. Overall, only a relatively small fraction of the mRNAs in mRNA-1647 drug product distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site (muscle), lymph nodes, and the spleen.

The submitted nonclinical PK evaluations also included SM-102 lipid metabolism and excretion in vivo studies in SD rats (Report QV-0236-DA-RE Amendment 2) and metabolite identification study in vitro (Report NCS-BA-2022-010). For these purposes, samples of plasma, urine and bile from male SD rats were obtained at different time points following a single 10-minute intravenous (IV) infusion administration of SM-102-containing LNPs. Samples for in vitro study were the cryopreserved primary hepatocytes, that were thawed, resuspended, and incubated with SM-102 at 10 µM concentration in 250 µL volume. Liquid chromatography (LC)-High Resolution Mass Spectrometry (HRMS) was employed to identifying and qualitatively characterizing metabolites of SM-102, whereas LC-MS/MS used for quantitation of the parent SM-102 in the in vivo samples. The SM-102 quantitation range was 0.2- 500 ng/mL with LLOQ – 0.2 ng/mL in rat urine; and 1- 500 ng/mL with LLOQ – 5 ng/mL in rat plasma and bile. The in vivo study showed rapid clearance of SM-102 and the elimination of SM-102 and its metabolites via the kidney (metabolites only) and liver (intact SM-102 and metabolites) to <3% of the maximum level by 24 hours after dosing. The metabolism of SM-102 in rats occurs primarily by hydrolysis of the ester groups followed by β-oxidation of the resulting aliphatic acidic linkers. Additionally, low abundance oxidative metabolites of ester-hydrolysed SM-102 fragments were detected. The in vitro incubation of SM-102 LNPs with rat, cynomolgus monkey, and human hepatocytes (report NCS-BMA-2023-06) yielded identical ester-hydrolysed and β-oxidized metabolites with no human-specific metabolites detected. Based on the observed extensive metabolism of SM-102, the oxidative nature of the metabolites, and the multiple, ubiquitous, high-capacity systems by which they are formed, combined with the rapid overall clearance of SM-102 and elimination of its metabolites, it is reasonably assumed that SM-102 is unlikely to accumulate upon repeat IM dosing or be a risk for elimination in patients with hepatic or renal insufficiency.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single-dose toxicity study with mRNA-1283 has been conducted. The local acute toxicity was analysed in the repeat-dose toxicity studies with mRNA-1283.

2.4.4.2. Repeat dose toxicity

One GLP-compliant repeat-dose study has been conducted with bivalent mRNA-1283.222 and one non-GLP-compliant repeat-dose toxicity study has been conducted with mRNA-1283.

In the GLP-compliant repeat-dose toxicity study 20462697, 2 IM doses of bivalent vaccine mRNA-1283.222 (Wuhan-Hu-1 strain and the BA.4/BA.5 in an equivalent mass ratio) were administered to Sprague Dawley (SD) rats, a suitable animal model for vaccine toxicity studies. The highest tested dose level was 10 µg/dose, which will be also the intended clinical dose. It has to be noted, that the drug product of this MAA is mRNA-1283.815, a monovalent XBB.1.5-specific SARS-CoV-2 vaccine. Both vaccines are based on mRNA-1283, have the same RNA/LNP ratio, the same LNP formulation is used and the same non-coding mRNA elements. Thus, toxicity data from the bivalent mRNA-1283.222 are acceptable bridging data to conclude on the safety of mRNA-1283.815 at a non-clinical perspective. SD rats were administered 2 IM doses of 2, 5, or 10 µg/dose mRNA 1283.222 or vehicle control via IM injection on Days 1 and 29 following a 2-week recovery period. 10 males and 10 females per group were evaluated within the main group and 5 males and 5 females per group (only control and 10 µg dose group) were evaluated for recovery of observed findings. No mortalities occurred during the course of the study. There were no mRNA 1283.222-related effects on clinical or injection site observations, body weights, food consumption, ophthalmologic findings, macroscopic (gross) necropsy findings, or organ weights. Wuhan- and BA.4/BA.5 S-specific IgG titres were detected in all vaccinated animals. This study part was not GLP-compliant, which is acceptable. The observed findings were mainly at the injection sites and draining lymph nodes. These findings are typical for IM administered vaccines and comparable to the findings in the supportive toxicity studies with mRNA vaccine encapsulated with the same SM-102 LNP (see following supportive toxicity studies). However, no swelling or skin redness were observed at the injection sites for mRNA-1283.222. In contrast, this was observed in all submitted supportive mRNA toxicity studies. Minimal transient swelling was already observed at ≤10 µg/dose at the injection sites in these supportive studies. mRNA-1283.222-related and dose-related increases were observed in neutrophil and/or fibrinogen at ≥2 µg/dose. In addition, mRNA-1283.222-related decreases in reticulocyte were observed in males at ≥2 µg/dose. mRNA-1283.222-related and dose-related decreases in lymphocyte were observed in females at ≥2 µg/dose. After the recovery period, all observed findings recovered fully or showed signs of recovery. The haematology and clinical chemistry were only analysed after 2nd dose and after the 2-week recover period. Thus, no clinical pathology data are available to evaluate potential acute toxicity. Since single-dose toxicity study was not conducted, these data would have been of value. Regarding safety data obtained from non-clinical and clinical studies with mRNA-1283 candidates and similar mRNA platform vaccines, the lack of acute nonclinical toxicity data is acceptable.

In the non-GLP compliant repeat-dose toxicity study 2308-161, 2 IM doses of monovalent vaccine mRNA-1283 (original Wuhan-Hu-1 strain) were administered to SD rats. Rats were administered 2 doses of 30, 60, or 100 µg/dose mRNA 1283 or control. 5 males and 5 females were included in each dose group. No recovery period was included in the study design. For necropsy and histopathology, only liver and spleen were analysed. There were no mRNA-1283-related mortalities, changes in body weight, or body weight gain during the study. The main observed findings in this study transient

swelling at the injection sites and haematological changes indicating slight inflammation. These findings are typical for IM administered vaccines and are comparable to the findings, which were observed in the other toxicity studies conducted with mRNA/SM-102 LNP vaccines. In addition, mRNA-1283 could induce S-protein specific IgG antibody response in all vaccinated rats. mRNA-1283-related clinical observations were seen 24 hours post each dose and generally consisted of transient, dose-dependent oedema with or without hindlimb impairment at ≥30 µg/dose. All oedema and/or hindlimb impairment resolved within 4 days following dose administration. mRNA-1283-related haematology changes consistent with inflammation were seen at ≥30 µg/dose and included increased neutrophil and/or eosinophil counts. In addition, there was a decrease in reticulocytes and/or platelets. Lastly, there were decreased lymphocytes. These effects resolved by Day 36 at all doses. mRNA-1283-related clinical chemistry changes consistent with inflammation were seen at ≥30 µg/dose in both sexes and included decreases in mean total protein, albumin and/or A/G ratio. By Day 36, there was evidence of resolution of these effects in all affected groups. Furthermore, minimal or mild mRNA-1283-related increase in extramedullary haematopoiesis was observed in the spleen at doses of ≥30 µg/dose.

Moreover, 6 GLP-compliant repeat-dose toxicity studies were included in this MAA dossier that were already part of the assessment of initial authorisation of Spikevax and mRESVIA. These supportive studies analysed different mRNA vaccines that are encapsulated in the same SM-102 LNP as mRNA-1283 but encoding for different antigens (ZIKV vaccines: mRNA-1706 and mRNA-1893, hMPV and PIV3 vaccine: mRNA-1653, and CMV vaccines: mRNA-1647 and mRNA-1443). Thus, the results are summarised only briefly. Main findings were swelling at injection site, increased neutrophil and eosinophil counts, decreased lymphocytes, reticulocytes and platelet, increased cytokine level, enlarged and mixed-cell infiltration at lymph nodes and/or depletion of lymphocytes in spleen. These findings were consistent within all these supportive toxicity studies.

2.4.4.3. Genotoxicity

The conducted genotoxicity studies were already submitted for the initial marketing authorisation of Spikevax and mRESVIA. The GLP-compliant Ames tests in *Salmonella typhimurium* and *Escherichia coli* and in vitro micronucleus tests in human peripheral blood lymphocytes for the LNP components SM-102 and PEG2000-DMG were negative for mutagenicity. To support the use of SM-102 lipid and PEG2000-DMG in LNP-formulated mRNA-based drug products, one GLP-compliant and another non-GLP-compliant in vivo erythrocyte micronucleus study were completed in bone marrow from rats applying an IV route of administration, using representative mRNA drug products formulated in the same LNPs then mRNA-1345. Results from non-GLP-compliant micronucleus studies were negative for clastogenicity, while results from the GLP-compliant in vivo study were weakly positive for clastogenicity. Significant increases in micronucleated immature erythrocytes were observed in male rats at both 24 and 48 hours and in females at 48 hours only, but there was no clear dose response after IV administration. Overall, the genotoxic risk to humans is considered to be low for SM-102-containing mRNA vaccines due to minimal systemic exposure following intramuscular administration, limited duration of exposure, negative in vitro results, and equivocal in vivo results.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been conducted.

2.4.4.5. Reproductive and developmental toxicity

One GLP-compliant combined reproduction and development toxicity study has been conducted in female SD rats when administered mRNA-1283. The applicant clarified that monovalent mRNA-1283 of

the original D614G strain was used in this study. Female rats were administered four doses of 80 µg/dose mRNA-1283 or control on Study Days 1 and 15 (28 and 14 days prior to mating, respectively) and on Gestation Days 1 and 13, via IM injection. Rats were divided into either a caesarean-sectioning phase cohort (cohort 1) or a natural delivery phase cohort (cohort 2). F0 generation rats (dams) in cohorts 1 and 2 were monitored for clinical observations, body weight, food consumption, oestrous cycling, mating, and fertility. In addition, cohort 1 dams were euthanized on GD 21 for caesarean-sectioning, gross pathology, organ weights (gravid uterus), and ovarian and uterine contents examinations; and the foetuses were euthanized for gross pathology and foetal examinations (external abnormalities, visceral examination, skeletal examination, and foetal ossification). Cohort 2 dams were allowed to deliver their litters and were euthanized for gross pathology after completion of the 21-day postpartum period. The pups were monitored for clinical observations, body weight, and reflex and physical development. Pups were euthanized on Postnatal Day 21 for gross pathology. There were no mRNA-1283-related mortalities in dams throughout the study. During the premating period, mRNA-1283-related injection site reactions were observed in all F0 rats across both cohorts and included limited usage of the hindlimb and swollen hindlimbs. In general, these injection site reactions resolved within 2 to 6 days post each dose in each of the affected F0 rats. Administration of 80 µg/dose mRNA-1283 did not affect the number and length of oestrous cycles, or mating, fertility, or pregnancy indices. No macroscopic findings or effects on any ovarian, uterine, or litter parameters were observed. Administration of mRNA-1283 did not increase the incidence of foetal external, visceral, or skeletal malformations or variations. In addition, there were no mRNA-1283–related effects on any natural delivery, maternal/litter interactions, or any F1 generation preweaning parameters (e.g., viability, clinical observations, body weights, and pup macroscopic necropsy findings), including reflex and physical development.

Vaccinated dam serum samples had high NTD- and RBD-specific IgG antibody titre. Interesting, the serum samples of pups on GD21 had about a 10-fold lower IgG titre than in dams on GD21. However, on PND13 and PND 21, pup's serum samples had approximately same IgG titre levels than in dams. Also, milk samples on LD 13 and 21 had about a 10-fold lower IgG titre than serum samples of dams. Thus, mRNA-1283-induced maternal antibodies can be transferred in utero to the foetus and via lactation to the pups.

2.4.4.6. Toxicokinetic data

No toxicokinetic data have been submitted.

2.4.4.7. Local Tolerance

Local tolerance was evaluated within the repeat-dose toxicity studies.

2.4.4.8. Other toxicity studies

No other toxicity studies have been conducted.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant did not conduct Environmental Risk Assessment (ERA) studies on mRNA-1283. The mRNA drug substance in mRNA-1283 vaccine is composed of naturally occurring nucleosides and sugars and is degraded to natural metabolic products before excretion and to natural transformation products in the environment. Therefore, the prescribed use of mRNA-1283 vaccine does not significantly alter the concentration or distribution of mRNA building blocks and their degradants in the

environment. Furthermore, toxicological data in mammalian species show no population relevant alerts. Therefore, it is concluded that due to its nature mRNA-1283 is unlikely to result in a significant risk to the environment and ERA studies are not required. This justification is sufficient and in compliance with EMA guideline EMEA/CHMP/SWP/4447/00 Corr 2.

The LNP matrix used to formulate mRNA-1283, which is comprised of two synthetically derived lipid excipients (SM-102 and PEG2000-DMG) as well as cholesterol and DSPC, has also been used in other mRNA vaccines manufactured by the applicant, including Spikevax and mRESVIA. Due to the nature and toxicological properties of the lipid excipients in this LNP matrix, it is concluded that they are unlikely to result in a significant risk to the environment following the prescribed use of mRNA-1283 vaccine. In conclusion, the prescribed use of mRNA-1283 is of no immediate concern for the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacodynamics

The applicant conducted an in vitro assay to show cell surface expression of RBD and NTD in mRNA-1283 or mRNA-1273, both not encapsulated in LNPs, transfected cell line with human origin. Additionally, lymph nodes and spleen from mRNA-1273 or mRNA-1283 vaccinated mice showed comparable RBD and NTD expression. However, the individual samples showed a high variability. The applicant clarified that the flow cytometry assay utilized to assess protein expression was research grade and not qualified nor validated. The lower limit of detection or quantification was not determined. Thus, these experiments are considered as only supportive.

Furthermore, the applicant conducted several immunogenicity studies with monovalent or bivalent mRNA-1283 vaccine variants, which were specific against different SARS-CoV-2 variants (Wuhan, B.1.351, BA.1, XBB.1.5/XBB.1.9.1, XBB.1.16, BA.4/BA.5). Already at two low IM doses (0.1 µg/dose) mRNA-1283 in mice, high full Spike protein- and RBD-specific IgG binding antibody titre could be measured that were higher than binding antibody titres from low dose mRNA-1273 vaccinated mice. At higher doses (1 µg/dose), the binding antibody in mRNA-1283 and mRNA-1273 vaccinated mice increased to a similar high level. NTD-specific IgG binding antibody titre were in higher in mRNA-1283 vaccinated mice compared to mRNA-1273 vaccinated mice. However, the NTD-specific antibody titre was in general lower than for Spike protein and RBD.

High neutralising antibody titre were observed after two primary IM doses of higher mRNA-1283 dose levels (1 µg/dose) in mice. 2 doses at a low-level mRNA-1283 (0.1 µg/dose) was not enough to induce strong neutralising antibody signals, although low doses induced already high binding antibody titres. Similar levels of neutralising antibody titre were observed after two primary IM doses of higher mRNA-1283 or mRNA-1273 dose levels (1 µg/dose) in mice. However, the neutralising antibody titres in the low dose groups (0.1 µg/dose) were at a low level in mRNA-1283 and mRNA-1273 vaccinated mice in most studies. In general, no significant different immunogenicity was observed in mice after primary immunisation with mRNA-1283 or mRNA-1273. It has to be noted that the human dose of mRNA-1283 will be 10 µg/dose, which is a 5-fold lower dose than the indicated mRNA-1273 booster dose due to higher immunogenicity of mRNA-1283 vs. mRNA-1273 in human. Thus, these mouse data do not reflect very well the human situation. A 3rd dose booster was administered to mice to induce increased neutralising antibody titre. The different tested variant-matched mRNA-1283 vaccines also inducted SARS-CoV-2 variant-specific neutralising antibody titre in 2-dose vaccination scheme with mRNA-1283 variant vaccines and in 2-prime-dose with mRNA-1273 (Wuhan) plus a 3rd booster dose with the variant-matched mRNA-1283, which reflect real-world situation. In addition, T-cell response was evaluated in mRNA-1283 vaccinated mice in several studies. These data indicate a Th1-skwed T-cell

response with Th1 CD4+ T-cell expression in the vaccinated mice. Furthermore, the theoretical concern of ERD was addressed in vaccinated young, female BALB/c mice. The binding IgG antibody titres were well correlated with neutralising antibody activity, indicating that ERD was unlikely to occur following vaccination with mRNA-1283.

Additionally, a challenge study was conducted with mRNA-1283 vaccinated K18-hACE2 C57BL/6 J mice. After vaccination with 2 IM vaccine doses, animals were infected intranasal with D614G or BA.1 SARS-CoV-2 strains. Full protection was observed in lungs of high-dose groups (5 µg/dose) after D614G SARS-CoV-2 challenge, and partial protection after BA.1 challenge in high dose group. Low vaccine doses (0.1 µg/dose) showed partial protection against D614G and low protection against BA.1. Protection against D614G and BA.1 in nasal turbinate was observed in many mRNA-1283 vaccinated animals of the high dose group and only partly in few animals of the low dose group. Similar effects have been observed for mRNA-1273.

In the in vivo protein expression studies (BALB/c mice) and in the mouse SARS-CoV-2 challenge studies (K18-hACE2 C57BL/6) Stewart-Jones et al only used female animals. It might be possible that male mice would show a different immunogenicity reaction. Regarding to the significant differences of spike-specific IgG antibody responses in female and male rats (seen in previous repeat-dose toxicity studies), it can be assumed that the mRNA-induced immune responses differ generally between female and male rodents.

Besides, the comparability of two manufacturing versions of mRNA-1283.222 was demonstrated in mice by humoral and cellular immune response assays. Moreover, the immunogenicity of monovalent and variant-containing bivalent mRNA-1283 vaccines were evaluated in mice after a 2-dose primary series, including drug products that encode the following antigen strains: Wuhan-Hu-1 (original), Omicron B.1.351 (Beta), Omicron B.1.1.519 (BA.1), Omicron BA.4/BA.5, Omicron XBB.1.5, and Omicron XBB.1.16.

In another immunogenicity study MOD-5972.1283, mice were primed with two doses of mRNA-1273 and boosted with mRNA-1273.116, mRNA-1283.815, mRNA-1283.116 or mRNA-1283.222. The measured neutralising antibody titres against variants XBB.1.5 and XBB.1.16 provoked by mRNA-1283.815 or mRNA-1283.116 (both monovalent), were higher than those elicited by bivalent vaccines (original and BA.4/BA.5), mRNA-1283.222 and mRNA-1273.222. As the neutralising antibody titres against XBB.1.5 or XBB.1.16 were comparable for both XBB-containing mRNA-1283 vaccines, it can be assumed, that these variants (XBB) are antigenically alike. One limitation of this study was that the PBS control group showed detectable binding antibody titre indicating that the mice were not SARS-CoV-2 naive. Thus, these study results are not very meaningful in regard to immunogenicity of the vaccines.

Overall, mRNA-1283 variant vaccines show strong humoral and cellular dose-dependent increased immunogenicity in mice when vaccinated intramuscular in a 2-dose regime. Immunogenicity data also indicates a Th1-skwed T-cell response. In addition, protection of the upper and lower respiratory system from SARS-CoV-2 virus infection was shown in mRNA-1283 vaccinated mice. These results suggest that an antibody-dependent enhancement of the immune response is not expected. In total, the submitted pharmacodynamic studies are sufficient. In most cases, mRNA-1283 elicited similar immune response and protection from viral challenge compared to mRNA-1273 in primary, booster, and challenge studies in mice. However, it could not be confirmed in the mice studies that lower mRNA-1283 doses are sufficient to induce strong neutralising antibody titre and T-cell responses, which would have been comparable to higher dose mRNA-1273 immunogenicity. Thus, mice as animal model could show the general immunogenicity of mRNA-1283 but are not well suited to demonstrate the proposed higher immunogenicity of mRNA-1283 over mRNA-1273.

Secondary pharmacology, safety pharmacology and pharmacodynamic drug interactions were not investigated for mRNA-1283, which is acceptable according to applicable guidelines.

Pharmacokinetics

No pharmacokinetic (PK) studies have been conducted with mRNA-1283. The submitted PK data package consists of several biodistribution and metabolism studies, which were already submitted during prior regulatory interactions with EMA for the SARS-CoV-2 vaccine Spikevax (mRNA-1273) and/or the RSV vaccine mRESVIA (mRNA-1345). Both authorised vaccines as well as mRNA-1283 are based on the same SM-102 LNP/mRNA platform. The PK studies were conducted with different test products (mRNA-1647, NPI-Luc mRNA, mRNA-1273 or SM-102 NTFIX mRNA), all based on the same SM-102 LNP/mRNA platform as also used in mRNA-1283 and the authorised vaccines Spikevax and mRESVIA.

There were no adhesion studies, PK drug interaction studies and other PK studies conducted with mRNA-1283, which is in line with regulatory guidelines and thus acceptable.

Collectively, nonclinical PK data provide insight into the biodistribution, metabolism and excretion characteristics of SM-102-based mRNA platform products. Overall, pharmacokinetics aspect of investigations submitted for mRNA-1283 candidate vaccine is adequate.

Toxicity

The applicant conducted a complete toxicity study program with mRNA-1283 including GLP-compliant repeat-dose toxicity study with bivalent mRNA-1283.222, a non-GLP-compliant toxicity study with mRNA-1283 (Wuhan) and a GLP-compliant DART study with mRNA-1283 (Wuhan). In addition, GLP-compliant repeat-dose toxicity and genotoxicity data from the applicant's SM-102-based LNP/mRNA vaccine platform was submitted, using similar mRNA-based vaccines formulated in same LNPs encoding for different antigens (ZIKV vaccines: mRNA-1706 and mRNA-1893, hMPV and PIV3 vaccine: mRNA-1653, and CMV vaccines: mRNA-1647 and mRNA-1443). These platform data were already submitted and assessed for the initial Spikevax and mRESVIA marketing authorisations.

The SD rat was selected as the animal model for all conducted in vivo toxicity studies, which is a relevant species to assess the toxicity and immunogenicity of mRNA vaccines, as evidenced by an immunogenic response. In all repeat-dose toxicity, the intramuscular route of administration was used because this is the intended route of administration in humans. Overall, the observed findings are consistent across the toxicity studies using different mRNA vaccines. Thus, the applicant concluded that the toxicities associated with mRNA vaccines formulated in SM-102 LNPs are driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. The applicant's assumption is supported. In total, no toxicity concerns were observed for mRNA-1283 in SD rats.

The conducted genotoxicity studies were already submitted for the initial marketing authorisation of Spikevax and mRESVIA. Overall, the applicant considers the genotoxic risk to humans to be low for SM-102-containing mRNA vaccines due to minimal systemic exposure following intramuscular administration, limited duration of exposure, negative in vitro results, and equivocal in vivo results. This conclusion is accepted.

In the conducted DART study, mRNA-1283 had no effect on oestrous cycles, mating, fertility or pregnancy indices in vaccinated dams, and signs of teratogenicity in foetus of vaccinated dams were observed. Anti-NTD and anti-RBD IgG antibodies were detected in serum samples of the dams after vaccination and remained detectable through end of study. Anti-NTD and anti-RBD IgG antibodies were also detected in foetal serum samples and maternal F0 generation milk samples, demonstrating

effective placental and lactation transfer of anti-COVID-19 antibodies to offspring when females are immunized prior to mating and during gestation.

Regarding the potential environmental risk of this mRNA vaccine, the active substance mRNA-1283 is a natural substance (mRNA), the use of which will not alter the concentration or distribution of the substance in the environment. In addition, the LNP composition includes two synthetic and two natural lipids. Therefore, mRNA-1283 is not expected to pose a risk to the environment.

Local tolerance was analysed in the repeat-dose toxicity studies. Toxicokinetic or other toxicity studies were not submitted, which is in line with regulatory guidelines on the non-clinical development of vaccine candidates.

Overall, intramuscular injections of mRNA-1283 were well tolerated in SD rats. No adverse toxicity and genotoxicity were observed in the animals treated with mRNA-1283 or similar mRNA vaccines. Furthermore, the toxicity study program was sufficient and compliant with WHO guidelines (WHO TRS No. 927, 2005, Annex 1; and WHO TRS No. 1024, 2020, Annex 2). The conducted toxicity study is considered adequate.

2.4.7. Conclusion on the non-clinical aspects

The nonclinical testing of mRNA-1283 (mNEXSPIKE) is overall adequate. There is no issue raised leading to objection to the authorisation of mRNA-1283 from the nonclinical perspective.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1. Clinical Studies

Study ID	Enrolment status	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
mRNA-1283-P301 Part 1 - EUDRA CT number 2023-000884-30	Ongoing	Phase 3 randomised, observer-blind, active-controlled study to investigate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283 compared to mRNA-1273.	mRNA-1283.222 10 µg: n=5706 mRNA-1273.222 50 µg: n=5711	Previously vaccinated, medically stable individuals 12 years and older.
mRNA-1283-P301	Ongoing	Phase 3 randomised, observer-blind, active-	mRNA-1283.815 10 µg: n=343	Japanese participants

Study ID	Enrolment status	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
(country-specific amendment Japan)		controlled study to investigate the safety, immunogenicity, of a single dose of mRNA-1283 compared to mRNA-1273.	mRNA-1273.815 50 µg): n=346	12 years and older.
mRNA-1283-P201	Completed	Phase 2a observer-blind, dose-ranging, single-dose study which consisted of 2 parts: Part A was a randomised, observer-blinded study that evaluated the immunogenicity, reactogenicity, and safety of a single injection of mRNA-1283 or the active comparator mRNA-1273. Part B was an open-label study that evaluated the immunogenicity, reactogenicity, and safety of a single injection of mRNA-1283.529 with no comparator group.	**Part A:** mRNA-1283: 2.5 µg: n=57 5 µg: n=63 10 µg: n=56 mRNA-1283.211 5 µg: n=53 10 µg: n=54 mRNA-1273 50 µg n=57 **Part B:** mRNA-1283.529 5 µg: n=103 10 µg: n=97	Previously vaccinated, healthy adults 18 years of age and older.
mRNA-1283-P101	Completed	A Phase 1, randomised, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1283 and mRNA-1273.	Three dose levels (10, 30, and 100 µg) of mRNA-1283 (Arms 1 through 3) and 1 dose level (100 µg) of mRNA-1273 (Arm 5) were evaluated in a 2-dose regimen, with the doses administered 28 days apart. One dose level (100 µg) of mRNA-1283 was evaluated in a single dose regimen (Arm 4). Arm 1: mRNA-1283 10 µg: n=21 Arm 2: mRNA-1283 30 µg: n=22 Arm 3: mRNA-1283 100 µg: n=21 Arm 4:Placebo+ mRNA-1283 100 µg: n=18	Unvaccinated adults aged 18-55 years

Study ID	Enrolment status	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
			Arm 5:mRNA-1273 100 µg: n=22	

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetic studies have been conducted for mNEXSPIKE. This is in line with the guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) and acceptable, since no new delivery system is employed.

2.5.2.1. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/05 Rev. 1). As immunogenicity data of this vaccine are used to support the authorisation of this vaccine, immunogenicity data are included under the clinical efficacy section.

In this section the mechanism of action and the respective assays applied to determine the immunogenicity data are discussed.

Mechanism of action

mRNA-1283 is expected to exert its protective effect by eliciting antibodies and cell-mediated immunity against the SARS-CoV-2 Spike protein NTD and RBD. These two domains are known to harbour important epitopes for neutralising antibodies, which contributes to protection against COVID-19.

Primary and Secondary pharmacology

The bioanalytical methods used to support the clinical development of mNEXSPIKE are described below.

RT-PCR

The commercially available Abbott RealTime SARS-CoV-2 PCR assay was used for qualitative detection of SARS-CoV-2 nucleic acid in nasopharyngeal swabs or saliva. Samples are reported as positive or negative for SARS-CoV-2 RNA. The method was validated at PPD GCL, USA where samples for Studies P101 and P201 have been analysed. Sample analysis for Study P301 was performed at Eurofins ECL, Lancaster, USA, using the qualitative RT-PCR SARS-CoV-2 Cobas 6800 kit supplied by Roche. Method performance was verified at Eurofins ECL.

Pseudotyped virus neutralisation assays (PsVNA)

The applicant established pseudotyped virus neutralisation assays for quantitation of neutralising antibodies against SARS-CoV-2 variants D614G, Beta B.1.351, Omicron B.1.1.529/BA.1, Omicron BA.4/BA.5, and Omicron XBB.1.5. in Phase I-III clinical studies for mRNA-1283. The methods have been validated at the respective testing sites, i.e. Duke University Medical Center Durham, NC 27710, USA for Studies P101 and P201 (D614G, Beta B.1.351, Omicron B.1.1.529/BA.1 variants) or PPD

Laboratories, 2244 Dabney Road, Richmond, Virginia 23230, USA for Study 301 (D614G, Omicron BA.4/BA.5, and Omicron XBB.1.5 variants), respectively.

CMI

Cell-mediated immunity was investigated as an exploratory objective in the Phase 1/2 studies P101 and P201.

2.5.3. Discussion on clinical pharmacology

No human pharmacokinetic studies have been performed. This can be agreed upon as pharmacokinetic studies are not usually required for vaccines as per the guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

The applicant utilised a RT-PCR assay to determine the viral presence and several different assays to evaluate humoral and cellular immunogenicity. Immunogenicity comparisons between mRNA-1283 and mRNA-1273 were performed in Phase 1, 2 and 3 studies to support efficacy data generated in the Phase 3 study. There is no established correlate of protection but the induction of neutralising antibodies against SARS-CoV-2 is generally considered a relevant surrogate for vaccine efficacy.

For the RT-PCR method, the presented validation/verification data together with the manufacturer´s data on analytical specificity show that the Abbott RealTime SARS-CoV-2 PCR assay and the Roche SARS-CoV-2 Cobas 6800 RT-PCR kit are suitable for the intended purpose. The same method has previously used for the same purpose in clinical studies for Spikevax.

For the Pseudotyped virus neutralisation assays (PsVNA), the method validations performed at PPD Laboratories are satisfactory and demonstrate that the respective PsVNAs are suitable for the intended purpose (i.e. support of primary study endpoints of the pivotal study mRNA-1283-P301). Large parts of the validation documentation had already been assessed for Spikevax in support of extensions of indications and introduction of variant-adapted vaccines based on immunobridging.

2.5.4. Conclusions on clinical pharmacology

Overall, the analytical methods used to support primary study endpoints in the pivotal study mRNA-1283-P301 (i.e. PsVNA assays and SARS-CoV-2 specific RT-PCR) have been adequately validated/verified and are suitable for the intended purpose.

2.5.5. Clinical efficacy

2.5.5.1. Dose response studies

Two dose-ranging studies, P101 and P201, were performed for mRNA-1283 vaccines. They compared the immunogenicity and safety of mRNA-1283 with that of the approved mRNA-1273 vaccine. In these studies, 10 µg mRNA-1283 (the dose proposed for MA) elicited immune responses that were comparable to mRNA-1273 50 µg or 100 µg. Lower doses (2.5 and 5 µg) of mRNA-1283 were generally associated with numerically lower titres compared to the 10 µg dose but were still comparable to results obtained with mRNA-1273. Overall, the tested 30 and 100 µg doses of mRNA-1283 did not yield an increase of neutralising antibodies compared to the 10 µg dose.

In Study mRNA-1283-P201, a clear dose-response relationship was observed for mRNA-1283, with GMT and GMFR increasing with dose for SARS-CoV-2 D614G, Beta, and Omicron BA.1. The highest

antibody responses were detected in the mRNA-1283 10 µg group, supporting a dose-dependent effect. In contrast, mRNA-1283.211 exhibited a reverse dose-response trend across all investigated variants, with lower GMT and GMFR at the higher dose of 10 µg compared to 5 µg. The Applicant attributes this finding to the smaller sample sizes, though further scrutiny is warranted to rule out systematic bias. No meaningful dose-response relationship was identified for mRNA-1283.529, as GMT and GMFR against D614G and Omicron BA.1 showed no detectable difference between the 5 µg and 10 µg groups.

In Study mRNA-1283-P101, no consistent dose-response relationship was observed. GMFR in neutralising and binding antibodies remained comparable across all tested dose levels at multiple time points post-second dose. Notably, a paradoxical trend was observed for the 30 µg dose, where nAb and bAb responses were lower than at 10 µg, contradicting the expected dose-response effect. This pattern raises concerns regarding potential confounding factors, such as participant variability or assay inconsistencies, which may have influenced the immunogenicity outcomes.

Upon request the applicant sufficiently justified the choice of the 10 µg dose mRNA-1283.

2.5.5.2. Main study

Study-mRNA-1283-P301: Phase 3 randomised, observer-blind, active-controlled study to investigate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283 compared to mRNA-1273

Methods

- **Study Participants**

Key inclusion criteria

- medically stable individuals, aged 12 and above who had previously received a primary series of an authorized/approved COVID-19 vaccine.
- to have received at least 1 booster dose, but no more than 5 vaccine doses, for participants ≥18 years of age.

Key exclusion criteria

- individuals having received a COVID-19 vaccine within 90 days prior to enrolment or had positive SARS-CoV-2 testing within 90 days prior to enrolment
- Has history of myocarditis, pericarditis, or myopericarditis that has not fully resolved within 3 months prior to Screening.
- Has received a total of 6 doses or more of COVID-19 vaccine.
- participants with chronic diseases requiring ongoing medical intervention or within the last 2 months prior to enrolment
- Participants with immunocompromising conditions or medications, or malignancy within 5 years (excluding nonmelanoma skin cancer)

- **Treatments**

Study participants were provided either one injection (IM) of 10µg of mRNA-1283.222 (original SARS-CoV-2: Omicron BA.4-BA5) or IM of 50µg of mRNA-1273.222 (original SARS-CoV-2: Omicron BA.4-BA5).

- **Objectives and estimands**

Primary objectives

The primary rVE objective in Study P301 was to demonstrate the noninferiority of the vaccine efficacy of mRNA-1283 compared to mRNA-1273 in preventing the first event of COVID-19 starting 14 days after study vaccination (the null hypothesis H_0: rVE ≤-10%).

The primary immunogenicity objective was to demonstrate a noninferior antibody response of mRNA-1283 compared to mRNA-1273 against Omicron BA.4-5 and D614G on Day 29 based on the GMR and SRR difference (lower bound of the GMR 95% CI needed to be >0.667 and lower bound of the SRR difference 95% CI needed to be above -10%).

The third primary objective of the study was to evaluate the safety and reactogenicity of 10 µg mRNA-1283.222 (refer to the clinical safety section).

Secondary objectives

The secondary objectives were:

- the characterization of the neutralising antibody response against Omicron BA.4/5 and the ancestral SARS-CoV-2 D614G for both products at all timepoints (Days 91, 181, 365).
- the assessment of SARS-CoV-2 infection regardless of symptoms

Exploratory objectives

The exploratory objectives comprised the characterization of the antibody response against emerging variants, the characterization of SARS-CoV-2 isolates and the evaluation of immune response markers.

Estimands for the primary objective

Table 2. Primary Estimand for rVE Primary Objective

Population	Medically stable individuals, ages 12 and above. The target population excludes those who received a COVID-19 vaccine within 90 days prior to enrolment or had positive SARS-CoV-2 testing within 90 days prior to enrolment. Participants with chronic diseases requiring ongoing medical intervention or within the last 2 months prior to enrolment were excluded. Participants with immunocompromising conditions or medications, or malignancy within 5 years (excluding nonmelanoma skin cancer) were excluded. The primary analysis population consists of the PPSE defined as all participants in the full analysis set who received the planned dose of study vaccine and had no major protocol deviations that impacted efficacy data.
Treatment condition<s>	Test: mRNA-1283 (variants formulation) Reference: mRNA-1273 (variants formulation)
Endpoint (variable)	The time to first occurrence of COVID-19, occurring ≥ 14 days after the study vaccine.
Population-level summary	rVE defined as 1 - HR of mRNA-1283/mRNA-1273
Intercurrent events and strategy to handle them	
Death unrelated to COVID-19	Hypothetical strategy

	Rationale: Death unrelated to COVID-19 is considered occurring completely at random. Therefore, observations were censored at time of death.
Early COVID-19	Hypothetical strategy Rationale: It is based on the understanding that the clinical interest is the rVE of time to first COVID-19 event occurring ≥14 days post study vaccination (i.e. after having adequate immune response). In addition, as early COVID-19 may change the risk of events in future, censoring follow-up from participants after early infection, may more closely represent the vaccine's efficacy induced by the biological effect from vaccine.
Off-study COVID-19 vaccine use	While-on-condition strategy Rationale: The receipt of an off-study vaccine is anticipated to confound the treatment effect of the study vaccine. As the estimand of interest focuses on the effect of the study vaccine, participants were censored at the time they received an off-study COVID-19 vaccine.

Table 3. Estimands for Primary Immunogenicity Objective

Population	Per-protocol immunogenicity subset (PPIS): consists of a randomly sampled immunogenicity subset of participants who received the planned dose of study vaccination, had baseline and day 29 neutralising antibody data, and had no major protocol deviations that impacted immunogenicity data.
Treatment condition<s>	Test: mRNA-1283 (variants formulation) Reference: mRNA-1273 (variants formulation)
Endpoint (variable)	Neutralising antibody level against SARS-CoV-2 BA.4/BA.5 at Day 29 visit Neutralising antibody level against original SARS-CoV-2 D614G at Day 29 visit Seroresponse for neutralising antibody against SARS-CoV-2 BA.4/BA.5 at Day 29 visit Seroresponse for neutralising antibody against original SARS-CoV-2 D614G at Day 29 visit (Seroresponse at the participant level is defined as an antibody value change from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ and <4 × LLOQ, or at least a 2-fold rise if baseline is ≥4 × LLOQ.)
Population-level summary	Geometric mean ratio (mRNA-1283.222 vs mRNA-1273.222) at Day 29 Seroresponse rate difference (mRNA-1283.222-mRNA-1273.222) at Day 29
Intercurrent events and strategy to handle them	
SARS-CoV-2 infection	Treatment strategy Rationale: Treatment policy was used to handle this intercurrent event as the clinical interest is to assess immune response in a real-world scenario where the population is exposed to SARS-CoV-2 virus.
Off-study COVID-19 vaccine use	While-on-condition

	Rationale: the receipt of an off-study vaccine is anticipated to confound the treatment effect of the study vaccine. As the estimand of interest focuses on the effect of the study vaccine, participant's immunogenicity data were not to be used after receiving off-study COVID-19 Vaccine.

rVE was measured using 1- HR (mRNA-1283/mRNA-1273 [variant formulation]) of COVID-19 from 14 days after injection. A hypothetical strategy was used for deaths unrelated to COVID-19 and early COVID-19 in participants in the PPSE. A while-on-condition strategy was used for participants taking an off-study COVID-19 vaccine during the study. For a tabular overview of the primary rVE estimand see above.

The PPSE in this study consisted of all participants in the full analysis set who received the planned dose of study vaccine and had no major protocol deviations that impact vaccine efficacy data. Participants were analysed according to their randomised study arm.

The rVE objective was based on the primary definition of COVID-19 (CDC definition), which required the presence of at least 1 symptom from a list of COVID-19 symptoms and a positive NP swab for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38° C/≥100.4° F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea.

A secondary "protocol-defined" COVID-19 case definition was pre-specified and required at least two systemic symptoms (fever (≥ 38° C/100.4° F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s)), OR ≥1 respiratory signs/symptoms (cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia) and a NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

COVID-19 symptom surveillance was conducted biweekly using electronic Diary prompts. If the participant had a qualifying symptom, the participant was requested to present for an unscheduled visit for clinical evaluation and collection of respiratory samples for SARS-CoV-2 PCR. SARS-CoV-2 PCR testing was also conducted in routine clinic visits based on qualifying symptoms. All PCR samples were sent to and analysed in a central, certified laboratory. Any rapid antigen testing information for SARS-CoV-2 infection (ie, testing at home or in an urgent care setting) was used for descriptive analyses; rapid antigen testing results did not support the primary rVE objective.

A hypothetical strategy was used for early COVID-19 because it takes approximately 2 weeks for the COVID-19 vaccine to become fully effective, which is why the relevant period for evaluating vaccine efficacy begins 14 days after vaccination. Early COVID-19 cases (those occurring before 14 days post-vaccination) were treated as a competing risk. Participants who developed early COVID-19 were censored at the time of case onset, as if the event had not occurred (hypothetical strategy) and were considered no longer at risk of the clinical endpoint after infection.

Unrelated death without confirmation of COVID-19 was censored at the time of death as if there was no event (hypothetical strategy), handled with independent censoring.

A while-on-condition strategy was used for participants taking an off-study COVID-19 vaccine during the study, as this event was likely confounded with treatment effect, and participants' data following these events are likely impacted. Therefore, observation time of interest was restricted to the period before the intercurrent event.

- **Outcomes/endpoints**

Primary outcomes/endpoints are defined in the estimand definitions.

- **Sample size**

The study sample size was driven by the sample size required for the primary rVE objective.

Primary rVE Objective

The primary rVE objective was to demonstrate a noninferior rVE of mRNA-1283 compared with mRNA-1273 in preventing the first event of COVID-19 starting 14 days after study vaccination with a noninferiority margin of 10%.

According to Protocol Amendment 3 and SAP 2.0, the initial assumption for the true rVE (mRNA-1283 vs mRNA-1273) was 3%. In addition, it was assumed that the COVID-19 incidence rate would be 1 per 100 person-months for the first 6 months after study vaccination and 1.25 per 100 person-months for Months 6 to 12 and that the drop-out rate would be 10%. Based on these assumptions, the total number of COVID-19 events needed for a sufficiently powered (80% power) rVE analysis was estimated to be 2087 events (~20,122 participants). However, if the true rVE was 0%, then it was estimated that 3500 COVID-19 events (~33,574 participants) would be needed for an rVE analysis with 80% power.

To ensure an rVE analysis with at least 80% power, Protocol Amendment 3 introduced an adaptive study design with a sample size re-estimation based on an early rVE interim analysis, where a Lan-DeMets O'Brien-Fleming alpha spending function was utilized to control the type I error (1-sided alpha of 0.025). At the time of Protocol Amendment 3 (Dec 2023), 11,454 participants had already been enrolled. According to the adaptive study design, the study's DSMB would review interim rVE information in a closed session and, based on prespecified conditional power rules, recommend to the Sponsor whether a sample size increase was needed. The sample size increase would be based on further enrolment in a second study part (P301 Part 2).

The conditional power was defined as the probability of rVE success at the end of the study (demonstration of noninferior rVE with a 10% margin) based on the observed rVE at the time of the DSMB review and the originally estimated total number of COVID-19 events needed (ie, 2087 events), assuming the same data trend (Mehta and Pocock 2011). The DSMB review would be triggered when at least 700 COVID-19 events had been accrued. The DSMB would then make a recommendation to the Sponsor based on the following prespecified rules:

1. If the observed rVE met success criteria for efficacy based on the O'Brien-Fleming boundary, the DSMB would inform the Sponsor regarding early success (rVE objective) due to overwhelming efficacy, which would trigger no enrolment for study Part 2. If the early success criterion was not met, then:
2. If the conditional power was ≥0.8, the DSMB would recommend a sample size increase by initiating Part 2 enrolment to accrue approximately 2087 COVID-19 events. Based on the COVID-19 incidence rate and drop-out rate assumptions, it was estimated that approximately 8622 participants should be enrolled in Part 2 for a total of approximately 20,122 participants (Part 1 and Part 2 combined). A pooled rVE analysis (Part 1 and Part 2) would be required for the primary rVE objective.
3. If the conditional power was ≥0.35 and <0.8, the DSMB would recommend a sample size increase by initiating Part 2 enrolment to accrue approximately 3500 COVID-19 events (Part 1 and Part 2 combined); Based on the COVID-19 incidence rate and drop-out rate assumptions, it was estimated that approximately 22,074 participants should be enrolled in Part 2 for a total of approximately 33,574 participants (Part 1 and Part 2 combined). A pooled rVE analysis (Part 1 and Part 2) would be required for the primary rVE objective.

4. If the conditional power was <0.35, the DSMB would inform the Sponsor that enrolment might not lead to a favourable outcome.
5. If the interim rVE crossed the O'Brien-Fleming futility boundary, the DSMB would recommend not enrolling Part 2.

For a history of changes of the assumptions for sample size computations see Statistical methods below.

Primary Immunogenicity Objective

The primary immunogenicity objectives were to

- To demonstrate a noninferior neutralising antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against Omicron BA.4/5 based on GMR and SRR difference at Day 29.
- To demonstrate a noninferior neutralising antibody response of mRNA-1283.222 10 µg compared to mRNA-1273.222 50 µg against the original SARS-CoV-2 D614G based on GMR and SRR difference at Day 29.

Noninferiority margin for GMR was 0.667 (1/1.5) and noninferiority margin for SRR difference was 10%.

A subset of study participants was used for the primary immunogenicity objective. The Per-Protocol Immunogenicity Subset for the primary immunogenicity analysis included participants regardless of Baseline SARS-CoV-2 status (negative or positive). With approximately 882 evaluable participants (441:441 for mRNA-1283.222 vs mRNA-1273.222) in the PPIS, there was approximately 90% power to demonstrate noninferior antibody responses of mRNA-1283.222 vs mRNA-1273.222 for each co-primary immunogenicity endpoint at 2-sided alpha of 0.05. The assumptions were: the true GMR against ancestral SARS-CoV-2 and BA.4/5 at Day 29 (mRNA-1283.222 vs mRNA-1273.222) was 1, the standard deviation of the natural log-transformed level was 1.8, noninferiority margin for GMR was 1.5 (or 1/1.5 = 0.667), the true SRR against the ancestral SARS-CoV-2 D614G and against the Omicron BA.4/5 variant was 70% (same assumption for mRNA-1283.222 and mRNA-1273.222), and the noninferiority margin for SRR difference was 10%. It was also expected that approximately 10% participants might be excluded from the PPIS (e.g., reasons such as missing immunogenicity samples), and hence an immunogenicity subset sample size of 980 (490:490) was needed.

- **Randomisation and Blinding (masking)**

Randomisation

All participants were randomised 1:1 to one of the 2 groups using an interactive response technology with block randomisation (block size of 6). Age was a stratification factor (12 to <18, 18 to <65, and ≥65) with the goal to enrol approximately 1000 adolescents (12 to <18 years) and approximately 30% of participants to be in the ≥ 65 age group.

Adult immunogenicity Sample

An age-stratified (18 to <65, and ≥65 years) random sampling method was used to select a sub-sample of adult trial participants to assess antibody response. The sampling process was blinded to the treatment assignment. Adult participants were randomly sampled into the immunogenicity subset within each stratum based on the proposed proportion for each age group (approximately 70% of ≥18 and <65 years and approximately 30% of ≥65 years).

To have an adequate sample from United Kingdom participants, approximately 220 participants enrolled from the United Kingdom were sampled into the immunogenicity subset.

Table 4. Sample size by adult age group

	Number of Participants Needed	Number of Participants Sampled (increase by 10%)
Age Strata		
≥18 and <65 years	~686	~763
≥65 years	~294	~327
Total	~980	~1090

Note: Approximately 980 participants were needed, to account for potential sampling loss for any reasons, sample size was adjusted by additional 10%.

Adolescent Immunogenicity Sample

For the adolescent patient population (12 to <18 years), all dosed participants who were enrolled by 31 Jul 2023 (n=210) were included in the immunogenicity subset for the primary immunogenicity analysis.

Blinding

Study P301 was observer-blind. Dose preparation, administration and accountability was performed by designated unblinded site personnel who did not participate in any of the clinical study evaluations. Neither the participant nor participant's parent(s)/legal guardian(s) nor the Investigator nor clinical staff responsible for study assessments/safety had access to the treatment assignment during the conduct of the study.

The laboratory personnel in charge of immunogenicity testing were blinded to the treatment assignment of the samples tested throughout the course of the study.

An independent unblinded statistical and programming team who is not involved in study design and conduct was to perform the planned interim analyses. A prespecified Sponsor team including biostatistician(s) and statistical programmer(s) were to be unblinded to treatment-group level information at the Part 1 (Day 29) interim analysis results. Additional functions (unblinded medical writing, clinical safety, pharmacovigilance and unblinded program manager; pre-specified CMC team members) had access to subject-level data. The details regarding roles and corresponding unblinding were to be included in the Study Data Blinding Plan (DBP). The DBP V1 was finalized on 27 Nov 2023 and DBP V2 was finalized on 23 February 2024.

Safety and efficacy information were to be reviewed in an unblinded fashion by the independent DSMB. As prespecified in the adaptive design, the DSMB reviewed rVE information in a closed session and provided a recommendation to the Sponsor based on prespecified conditional power scenarios. After the study's primary rVE, immunogenicity, and safety analysis, a dedicated study team remained blinded and was responsible for the continued study conduct through completion of follow-up for the study participants. The Investigators and study participants also remained blinded to group assignments.

Table 5. DSMB Meeting timeline and key purposes

DSMB Meeting Dates	Purpose	Additional information
May 23, 2023	DSMB Orientation Meeting	
July 27, 2023	DSMB safety data review (Open and closed session)	Information provided to DSMB: study background characteristics, solicited adverse reaction, unsolicited adverse events, and summary of RT-PCR results.
November 1, 2023	Introduce adaptive design and solicit DSMB's feedback on the study design	Introduce adaptive design- updated data package was provided to DSMB prior to the meeting (data extraction date: 15 Sep 2023), information provided included: study background characteristics, solicited adverse reaction, unsolicited adverse events, and summary of RT-PCR results.
March 11, 2024	To prepare DSMB for the upcoming rVE data review and go through potential outcomes	Preparation for the upcoming DSMB rVE review
March 25, 2024	DSMB rVE data review in a closed session	

Except in the case of medical necessity, a participant's treatment was not unblinded without the approval of the Sponsor. If a participant became seriously ill or pregnant during the study, the blind could be broken only if knowledge of the treatment assignment may have affected that participant's clinical management. The Investigator (or designee) had access to unblind participants within IRT. All unblinding was tracked via an audit trail in IRT and documented in the final study report.

- **Statistical methods**

The analysis sets are described below.

Table 6. Populations Used for Analysis

Set	Description
FAS	The FAS consisted of all randomised participants who received study vaccine. Participants were analysed according to their randomised study arm.
PPSE	The PPSE consisted of all participants in the FAS who received the planned dose of study vaccine and had no major protocol deviations that impact vaccine efficacy data. Participants were analysed according to their randomised study arm.
PPIS	The PPIS consisted of participants in the immunogenicity subset who received the planned dose of study vaccination, have pre-booster and Day 29 (occurring between 21 and 42 days after vaccination) neutralising antibody data, and had no major protocol deviations that impact key or critical data. Participants were analysed according to their randomised study arm. PPIS was the primary analysis set for analyses of immunogenicity unless otherwise specified. A randomly selected group from the immunogenicity subset was also used to evaluate neutralising antibody responses against XBB.1.5.
Randomisation Set	The Randomisation Set consisted of all participants who were randomised, regardless of the participant's treatment status in the study. Participants were analysed according to the vaccine group to which they were randomised.
Safety Set	The Safety Set consisted of all randomised participants who received study vaccine. The Safety Set was used for all analyses of safety except for the

Set	Description
	solicited ARs. Participants were included in the study arm that they actually received.
Solicited Safety Set	The Solicited Safety Set consisted of all randomised participants who received study vaccine and contributed any solicited AR data. The Solicited Safety Set was used for the analyses of solicited ARs. Participants were included in the study arm that they actually received.

Abbreviations: AR = adverse reaction; FAS = full analysis set; PPIS = Per-Protocol Immunogenicity Subset; PPSE = Per-protocol Set for Efficacy.

Analysis of rVE

The primary rVE objective was to demonstrate a noninferior VE of mRNA-1283 compared with mRNA-1273 in preventing the first event of COVID-19 starting 14 days after study vaccination with a noninferiority margin of 10%. The rVE statistical criterion for success was that the lower bound of the rVE alpha-adjusted CI needed to be above -10% (10% noninferiority margin).

A stratified Cox proportional hazard model was used to assess the hazard ratio between mRNA-1283 and mRNA-1273. Study vaccination group was included as a fixed effect, stratified by stratification factor age group at randomisation: (≥12 to <18 years, ≥18 to <65 years, or ≥65 years). According to the protocol, SARS-CoV-2 status at pre-injection, number of prior injections, and type of prior vaccine could be included in the Cox model, if applicable, which was then considered to be performed as a sensitivity analysis in the SAP. Efron's method was used to handle ties.

Immunogenicity Analyses

The primary immunogenicity objective was to demonstrate a noninferior antibody response of mRNA-1283 compared to mRNA-1273 against Omicron BA.4/5 and D614G on Day 29 based on the GMR and SRR difference (lower bound of the GMR 95% CI needed to be >0.667 and lower bound of the SRR difference 95% CI needed to be above -10%). An ANCOVA model was used with the dependent variable of the serum Ab level at Day 29 and a group variable (mRNA-1283.222 vs mRNA-1273.222) as the fixed effect, adjusted by SARS-CoV-2 status at Baseline, age group, number of prior boosters, and type of prior vaccination. The GMR and 95% CI of Omicron BA.4/5 and D614G were estimated from ANCOVA model. For SRR difference, 95% CI was based on Miettinen-Nurminen score method.

Planned subgroup analyses

Subgroup analyses were performed in select subgroups, including:

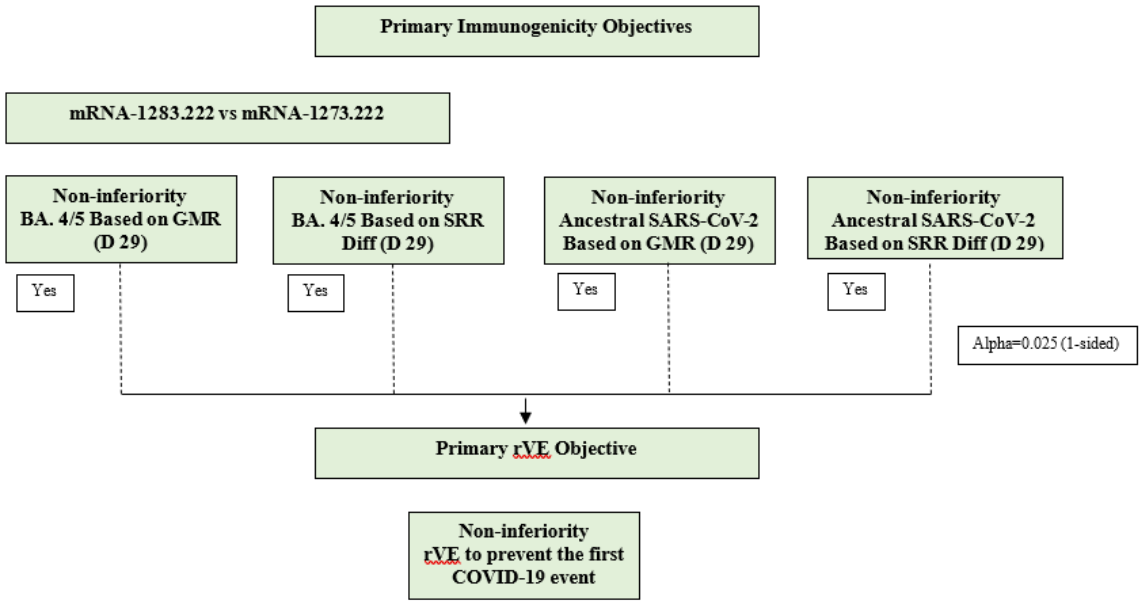
- Age (12 to <18 Years, 18 to <65 Years, ≥65 Years).
- Baseline SARS-CoV-2 Status (Positive, Negative).
- Number of prior booster doses (0, 1, 2, ≥3).

Adjustment for multiplicity and interim analyses

The primary rVE endpoint and 4 co-primary immunogenicity endpoints were tested using a prespecified sequential testing strategy (Figure 1). The hypothesis for the rVE endpoint was tested only after meeting of noninferiority criteria for the 4 co-primary immunogenicity endpoints. For the primary rVE endpoint, O'Brien-Fleming alpha spending function was used for the rVE interim analysis to preserve the overall 0.025 (1-sided) type I error rate (Study P301 CSR Appendix 16.1.9.1). The interim analysis was planned to be conducted when at least 700 COVID-19 events had accrued.

At the time of analysis, Alpha-adjusted 2-sided (99.4%) confidence level was calculated using Lan-DeMets O'Brien-Fleming spending function (nominal one-sided alpha = 0.0028). It was based on 1177 CDC-defined COVID-19 events, representing 56.4% information fraction of target total number of events (N=2087, target rVE of 3% [mRNA-1283.222 vs mRNA-1273.222]).

Figure 1. mRNA-1283-P301 Testing Strategy



Abbreviations: BA.4/5 = BA.4/BA.5; COVID-19 = coronavirus disease 2019; D = day; Diff = difference; GMR = geometric mean ratio; mRNA = messenger ribonucleic acid; rVE = relative vaccine efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

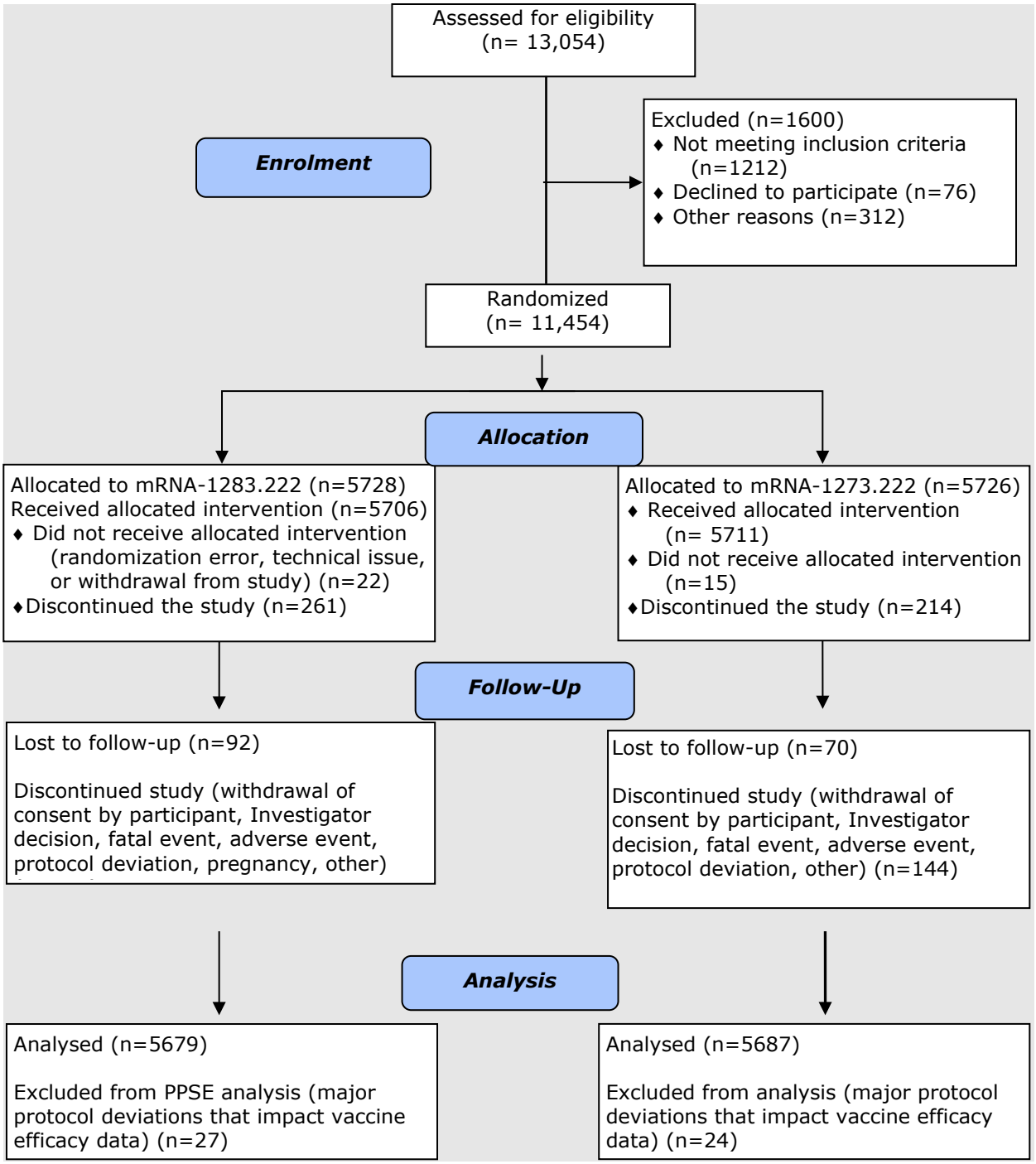
Results

- **Participant flow**

A total of 11,454 participants were randomised and 11,417 participants were dosed, of which 5706 participants were in the mRNA-1283.222 group and 5711 participants were in the mRNA-1273.222 group. Of the 37 participants who were not dosed, the main reasons included randomisation error, technical issue, or withdrawal from study.

Of the 11,417 participants who were dosed, 475 participants (4.16% of those dosed) discontinued from the study. Reasons for discontinuation from the study were most often due to withdrawal of consent (263 [2.30%] participants), followed by lost to follow-up (162 [1.42%] participants). Fifteen (0.13%) participants discontinued due to death (5 participants in the mRNA-1283.222 group and 10 participants in the mRNA-1273.222 group. Five (0.04%) participants discontinued due to an AE (3 participants in the mRNA-1283.222 group and 2 participants in the mRNA-1273.222 group).

Figure 2. Participant Flow



Abbreviations: CSR = clinical study report; mRNA = messenger ribonucleic acid; PPSE = Per-protocol Set for Efficacy.
Source: Study P301 CSR, Table 14.1.1.3.

- **Recruitment**

Recruitment occurred from 28 Mar 2023 to 23 Aug 2023, during which a total of 11,454 participants were randomised and 11,417 participants were dosed, of which 5706 participants were in the mRNA 1283.222 group and 5711 participants were in the mRNA-1273.222 group.

The study was conducted at 196 sites in the US (150 sites), United Kingdom (38 sites), and Canada (8 sites). Participants 12 to <18 years of age had no booster dose requirement prior to study entry.

- **Conduct of the study**

Protocol Amendments

The protocol has been subject to 4 amendments: amendment 1 (02 May 2023), amendment 2 (08 August 2023), Japan Country Amendment (12 September 2023) and amendment 3 (20 December 2023).

- The assumptions for sample size computations for rVE were modified through the trial without any justification:
- The target rVE was changed from 0% to 3% (with *Protocol Amendment 3*) to maintain a reasonable power of 80% when changing the NI-margin (see below).
- The incidence of COVID-19 was changed from 3 per 100 person-months (up to *Protocol Amendment 2*) to 1 per 100 person-months in the first 6 months after vaccination and 1.25 per 100 person-months thereafter (with *Protocol Amendment 3*).

The assumed dropout rate was changed from 10% (up to *Protocol Amendment 1*) in 6 months to 15% in 6 months (*Protocol Amendment 2*) to ensure sufficient power under conservative assumptions, and finally to 10% in 12 months (with *Protocol Amendment 3*) based on observed monitoring data from the study.

With *Protocol Amendment 3* the non-inferiority margin for rVE was changed from -15% to -10%. To allow for the enrolment of more patients Study Part 2 was added which planned to enrol up to approximately 22,074 participants to increase the total sample size based on an adaptive, 2-stage group sequential design. The targeted number of events was increased from 1,615 COVID-19 cases to 2,078 for the initial primary analysis and up to 3,500 events after sample-size re-assessment. And interim analysis for Part 1 was added which was to be performed when at least 700 COVID-19 events had been confirmed.

The rationale for the addition of Part 2 was to increase the total sample size to enable a pooled relative vaccine efficacy analysis with both study parts (Part 1 and Part 2). Up to approximately 33,574 participants in Part 1 and Part 2 combined were to be enrolled to support the primary relative vaccine efficacy objective. The 2023/2024 COVID-19 variant vaccine sequence (Omicron XBB.1.5-containing study vaccines [mRNA-1283.815 or mRNA-1273.815]) was to be used in Part 2. The decision rules for the DSMB introduced with the Protocol Amendment are discussed above.

The estimand for rVE was changed for the treatment of participants who take off-study COVID-19 vaccines from a treatment policy strategy, where events were counted regardless of off-study vaccination, to a "while on treatment" strategy, where events were censored after off-study vaccination.

Changes in the SAP

The following changes were made in the conduct of the study for the planned analysis in the SAP Version 2.0 (13 February 2024).

- COVID-19 is a primary efficacy endpoint for this study. Confirmed COVID-19 events and suspected COVID-19 events were not considered as AEs and, thus, were not included in the analysis of AEs.

- Unsolicited AE summaries were to include solicited ARs only if any solicited AR met seriousness criteria.

- These changes were reflected in all safety tables and listings.

Changes after unblinding

In addition to above changes, the following summarizes additional modifications and post-hoc analyses conducted after unblinding.

For the primary immunogenicity endpoints, an analysis that excluded participants who had SARS-CoV-2 infection up to Day 29 after study vaccination was not performed because there were only 5 participants (3 participants in 1283.222 and 2 participants in 1273.222) in the PPIS who had an infection within 28 days postvaccination, and excluding these 5 participants is not expected to impact the immunogenicity results.

For the primary safety analysis, unsolicited AEs were censored after off-study COVID-19 vaccination. An analysis was performed after unblinding to summarize all unsolicited AEs, including SAEs, AEs of interest, and programmed SMQ AEs up to the data cutoff date (23 Feb 2024) in all participants, including events reported after off-study COVID-19 vaccine use, and in those participants who received off-study COVID-19 vaccine during the study follow-up period.

- **Baseline data**

Study P301 included 5706 mRNA 1283.222 and 5711 mRNA-1273.222 recipients. Demographic and Baseline characteristics were balanced (Table 7). In the mRNA-1283 group, 8.7% (497/5706) of participants were adolescents (≥12 and <18 years of age), 62.7% (3575/5706) were adults (≥18 and <65 years of age), and 28.6% (1634/5706) were participants ≥65 years of age.

Table 7. Study P301: Baseline Demographics (Safety Set)

	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Age (Years)			
N	5706	5711	11417
Mean (SD)	51.1 (18.58)	51.2 (18.32)	51.2 (18.45)
Median	56.0	55.0	56.0
Q1, Q3	38.0, 66.0	39.0, 66.0	38.0, 66.0
Min, Max	12, 96	12, 90	12, 96
Age Group, n (%)			
≥12 to <18 Years	497 (8.7)	495 (8.7)	992 (8.7)
≥18 Years	5209 (91.3)	5216 (91.3)	10425 (91.3)
≥18 to <65 Years	3575 (62.7)	3576 (62.6)	7151 (62.6)
≥65 Years	1634 (28.6)	1640 (28.7)	3274 (28.7)
≥75 Years	322 (5.6)	269 (4.7)	591 (5.2)
Sex, n (%)			
Male	2586 (45.3)	2631 (46.1)	5217 (45.7)
Female	3120 (54.7)	3080 (53.9)	6200 (54.3)
Race, n (%)			
White	4670 (81.8)	4711 (82.5)	9381 (82.2)
Black or African American	640 (11.2)	635 (11.1)	1275 (11.2)
Asian	225 (3.9)	183 (3.2)	408 (3.6)
American Indian or Alaska Native	20 (0.4)	26 (0.5)	46 (0.4)

	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Native Hawaiian or Other Pacific Islander	9 (0.2)	6 (0.1)	15 (0.1)
Multiple	81 (1.4)	94 (1.6)	175 (1.5)
Other	20 (0.4)	20 (0.4)	40 (0.4)
Not Reported	36 (0.6)	26 (0.5)	62 (0.5)
Unknown	5 (0.09)	10 (0.2)	15 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	769 (13.5)	741 (13.0)	1510 (13.2)
Not Hispanic or Latino	4860 (85.2)	4864 (85.2)	9724 (85.2)
Not Reported	59 (1.0)	87 (1.5)	146 (1.3)
Unknown	18 (0.3)	19 (0.3)	37 (0.3)
Body Mass Index (kg/m^2)			
N	5644	5645	11289
Mean (SD)	29.45 (7.167)	29.50 (7.331)	29.47 (7.249)
Median	28.30	28.30	28.30
Q1, Q3	24.40, 33.30	24.40, 33.30	24.40, 33.30
Min, Max	14.4, 81.9	14.6, 76.7	14.4, 81.9
Body Mass Index Group, n (%)			
<30 kg/m^2	3338 (58.5)	3372 (59.0)	6710 (58.8)
≥30 kg/m^2	2306 (40.4)	2273 (39.8)	4579 (40.1)
≥40 kg/m^2	451 (7.9)	489 (8.6)	940 (8.2)
Missing	62 (1.1)	66 (1.2)	128 (1.1)
Geographic Region, n (%)			
North America	4424 (77.5)	4424 (77.5)	8848 (77.5)
Europe	1282 (22.5)	1287 (22.5)	2569 (22.5)
Country, n (%)			
United States	4323 (75.8)	4312 (75.5)	8635 (75.6)
Canada	101 (1.8)	112 (2.0)	213 (1.9)
United Kingdom	1282 (22.5)	1287 (22.5)	2569 (22.5)

Abbreviations: Max = maximum; Min = minimum; n = number; Q = quartile; SD = standard deviation.
Note: Participants are included in the study intervention group that they actually received.
Note: Percentages are based on the number of participants in Safety Set.
Source: Study P301 CSR Table 14.1.3.1

All participants except for 1 in the mRNA 1283 group had previously received at least 1 dose of COVID-19 vaccine prior to the study with a median time of 9.8 months since the last dose and study injection.

- **Numbers analysed**

The participant flow, including participants randomised, vaccinated, discontinued and evaluable, is presented above.

Table 8. Number of Participants in Each Analysis Set

	Number (%) of Participants		
	mRNA-1283.222 10 µg	mRNA-1273.222 50 µg	Total
Randomisation Set	5728	5726	11454
Full Analysis Set (FAS), n (%)[a]	5706 (99.6)	5711 (99.7)	11417 (99.7)

	Number (%) of Participants		
	mRNA-1283.222 10 µg	mRNA-1273.222 50 µg	Total
Per-Protocol Set for Efficacy (PPSE), n (%)[a]	5679 (99.1)	5687 (99.3)	11366 (99.2)
Immunogenicity Subset, n (%) [a]	678 (11.8)	622 (10.9)	1300 (11.3)
Per-Protocol Immunogenicity Subset (PPIS) [b]	621 (91.6)	568 (91.3)	1189 (91.5)

Abbreviations: CSR = clinical study report; FAS = Full Analysis Set; PPIS = Per-Protocol Immunogenicity Subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
The Randomisation Set consists of all participants who are randomised, regardless of the participant's treatment status in the study.
The FAS consists of all randomised participants who receive the study vaccine.
Immunogenicity Subset comprises: 1) a stratified random sample of adult participants (age group: >18 and <65 years, and >65 years) in the FAS regardless of Baseline SARS-CoV-2 infection status (Baseline negative or positive status available), and with non-missing age strata information; 2) First 210 dosed adolescents.
The PPSE included all participants in the FAS who received the planned dose of study vaccine and had no major protocol deviations that impacted vaccine efficacy data.
PPIS consists of participants in Immunogenicity Subset who have Baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralising antibody data, received treatment as planned and have no major protocol deviations that impact vaccine immunogenicity data.
a. Numbers are based on planned treatment group and percentages are based on the number of participants in Randomisation Set.
b. Percentages are based on the number of participants in Immunogenicity Subset.
Source: Study P301 CSR, Table 14.1.2.1

- **Outcomes and estimation**

Primary analysis

Primary rVE Analysis

A total of 1,177 COVID-19 events were included in this analysis. There were 560 (9.9%) COVID-19 events in the mRNA-1283.222 group and 617 (10.8%) COVID-19 events in the mRNA-1273.222 group. The rVE and 99.4% CI (alpha-adjusted CI) was 9.31% (-6.58, 22.83), which met the prespecified noninferiority statistical success criterion given that the lower bound of rVE CI was -6.58 which was >-10%; the rVE point estimate was positive.

Table 9. Study P301 Primary Analysis of Relative Vaccine Efficacy — COVID-19 Events Through 31 Jan 2024 (PPSE)

	mRNA-1283.222 10 µg (N=5679)	mRNA-1273.222 50 µg (N=5687)
Number of participants with COVID-19, n (%)	560 (9.9)	617 (10.8)
Person-months[a]	40778.0	40781.7
Incidence rate per 100 person-months (95% CI)[b]	1.373 (1.262, 1.492)	1.513 (1.396, 1.637)
rVE based on Hazard Ratio, % (99.4% CI)[c,d]	9.31 (-6.58, 22.83)	
p-value[e]	0.0005	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; CSR = clinical study report; mRNA = messenger ribonucleic acid; PPSE = Per-protocol Set for Efficacy; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy.
CDC COVID-19 Definition: the presence of at least 1 CDC listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); and positive RT-PCR test on a respiratory sample.
Date of COVID-19 is the later date of symptom and positive RT-PCR test, and the 2 dates of symptom and positive RT-PCR test should be within 14 days of each other.
a. Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date or efficacy data cutoff date, whichever is the earliest. 1 month = 30.4375 days.

[b.] Incidence rate is defined as the number of participants with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months, incidence rate is presented as number of events per 100 person-months.
[c.] rVE = 1-hazard ratio (mRNA-1283.222 vs mRNA-1273.222), hazard ratio and CI are estimated using a stratified Cox proportional hazard model (stratified by age group per randomisation) with Efron's method of tie handling and with the treatment group as a fixed effect.
[d.] Alpha-adjusted 2-sided (99.4%) confidence level is calculated using Lan-DeMets O'Brien-Fleming spending function (nominal one-sided alpha = 0.0028). It is based on 1177 CDC-defined COVID-19 events, representing 56.4% information fraction of target total number of events (N=2087, target rVE of 3% [mRNA-1283 vs mRNA-1273]).
[e.] Based on stratified Cox proportional hazard model to test the null hypothesis log (Hazard Ratio) ≥log(1.1).
Source: Study P301 CSR Table 14.2.2.1.2.

Primary immunogenicity analysis

Omicron BA.4/BA.5

The observed GM neutralising antibody titre prevaccination and at Day 29 for Omicron BA.4/BA.5 as well as the GMFR between prevaccination and Day 29 for both vaccine groups are shown below. For the prespecified GMR endpoint, the GMR was 1.335 (95% CI: 1.194, 1.492) and met the prespecified noninferiority criterion given that the lower bound of the 95% CI of the GMR was >0.667.

For the prespecified endpoint of the difference in SRR (SRR difference) between the 2 groups, the SRR difference was 14.4% (95% CI: 9.3, 19.4) and met the noninferiority criterion given that the lower bound of the 95% CI of the SRR difference was >-10%.

Table 10. Study P301: Summary of Pseudovirus Neutralising Antibody Level Against BA.4/BA.5 Variant (PPIS)

	mRNA-1283.222 10 µg (N=621)	**mRNA-1273.222 50 µg (N=568)**
Predose		
GM (95% CI[a])	355.9 (324.8, 389.9)	346.1 (312.2, 383.7)
Day 29		
GM (95% CI[a])	2346.2 (2158.0, 2550.9)	1753.8 (1607.0, 1914.0)
GMFR (95% CI[a])	6.59 (6.03, 7.21)	5.07 (4.63, 5.55)
GLSM (95% CI) [b]	2340.9 (2167.0, 2528.8)	1753.8 (1618.2, 1900.7)
GMR (mRNA-1283.222 vs mRNA-1273.222) (95% CI)[b]	1.335 (1.194, 1.492)	
Seroresponse (primary definition[c]) rate		
n (%)	496 (79.9)	372 (65.5)
95% CI[d]	(76.5, 83.0)	(61.4, 69.4)
Difference in seroresponse (primary definition) rates, % (95% CI) [e]	14.4 (9.3, 19.4)	
Seroresponse (secondary definition[c]) rate (%) (95% CI[d])		
n (%)	399 (64.3)	266 (46.8)
95% CI[d]	(60.3, 68.0)	(42.7, 51.0)
Difference in seroresponse (secondary definition) rates, % (95% CI)[e]	17.4 (11.8, 22.9)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; CSR = clinical study report; COVID_19 = coronavirus disease 2019; GLSM = geometric least square mean; GM = geometric mean; GMR = geometric mean ratio; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; LS = least squares; mRNA = messenger ribonucleic acid; PPIS = Per-Protocol Immunogenicity Subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5×LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
[a.] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM and GMFR, respectively, then back transformed to the original scale for presentation.

[b.] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by SARS-CoV-2 status at Baseline, randomisation age group, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA Omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for LS means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[c.] Seroresponse (primary definition) is defined as an antibody value change from Baseline below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if Baseline is ≥LLOQ and <4×LLOQ, or at least a 2-fold rise if Baseline is ≥4×LLOQ, where Baseline refers to prebooster. Seroresponse (secondary definition) is defined as an antibody value change from Baseline below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if Baseline is ≥LLOQ.

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

[e.] 95% CI is calculated using the Miettinen-Nurminen (score) method.

Source: Study P301 CSR Table 14.2.1.1.1.1, Table 14.2.1.1.1.2, Table 14.2.1.1.1.3, Table 14.2.1.1.1.4

SARS-CoV-2 D614G

The observed GM neutralising antibody titre prevaccination and at Day 29 for SARS-CoV-2 D614G as well as the GMFR between prevaccination and Day 29 for both vaccine groups are shown below. For the prespecified GMR endpoint, the GMR met the prespecified noninferiority criterion given that the lower bound of the 95% CI of the GMR was >0.667.

For the prespecified endpoint of the difference in SRR between the 2 groups, the SRR difference was 10.7% (95% CI: 6.0, 15.4) and met the noninferiority criterion given that the lower bound of the 95% CI of the SRR difference was >-10%.

Table 11. Study P301: Summary of Pseudovirus Neutralising Antibody Level Against SARS-CoV-2 D614G (PPIS)

	mRNA-1283.222 10 µg (N=621)	**mRNA-1273.222 50 µg (N=568)**
Predose		
Observed GM (95% CI[a])	2140.0 (1954.7, 2342.8)	2151.9 (1950.5, 2374.2)
Day 29		
GM (95% CI[a])	10657.6 (9960.2, 11403.9)	8576.5 (7990.4, 9205.6)
GMFR (95% CI[a])	4.98 (4.61, 5.38)	3.99 (3.67, 4.33)
GLSM (95% CI) [b]	10631.9 (9960.2, 11348.9)	8576.5 (8012.5, 9180.1)
GMR (mRNA-1283.222 vs mRNA-1273.222) (95% CI)[b]	1.240 (1.128, 1.362)	
Seroresponse (primary definition[c]) rate		
n (%)	519 (83.6)	414 (72.9)
95% CI[d]	(80.4, 86.4)	(69.0, 76.5)
Difference in seroresponse (primary definition) rates, % (95% CI)[e]	10.7 (6.0, 15.4)	
Seroresponse (secondary definition[c]) rate (%) (95% CI[d])		
n (%)	329 (53.0)	241 (42.4)
95% CI[d]	(49.0, 57.0)	(38.3, 46.6)
Difference in seroresponse (secondary definition) rates, % (95% CI)[e]	10.5 (4.9, 16.2)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; CSR = clinical study report; GLSM = geometric least square mean; GM = geometric mean; GMR = geometric mean ratio; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; LS = least squares; mRNA = messenger ribonucleic acid; PPIS = Per-Protocol Immunogenicity Subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

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

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

[b] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by SARS-CoV-2 status at Baseline, randomisation age group, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA Omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for LS means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[c] Seroresponse (primary definition) is defined as an antibody value change from Baseline below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if Baseline is ≥LLOQ and <4×LLOQ, or at least a 2-fold rise if Baseline is ≥4×LLOQ, where Baseline refers to prebooster. Seroresponse (secondary definition) is defined as an antibody value change from Baseline below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if Baseline is ≥LLOQ, where Baseline refers to prebooster.

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

[e] 95% CI is calculated using the Miettinen-Nurminen (score) method.

Source: Modified from Study P301 CSR Table 14.2.1.1.1.1, Table 14.2.1.1.1.2, Table 14.2.1.1.1.3, Table 14.2.1.1.1.4

Subgroup analysis

To evaluate the consistency in rVE (mRNA-1283.222 and mRNA-1273.222) across planned subgroups, pre-defined descriptive rVE analyses were performed for the following subgroups: age (≥12 to <18 years, ≥18 to <65 years, and ≥65 years), pre-vaccination SARS-CoV-2 infection status, and number of prior booster doses received.

rVE subgroup analysis by age

The highest rVE point estimate was observed in adults ≥65 years of age (13.54%, 95% CI: -7.67, 30.57). In the adolescent subgroup, the fewest number of COVID-19 events (29 and 23 in mRNA-1283.222 and mRNA-1273.222, respectively) and the corresponding wide CIs precluded a meaningful interpretation of the rVE point estimate.

Table 12. Study P301: Primary COVID-19 Events Through 31 Jan 2024 — Subgroup Analysis Based on Age (PPSE)

	≥12 to <18 Years		≥18 to <65 Years		≥65 Years	
	mRNA-1283.222 10 µg N=491	mRNA-1273.222 50 µg N=490	mRNA-1283.222 10 µg N=3558	mRNA-1273.222 50 µg N=3562	mRNA-1283.222 10 µg N=1630	mRNA-1273.222 50 µg N=1635
Number of Participants with COVID-19, n (%)	29 (5.9)	23 (4.7)	382 (10.7)	422 (11.8)	149 (9.1)	172 (10.5)
rVE Based on Hazard Ratio, % (95 % CI)[a]	-29.17 (-123.27, 25.27)		9.66 (-3.75, 21.34)		13.54 (-7.67, 30.57)	
Person-months[b]	2852.9	2906.2	26393.2	26343.4	11531.9	11532.1
Incidence rate per 100 person-months (95% CI)[c]	1.016 (0.681, 1.460)	0.791 (0.502, 1.188)	1.447 (1.306, 1.600)	1.602 (1.453, 1.762)	1.292 (1.093, 1.517)	1.491 (1.277, 1.732)

Abbreviations: CDC = Center for Disease Control; CI = confidence interval; COVID-19 = coronavirus disease 2019; CSR = clinical study report; mRNA = messenger ribonucleic acid; PPSE = Per-protocol Set for Efficacy; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy.

CDC COVID-19 Definition: the presence of at least 1 CDC listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); and positive RT-PCR test on a respiratory sample.

Date of COVID-19 is the later date of symptom and positive RT-PCR test, and the 2 dates of symptom and positive RT-PCR test should be within 14 days of each other.

[a] rVE = 1-hazard ratio (mRNA-1283.222 vs mRNA-1273.222), hazard ratio and 95% CI are estimated using a Cox proportional hazard model with the treatment group as a fixed effect. Efron's method is used for tie handling.

[b.] Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date or efficacy data cutoff date, whichever is the earliest. 1 month = 30.4375 days.
[c.] Incidence rate is defined as the number of participants with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months, incidence rate is presented as number of events per 100 person-months.
Source: Study P301 CSR Table 14.2.2.1.2.

The P301 CSR provides results on rVE in adolescents from a second interim analysis until cut-off date 23 February 2024. There were 70 SARS-CoV-2 infections (14.3%) in the mRNA-1283.222 group and 59 SARS-CoV-2 infections (12.0%) in the mRNA-1273.222 group ≥14 days after vaccination, translating to a rVE of -22.24 (95% CI: -72.84, 13.55) for mRNA-1283.222.

Table 14.2.2.5.2.2
Analysis of Relative Vaccine Efficacy (mRNA-1283.222 vs mRNA-1273.222) to Prevent SARS-CoV-2 Infection (Regardless of Off-Study COVID-19 Vaccine Use) Starting 14 Days After Injection (Overall and by Age Groups)
Per-Protocol Set for Efficacy

Age group: Adolescent (>=12 to <18 years)

	mRNA-1283.222 10 µg (N=491)	mRNA-1273.222 50 µg (N=490)
SARS-CoV-2 Infection (Symptomatic or Asymptomatic)		
Number of Subjects with SARS-CoV-2 Infection, n (%)	70 (14.3)	59 (12.0)
Number of Subjects Censored, n (%)	421 (85.7)	431 (88.0)
Hazard Ratio (95% CI) [1]	1.222 (0.865, 1.728)	
Relative Vaccine Efficacy Based on Hazard Ratio, % (95% CI) [2]	-22.24 (-72.84, 13.55)	
Person-Months [3]	3097.1	3177.6
Incidence Rate per 100 Person-Months (95% CI) [4]	2.260 (1.762, 2.856)	1.857 (1.413, 2.395)
Relative Vaccine Efficacy Based on Incidence Rate, % (95% CI) [5]	-21.73 (-75.15, 15.14)	
Asymptomatic SARS-CoV-2 Infection		
Number of Subjects with SARS-CoV-2 Infection, n (%)	31 (6.3)	30 (6.1)
Number of Subjects Censored, n (%)	460 (93.7)	460 (93.9)
Hazard Ratio (95% CI) [1]	1.061 (0.643, 1.753)	
Relative Vaccine Efficacy Based on Hazard Ratio, % (95% CI) [2]	-6.14 (-75.34, 35.75)	
Person-Months [3]	3097.1	3183.0
Incidence Rate per 100 Person-Months (95% CI) [4]	1.001 (0.680, 1.421)	0.943 (0.636, 1.345)
Relative Vaccine Efficacy Based on Incidence Rate, % (95% CI) [5]	-6.20 (-81.61, 37.82)	

rVE subgroup analysis based on Prior SARS-CoV-2 Infection

In participants with a history of prior SARS-CoV-2 infection, there were 350 (8.4%) events (incidence rate: 1.156 per 100 person-months) in the mRNA-1283.222 group and 380 (8.9%) events (incidence rate: 1.237 per 100 person-months) in the mRNA-1273.222 group (Table 13). The hazard ratio-based rVE was 6.53% (95% CI: -8.09, 19.16).

In participants without evidence of prior SARS-CoV-2 infection, there were 195 (13.9%) events (incidence rate: 1.982 per 100 person-months) in the mRNA-1283.222 group and 232 (17.0%) events (incidence rate: 2.428 per 100 person-months) in the mRNA-1273.222 group. The hazard ratio-based rVE was 18.88% (95% CI: 1.85, 32.95).

Therefore, based on this subgroup analysis, the rVE had a positive point estimate, regardless of SARS-CoV-2 infection before study vaccination.

Table 13. Descriptive Analysis of Relative Vaccine Efficacy - COVID-19 Events Through 31 Jan 2024 - Subgroup Analysis Based on Baseline SARS-CoV-2 Infection (PPSE)

	Positive		Negative	
	mRNA-1283.222 10 µg N=4186	mRNA-1273.222 50 µg N=4254	mRNA-1283.222 10 µg N=1401	mRNA-1273.222 50 µg N=1366
Number of Subjects with COVID-19, n (%)	350 (8.4)	380 (8.9)	195 (13.9)	232 (17.0)
rVE Based on Hazard Ratio, % (95 % CI)[a]	6.53 (-8.09, 19.16)		18.88 (1.85, 32.95)	
Person-months[b]	30287.0	30709.6	9839.9	9554.1
Incidence rate per 100 person-months (95% CI)[c]	1.156 (1.038, 1.283)	1.237 (1.116, 1.368)	1.982 (1.713, 2.280)	2.428 (2.126, 2.762)
rVE based on incidence rate, % (95% CI)[d]	6.61 (-8.27, 19.46)		18.39 (0.84, 32.89)	

CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy.

CDC COVID-19 Definition: the presence of at least 1 CDC-listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); and positive RT-PCR test on a respiratory sample.

Date of COVID-19 is the later date of symptom and positive RT-PCR test, and the 2 dates of symptom and positive RT-PCR test should be within 14 days of each other.

a. rVE = 1-hazard ratio (mRNA-1283.222 vs mRNA-1273.222), hazard ratio and 95% CI are estimated using a stratified Cox proportional hazard model the treatment group as a fixed effect. Efron's method is used for tie handling.

b. Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date or efficacy data cutoff date, whichever is the earliest. 1 month = 30.4375 days.

c. Incidence rate is defined as the number of subjects with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months, incidence rate is presented as number of events per 100 person-months.

d. rVE is defined as 1 – ratio of incidence rate (mRNA-1283.222 vs mRNA-1273.222). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-months.

Source: Table 14.2.2.4.1.1

rVE subgroup analysis Based on Number of Prior Booster Doses Received

In participants with one booster dose prior to enrollment, there were 176 (8.3%) events (incidence rate: 1.082 per 100 person-months) in the mRNA-1283.222 group and 163 (7.7%) events (incidence rate: 0.994 per 100 person-months) in the mRNA-1273.222 group (Table 14). The hazard ratio-based rVE was -8.77% (95% CI: -34.60, 12.11).

In participants with 2 booster doses prior to entry, there were 198 (10.5%) events (incidence rate: 1.457 per 100 person-months) in the mRNA-1283.222 group and 245 (12.9%) events (incidence rate: 1.795 per 100 person-months) in the mRNA-1273.222 group. The hazard ratio-based rVE was 19.00% (95% CI: 2.31, 32.84).

In participants with 3 or more booster doses prior to entry, there were 177 (12.2%) events (incidence rate: 1.857 per 100 person-months) in the mRNA-1283.222 group and 202 (13.8%) events (incidence rate: 2.108 per 100 person-months) in the mRNA-1273.222 group. The hazard ratio-based rVE was 11.59% (95% CI: -8.19, 27.75).

Based on this subgroup analysis, the COVID-19 incidence rates (mRNA-1283.222 vs mRNA-1273.222) were similar between the 2 vaccine groups for participants who had received a varying number of prior booster doses.

Table 14. Analysis of Relative Vaccine Efficacy - COVID-19 Events Through 31 Jan 2024 – Subgroup Analysis Based on Number of Prior Booster Doses Received (PPSE)

	1		2		≥3	
	mRNA-1283.222 10 µg N=2120	mRNA-1273.222 50 µg N=2129	mRNA-1283.222 10 µg N=1881	mRNA-1273.222 50 µg N=1899	mRNA-1283.222 10 µg N=1448	mRNA-1273.222 50 µg N=1467
Number of Subjects with COVID-19, n (%)	176 (8.3)	163 (7.7)	198 (10.5)	245 (12.9)	177 (12.2)	202 (13.8)
rVE Based on Hazard Ratio, % (95 % CI)[a]	-8.77 (-34.60, 12.11)		19.00 (2.31, 32.84)		11.59 (-8.19, 27.75)	
Person-months[b]	16266.7	16392.7	13587.6	13652.3	9532.2	9583.6
Incidence rate per 100 person-months (95% CI)[c]	1.082 (0.928, 1.254)	0.994 (0.848, 1.159)	1.457 (1.261, 1.675)	1.795 (1.577, 2.034)	1.857 (1.593, 2.151)	2.108 (1.827, 2.419)
rVE based on incidence rate (95% CI)[d]	-8.81 (-35.49, 12.57)		18.80 (1.67, 33.01)		11.90 (-8.33, 28.41)	

CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; rVE = relative vaccine efficacy.

CDC COVID-19 Definition: the presence of at least 1 CDC-listed symptom (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); and positive RT-PCR test on a respiratory sample.

Date of COVID-19 is the later date of symptom and positive RT-PCR test, and the 2 dates of symptom and positive RT-PCR test should be within 14 days of each other.

a. rVE = 1-hazard ratio (mRNA-1283.222 vs mRNA-1273.222), hazard ratio and 95% CI are estimated using a stratified Cox proportional hazard model the treatment group as a fixed effect. Efron's method is used for tie handling.

b. Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date or efficacy data cutoff date, whichever is the earliest. 1 month = 30.4375 days.

c. Incidence rate is defined as the number of subjects with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months, incidence rate is presented as number of events per 100 person-months.

d. rVE is defined as 1 – ratio of incidence rate (mRNA-1283.222 vs mRNA-1273.222). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-months.

Source: Table 14.2.2.4.1.1

Immunogenicity subgroup analysis based on age

Baseline titres are similar between the vaccination groups in all age strata. Naturally, baseline titres are significantly higher for variant D614G in all age groups.

The youngest age group shows the highest fold-increase of antibody titres against both variants (5.5 for D614G and 7.4 for B4/5). The two adult age groups show similar fold-increases with ~ 5 against D614G and ~ 6.5 against B4/5.

Overall, the new vaccine shows better immune responses compared to the authorised product irrespective of age, especially in the elderly.

Table 15. Summary of Pseudovirus Neutralising Antibody Level Against BA.4/BA.5 Variant - Subgroup Immunogenicity Analysis Based on Age (PPIS)

	≥12 to <18 Years		≥18 to <65 Years		≥65 Years	
	mRNA-1283.222 10 µg N=91	mRNA-1273.222 50 µg N=93	mRNA-1283.222 10 µg N=378	mRNA-1273.222 50 µg N=316	mRNA-1283.222 10 µg N=152	mRNA-1273.222 50 µg N=159
GM Baseline, 95% CI[a]	479.2 (388.4, 591.2)	593.0 (468.9, 749.9)	325.0 (290.2, 363.9)	319.2 (278.9, 365.2)	373.3 (302.5, 460.6)	296.8 (242.1, 363.8)
GM Day 29, 95% CI	3557.8 (3037.2, 4167.8)	3398.9 (2909.5, 3970.7)	2124.0 (1907.7, 2364.8)	1661.0 (1481.6, 1862.2)	2342.0 (1946.3, 2818.3)	1326.8 (1114.5, 1579.4)
GLSM[b], 95% CI	3561.4 (3037.5, 4175.7)	3398.9 (2908.9, 3971.4)	2120.6 (1917.3, 2345.6)	1661.0 (1487.8, 1854.4)	2339.5 (1984.3, 2758.3)	1326.8 (1130.0, 1557.7)
GM Ratio, 95% CI	1.048 (0.839, 1.309)		1.277 (1.100, 1.482)		1.763 (1.401, 2.219)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least square mean; GM = geometric mean; LLOQ = lower limit of quantification; LS = least square; PPIS = per-protocol immunogenicity subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

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

a. 95% CI is calculated based on the t-distribution of the log-transformed values for GM, then back transformed to the original scale for presentation.

b. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by SARS-CoV-2 status at pre-booster, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for Least Square Means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.1.1.4.1, Table 14.2.1.1.4.2

Table 16. Summary of Pseudovirus Neutralising Antibody Level Against SARS-CoV-2 D614G - Subgroup Immunogenicity Analysis Based on Age (PPIS) (source: Table 24, report body P301)

	≥12 to <18 Years		≥18 to <65 Years		≥65 Years	
	mRNA-1283.222 10 µg N=91	mRNA-1273.222 50 µg N=93	mRNA-1283.222 10 µg N=378	mRNA-1273.222 50 µg N=316	mRNA-1283.222 10 µg N=152	mRNA-1273.222 50 µg N=159
GM Baseline, 95% CI[a]	2492.7 (2061.2, 3014.5)	2946.4 (2367.6, 3666.6)	1961.4 (1744.9, 2204.8)	2051.6 (1802.7, 2334.8)	2425.8 (1988.9, 2958.6)	1968.9 (1609.5, 2408.5)
GM Day 29, 95% CI	13650.2 (11925.3, 15624.7)	12404.3 (11019.2, 13963.5)	9753.7 (8954.5, 10624.3)	8251.3 (7489.5, 9090.7)	11456.0 (9814.2, 13372.5)	7463.3 (6473.6, 8604.2)
GLSM[b], 95% CI	13617.7 (12006.3, 15445.3)	12404.3 (10966.5, 14030.6)	9734.8 (8938.8, 10601.7)	8251.3 (7517.2, 9057.1)	11451.1 (9936.3, 13196.9)	7463.3 (6499.4, 8570.1)
GM Ratio, 95% CI	1.098 (0.920, 1.309)		1.180 (1.040, 1.339)		1.534 (1.259, 1.871)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least square mean; GM = geometric mean; LLOQ = lower limit of quantification; PPIS = per-protocol immunogenicity subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

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

a. 95% CI is calculated based on the t-distribution of the log-transformed values for GM, then back transformed to the original scale for presentation.

b. The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by SARS-CoV-2 status at pre-booster, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for Least Square Means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.1.1.4.1, 14.2.1.1.4.2

Immunogenicity Based on Prior SARS-CoV-2 Infection

A subgroup analysis was conducted based on SARS-CoV-2 status prevaccination (participants with and without evidence of prior SARS-CoV-2 infection). The neutralising antibody responses and ANCOVA GMRs are shown below.

Table 17. Summary of Pseudovirus Neutralising Antibody Level Against BA.4/BA.5 Variant - Subgroup Immunogenicity Analysis Based on Baseline SARS-CoV-2 Infection (PPIS)

	Positive		Negative	
	mRNA-1283.222 10 µg N=487	mRNA-1273.222 50 µg N=434	mRNA-1283.222 10 µg N=132	mRNA-1273.222 50 µg N=134
GM Baseline, 95% CI[a]	433.7 (395.2, 475.8)	458.6 (411.9, 510.6)	170.4 (136.6, 212.6)	139.1 (114.1, 169.6)
GM Day 29 95% CI	2737.8 (2525.6, 2967.7)	2202.8 (2015.7, 2407.4)	1321.8 (1044.9, 1672.0)	838.1 (695.3, 1010.3)
GLSM[b], 95% CI	2735.8 (2526.0, 2963.1)	2202.8 (2024.4, 2397.0)	1312.8 (1066.2, 1616.6)	838.1 (682.3, 1029.6)
GM Ratio, 95% CI	1.242 (1.106, 1.395)		1.566 (1.169, 2.099)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least square mean; GM = geometric mean; LLOQ = lower limit of quantification; PPIS = per-protocol immunogenicity subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

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

a. 95% CI is calculated based on the t-distribution of the log-transformed values for GM, then back transformed to the original scale for presentation.

b. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by randomization age group, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for Least Square Means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.1.1.4.1, 14.2.1.1.4.2

Table 18. Summary of Pseudovirus Neutralising Antibody Level Against SARS-CoV-2 D614G - Subgroup Immunogenicity Analysis Based on Prior SARS-CoV-2 Infection (PPIS)

	Positive		Negative	
	mRNA-1283.222 10 µg N=489	mRNA-1273.222 50 µg N=433	mRNA-1283.222 10 µg N=132	mRNA-1273.222 50 µg N=134
GM Baseline, 95% CI[a]	2522.5 (2307.6, 2757.5)	2758.9 (2493.7, 3052.2)	1164.5 (909.7, 1490.7)	962.4 (782.0, 1184.4)
GM Day 29 95% CI	11225.5 (10467.6, 12038.3)	9576.1 (8873.8, 10333.9)	8765.6 (7285.2, 10546.8)	6001.3 (5124.3, 7028.5)
GLSM[b], 95% CI	11211.8 (10466.0, 12010.8)	9576.1 (8903.3, 10299.7)	8730.6 (7375.1, 10335.3)	6001.3 (5079.2, 7090.8)
GM Ratio, 95% CI	1.171 (1.059, 1.294)		1.455 (1.148, 1.844)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least square mean; GM = geometric mean; LLOQ = lower limit of quantification; PPIS = per-protocol immunogenicity subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

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

a. 95% CI is calculated based on the t-distribution of the log-transformed values for GM, then back transformed to the original scale for presentation.

b. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs mRNA-1273.222) as fixed effect, adjusted by randomization age group, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). Coefficients for Least Square Means use margins by level. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Source: Table 14.2.1.1.4.1, 14.2.1.1.4.2

Descriptive analysis

An analysis of rVE was also performed using the secondary protocol defined COVID-19 case definition (at least two clinical symptoms and PCR confirmed SARS-CoV-2 infection). Based on this definition, there were 498 COVID-19 cases (8.8%) in the mRNA-1283 group, and 556 cases (9.8%) in the mRNA-1273 group through 31 Jan 2024. The relative vaccine efficacy based on the hazard ratio was 10.5% with the 95% CI being (-1.01, 20.69). An analysis based on cases with the secondary COVID-19 definition through 23 Feb Jan 2024 (546 COVID-19 cases in the mRNA-1283 group, and 599 cases in the mRNA-1273 group) yielded similar results with an rVE of 8.92% (95% CI:-2.27, 18.9).

A descriptive rVE analysis was performed with all COVID-19 events meeting the primary COVID-19 definition (CDC definition), accrued through the data cutoff date of 23 Feb 2024. There were 613 (10.8%) events in the mRNA-1283.222 group and 661 (11.6%) events of COVID-19 in the mRNA-1273.222 group. The rVE analysis based on the FAS yielded consistent results with an rVE of 7.47% (95% CI: -3.28, 17.09).

- **Ancillary analyses**

Sensitivity analysis

The applicant conducted the rVE analysis with early COVID-19 cases (starting after study injection to <14 Days after injection) were to be considered as event based on events occurring after injection through 31 January 2024, as indicated in the SAP. There were 581 events in the 1283.222 group and 624 events in the 1273.222 group. The estimated rVE was 6.96% (95% CI: -4.17%, 16.90%), which is consistent with the primary rVE analysis. The results are presented below.

Table 19. Analysis of Relative Vaccine Efficacy (mRNA-1283.222 vs mRNA-1273.222) to Prevent COVID-19 (CDC Defined COVID-19) Post Injection, Based on COVID-19 Events Through 31 January 2024 (Per-Protocol Set for Efficacy)

	mRNA-1283.222 10 µg (N=5679)	**mRNA-1273.222 50 µg (N=5687)**
Number of Subjects with COVID-19, n (%)	581 (10.2)	624 (11.0)
Incidence Rate per 100 Person-Months (95% CI) [1]	1.425 (1.311, 1.545)	1.530 (1.412, 1.655)
Relative Vaccine Efficacy Based on Hazard Ratio, % (95% CI) [2]	6.96 (-4.17, 16.90)	

CDC = Centers for Disease Control and Prevention;
CDC COVID-19 Definition: the presence of at least 1 CDC listed symptom(https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html); and positive RT-PCR test on a respiratory sample.
[1] Incidence rate is defined as the number of subjects with an event (COVID-19) divided by total person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months. Person-months is defined as the total months from study injection date to the date of event (COVID-19), date of off-study COVID-19 vaccine, last date of study participation, death date or efficacy data cutoff date, whichever is the earliest. 1 month = 30.4375 days.
[2] Relative vaccine efficacy (rVE), defined as 1 - hazard ratio (mRNA-1283.222 vs. mRNA-1273.222). Hazard ratio and 95% CI are estimated using a stratified Cox proportional hazard model (stratified by age group per randomisation) with Efron's method of tie handling and with the treatment group as a fixed effect. For age subgroup analysis, actual age group is used. Age stratification was removed from Cox proportional hazard model for age subgroup analysis
Source: Table 14.2.2.1.3

Severe COVID-19

The applicant conducted an analysis using mRNA-1283-P301 Part 1 data for the relative vaccine efficacy (rVE) of mRNA-1283 versus mRNA-1273 against severe COVID-19 based on the definition of severe COVID-19 included in mRNA-1283 Part 2 protocol. A review was performed using the vital sign

and adverse event recorded data. The severe COVID-19 events identified in this review had PCR-confirmed SARS-CoV-2 and met any of the following criteria within 30 days of the positive PCR test date:

- Clinical signs at rest indicative of severe systemic illness: respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level; OR
- Respiratory failure or acute respiratory distress syndrome (requiring high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic BP <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); OR
- Significant acute renal, hepatic, or neurologic dysfunction; OR
- Admission to an intensive care unit or death.

A total of 55 severe events occurred from 14 days post-vaccination through 31 January 2024. Fifty one of the 55 events (92.7%) were due to a vital sign or oxygen saturation criterion. There were 21 (0.37%) severe COVID-19 events in the mRNA-1283 group and 34 (0.60%) in the mRNA-1273 group. The rVE (95% CI) based on these 55 events was 38.06% (-6.7%, 64.05%). In addition, 59 events occurred from 14 days post-vaccination through 23 February 2024, and 55 of these 59 events (93.2%) were due to a vital sign or oxygen saturation criterion. The rVE (95% CI) based on the 59 cases was 35.89% (-8.17%, 62.01). There were more events that met the severe COVID-19 definition in the mRNA-1273 group compared to mRNA-1283 across all age groups.

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20. Summary of Efficacy for trial mRNA-1283-P301

A randomised, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ⩾12 years for the prevention of COVID-19			
Study identifier	mRNA-1283-P301		
Design	randomised, observer-blind, active-controlled Phase 3 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		10 months not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	mRNA-1283.222 (bivalent original/BA.4/5)		N=5706
	mRNA-1273.222 (bivalent original/BA.4/5)		N=5711
Endpoints and definitions	Co-Primary endpoint	rVE	The primary rVE objective was to demonstrate a noninferior rVE of mRNA-1283 compared with mRNA 1273 in preventing the first event of COVID-19 starting 14 days after study vaccination with a noninferiority margin of 10%.

A randomised, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ⩾12 years for the prevention of COVID-19			
Study identifier	mRNA-1283-P301		
	Co-Primary endpoint	Immunogenicity	The primary immunogenicity objectives were to • To demonstrate a noninferior neutralising antibody response of mRNA-1283.222 10 μg compared to mRNA-1273.222 50 μg against Omicron BA.4/5 based on GMR and SRR difference at Day 29. • To demonstrate a noninferior neutralising antibody response of mRNA-1283.222 10 μg compared to mRNA-1273.222 50 μg against the original SARS-CoV-2 D614G based on GMR and SRR difference at Day 29. Noninferiority margin for GMR was 0.667 (1/1.5) and noninferiority margin for SRR difference was 10%.
Database lock	06 May 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol Efficacy Set (PPES) 31 Jan 2024		
Effect estimate and estimate variability: Co-Primary rVE	Treatment group	mRNA-1283.222	mRNA-1273.222
	Number of subjects	n=5679	n=5687
	Number of participants with COVID-19, n (%)	560 (9.9)	617 (10.8)
	Incidence rate per 100 person-months (95% CI)	1.373 (1.262, 1.492)	1.513 (1.396, 1.637)
	rVE based on Hazard Ratio, % (99.4% CI)	9.31 (-6.58, 22.83)	
	p-value	0.0005	

Effect estimate and estimate variability: Co-Primary Immunogenicity (BA.4-5)	Predose GM (95% CI)	mRNA-1283.222 (n=621)	mRNA-1273.222 (n=568)
		355.9 (324.8, 389.9)	346.1 (312.2, 383.7)
	Day 29 GM (95% CI)	2346.2 (2158.0, 2550.9)	1753.8 (1607.0, 1914.0)
	GMFR (95% CI)	6.59 (6.03, 7.21)	5.07 (4.63, 5.55)
	Day 29 GLSM (95% CI)	2340.9 (2167.0, 2528.8)	1753.8 (1618.2, 1900.7)
	GMR mRNA-1283.222 vs. mRNA-1273.222 (95% CI)	1.335 (1.194, 1.492)	
	Seroresponse (primary definition) rate n (%)	496 (79.9)	372 (65.5)

A randomised, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ⩾12 years for the prevention of COVID-19			
Study identifier	mRNA-1283-P301		
	Seroresponse (primary definition) rate 95% CI	(76.5, 83.0)	(61.4, 69.4)
	Difference in seroresponse (primary definition) rate % (95% CI)	14.4 (9.3, 19.4)	
	Seroresponse (secondary definition) rate n (%)	399 (64.3)	266 (46.8)
	Seroresponse (secondary definition) rate 95% CI	(60.3, 68.0)	(42.7, 51.0)
	Difference in seroresponse (secondary definition) rate % (95% CI)	17.4 (11.8, 22.9)	
Effect estimate and estimate variability: Co-Primary Immunogenicity (D614G)	Predose GM (95% CI)	2140.0 (1954.7, 2342.8)	2151.9 (1950.5, 2374.2)
	Day 29 GM (95% CI)	10657.6 (9960.2, 11403.9)	8576.5 (7990.4, 9205.6)
	GMFR (95% CI)	4.98 (4.61, 5.38)	3.99 (3.67, 4.33)
	Day 29 GLSM (95% CI)	10631.9 (9960.2, 11348.9)	8576.5 (8012.5, 9180.1)
	GMR mRNA-1283.222 vs. mRNA-1273.222 (95% CI)	1.240 (1.128, 1362)	
	Seroresponse (primary definition) rate n (%)	519 (83.6)	414 (72.9)
	Seroresponse (primary definition) rate 95% CI	(80.4, 86.4)	(69.0, 76.5)
	Difference in seroresponse (primary definition) rate % (95% CI)	10.7 (6.0, 15.4)	
	Seroresponse (secondary definition) rate n (%)	329 (53.0)	241 (42.4)
	Seroresponse (secondary definition) rate 95% CI	(49.0, 57.0)	(38.3, 46.6)
	Difference in seroresponse (secondary definition) rate % (95% CI)	10.5 (4.9, 16.2)	

A randomised, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ⩾12 years for the prevention of COVID-19	
Study identifier	mRNA-1283-P301
Notes	The analysis of rVE was to be conducted when "at least 700 COVID-19 events had been accrued". The actual analysis took place after 1177 events.

2.5.5.3. Clinical studies in special populations

Refer to results displayed on clinical efficacy for data in elderly population.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.5.5.6. Supportive studies

Study P301-Japan

The substudy conducted in Japan measured nAbs against the latest strain variant XBB1.5 in the same age cohorts as the main study. The primary immunogenicity objective was to demonstrate a noninferior nAb response of mRNA-1283.815 10 µg in terms of geometric mean concentrations of nAbs when compared to mRNA-1273.815 50 µg. This prespecified primary objective was based on GMR at Day 29 (nAb responses against Omicron XBB.1.5) and was successfully met. The nAb responses for Omicron XBB.1.5 are shown in Table 21.

Table 21. Study P301-Japan: Summary of Pseudovirus Neutralising Antibody Level Against Omicron XBB.1.5 (PPIS)

	mRNA-1283.815 10 µg (N=334)	**mRNA-1273.815 50 µg (N=334)**
Primary Endpoint		
Predose, n[a]	334	334
GM (95% CI[b])	115.9 (99.8, 134.6)	133.8 (114.9, 155.9)
Day 29, n	334	334
GM (95% CI[b])	1726.4 (1523.1, 1957.0)	1510.1 (1333.5, 1710.0)
GMFR (95% CI[b])	14.90 (13.14, 16.90)	11.28 (9.83, 12.95)
GLSM (95% CI)[c]	1757.2 (1580.1, 1954.3)	1470.4 (1322.4, 1635.0)
GMR (mRNA-1283.815 vs mRNA-1273.815) (95% CI)[c]	1.195 (1.028, 1.389)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; CSR = clinical study report; GLSM = geometric least square mean; GM = geometric mean; GMFR = geometric mean fold rise; GMR = geometric mean ratio; LS = least square; mRNA = messenger ribonucleic acid; PPIS = Per-Protocol Immunogenicity Subset; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Number of participants with non-missing data at the timepoint (Baseline or postBaseline).

[b.] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM and GMFR, respectively, then back transformed to the original scale for presentation.
[c.] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.815 vs mRNA-1273.815) as fixed effect, adjusted by SARS-CoV-2 status at Baseline, randomisation age group, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA Omicron bivalent vs mRNA Original monovalent + Non-mRNA vaccine). LS means are based on observed margin. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
Source: Study P301-Japan CSR Addendum Table 14.2.1.1.1.1, Table 14.2.1.1.1.2.

The Japan-study also measured the immune response against the original variant D614G as an exploratory endpoint. The results are very similar to those of the main pivotal study (Table 22).

Table 22. GM and GMFR baseline and on D29 per age groups for D614G with mRNA-1283 used in study P301 and P301-Japan (source: Table 14.2.1.1.4.1, study reports)

Age group		≥12 to <18 Years		≥18 <65 Years		≥65 Years	
Strainvariant **D614G**		P301	P301-Japan	P301	P301-Japan	P301	P301-Japan
Baseline	*n*	*91*	*70*	378	194	*152*	*69*
	GM	**2492.7**	**1583.2**	**1961.4**	**1423.2**	**2425.8**	**1448.1**
	CI	(2061.2, 3014.5)	(1239.4, 2022.2)	(1744.9, 2204.8)	(1202.3, 1684.7)	(1988.9, 2958.6)	(1073.3, 1953.6)
D29	*n*	*91*	*68*	378	188	*152*	*68*
	GM	**13650.2**	**8597.7**	**9753.7**	**6220.9**	**11456.0**	**6807.9**
	CI	(11925.3, 15624.7)	(7076.6, 10445.6)	(8954.5, 10624.3)	(5538.8, 6987.0)	(9814.2, 13372.5)	(5442.4, 8516.0)
	GMFR	**5.48**	**5.55**	**4.97**	**4.24**	**4.72**	**4.71**
	CI	(4.49, 6.68)	(4.52, 6.81)	(4.49, 5.51)	(3.72, 4.83)	(4.07, 5.48)	(3.71, 5.98)

Baseline GMs are lower in the Japan-substudy in all age groups. The fold-increase after vaccination is very similar to the pivotal study.

Studies mRNA-1283-P101 and -P201

Study mRNA-1283-P201 evaluated immunogenicity primarily at Day 29, with all other time points considered secondary objectives. Results showed that GMFR and SRR were comparable between the control group (mRNA-1273 50 µg) and all study groups for the original SARS-CoV-2 strain (D614G), the Beta variant (tested only in Part A) and Omicron BA.1. Binding antibody responses were consistent with neutralising antibody results, with GM levels and GMFR comparable between the control and study groups. Antibody responses in the mRNA-1283 (2.5, 5, and 10 µg), mRNA-1283.211 (5 and 10 µg), and mRNA-1283.529 groups (Part B) persisted at multiple post-vaccination time points (Day 91, Day 181, Day 366), suggesting a durable immune response. Results were generally consistent across age groups (18‑55 years and ≥56 years), though the small sample sizes reduced interpretability. The ANCOVA analysis identified the mRNA-1283 10 µg group at Day 29 as the only group achieving a statistically significant increase in antibody response compared to the mRNA-1273 control, with the 95% CI of the GMR not including 1. Furthermore, the bivalent mRNA-1283.211 vaccine, specifically designed for the Beta variant, did not provide superior immunogenicity compared to the control mRNA-1273. ANCOVA analysis was not conducted for Part B due to the absence of a control group.

Study mRNA-1283-P101 designated immunogenicity endpoints as secondary objectives. Comparisons were only descriptive. No formal hypothesis was tested. Overall, design and conduct of this first-in-human study are acceptable. The participant flow is comprehensible. Baseline characteristics are not perfectly balanced between groups, but no concerns are raised in this regard. GMFR in neutralising

antibodies against SARS-CoV-2 D614G was comparable across all tested dose levels (10, 30 and 100 µg) at all time points. The applicant claims that neutralising antibody responses remained detectable through Day 394; however, data from this time point appear heavily confounded, suggesting that nAb and bAb measurements were influenced by SARS-CoV-2 infections occurring during the study. It should also be mentioned that the exploratory endpoint "to characterize the immune response of participants infected by SARS-CoV-2 during the study" is listed but the results are not addressed in the mRNA-1283-P101 CSR. While mRNA-1283 at all dose levels induced comparable binding antibody responses to mRNA-1273 against D614G, the results do not show a clear dose-response relationship, with nAb and bAb responses at 30 µg even lower than at 10 µg, contradicting the expected trend. Cell-mediated immune responses were investigated as an exploratory objective and not considered relevant for the overall assessment. Additionally, 58.1% of the cell mediated immunity samples were mishandled, rendering their viability uncertain. According to Section 4.1.1 of the mRNA-1283-P101 CSR, a sensitivity analysis on the FAS was required if the FAS and PP set differed by more than 10%. This criterion was met for all groups except mRNA-1283 100 µg (arm 3), yet the corresponding data are missing.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program of mRNA-1283 comprises a completed Phase 1 dose-ranging study (P101), a completed Phase 2 dose-ranging study (P201), an ongoing active controlled Phase 3 study (P301) and an ongoing active-controlled Phase 3 country specific amendment (P301 Japan). This application mainly relies on establishing a bridge based on immunogenicity and relative vaccine efficacy between mRNA-1283.222 and the authorised mRNA-1273.222 in the main study P301. Thus, while absolute efficacy of the vaccine cannot be estimated with the chosen design, the immuno-bridging approach is principally acceptable. The design and results of the respective studies will be discussed below. Throughout the studies, different vaccine variants were used. While the vaccine composition in the SmPC reflects the variant XBB.1.5, which is regarded acceptable, the expectation is that mRNA-1283 will be updated for vaccination campaigns following regulatory recommendations.

Study mRNA-1283-P301 was a randomised, observer-blind, multicentre, active-controlled, 2-arm, Phase 3 study in participants aged ≥12 years to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273. The screening period lasted up to 28 days. On day 1 participants were randomised 1:1 to receive either mRNA-1283.222 or mRNA-1273.222. Assessments of efficacy, immunogenicity and safety were foreseen over 12 months. Overall, the design of study mRNA-1283-P301 is acceptable. The applicant received EMA scientific advice in January 2023 (EMA/SA/0000121008). In the EMA scientific advice, a design and marketing authorisation based on immunogenicity data was discussed and this would have been principally acceptable. Nevertheless, the applicant also evaluated the relative vaccine efficacy of mRNA-1283 compared to the approved mRNA-1273, which will be further discussed below. Other design aspects are generally in agreement with the advice received. Specific design aspects will be discussed below.

Study P301 was conducted at 196 sites across three countries (United States, United Kingdom and Canada). The selection of countries and study centres is regarded acceptable. The main inclusion criteria of study P301 were: an age of ≥12 years and the previous receipt of a primary series of an authorised COVID-19 vaccine. Participants ≥18 years must also have received at least one booster dose (maximum five vaccine doses). A heterologous vaccine regimen was permitted. This is appropriate. In the EMA Scientific Advice (EMA/SA/0000121008) it was discussed that the study does not specifically exclude subjects who already received a bivalent mRNA vaccine. The Applicant was advised to consider restricting the analysis population of the immunogenicity subset to those who have

received only monovalent mRNA vaccines. Additional analyses could have been planned to explore immune responses between mRNA-1283.222 and mRNA-1273.222 in subsets who previously received at least one dose of a bivalent ancestral/BA.1 or ancestral/BA.4/5 vaccine. This advice does not seem to have been followed. However, the Applicant performed analyses based on the type of last prior COVID-19 vaccine, the results of which do not give rise to concern (please see results section further below). Therefore, no further concern is raised on this issue. The main exclusion criteria were a positive SARS-CoV-2 test within 90 days of screening, a COVID-19 vaccination within 90 days of screening and being acutely ill or febrile. Furthermore, participants with a history of myocarditis, pericarditis, or myopericarditis that has not fully resolved within 3 months prior to Screening were excluded. This is adequate.

Participants were randomised 1:1 to one of the two treatment groups mRNA-1283.222 or mRNA-1273.222. Randomisation was stratified by age groups (12 to <18, 18 to <65, and ≥65 years), which is acceptable. The study was observer-blind. There were unblinded site personnel preparing and administering the dose. These personnel did not participate in any of the clinical study evaluations. Participants and investigators did not have access to the treatment assignments. Furthermore, there was an independent DSMB that reviewed safety and efficacy information in an unblinded manner and provided recommendations to the Sponsor as pre-specified for the adaptive design (see further below for a discussion on this issue). The DBP further defined sponsor personnel which was unblinded at the treatment group level and/or at the subject level.

The study was termed a randomised, observer blind study. The randomisation approach for treatment allocation is overall acceptable. The approach to randomly sample adult subjects for immunogenicity assessment as described in the CSR is acceptable as well. However, it is noted that no details on the methods were provided in the protocol or SAP. The protocol does not even mention that a random sample will be used for adults and the SAP only refers to a "Immunogenicity Data Sampling Plan", which was not available in the submission. The pragmatic approach to use the first 210 adolescent subjects is understandable but not considered optimal. A random selection would have been preferable as differences in subjects and the subjects' immune response over time cannot be excluded in this highly volatile situation. The approach to blind participants and investigators is overall endorsed, although the label "observer-blind" is somewhat misleading.

The participants of study P301 received either 10 µg mRNA-1283.222 or 50 µg mRNA-1273.222 (bivalent ancestral and Omicron BA.4/5 vaccines). The assigned study intervention was administered as a single intramuscular injection into the deltoid muscle or thigh. This is adequate.

For the evaluation of efficacy, participants underwent symptom surveillance based on electronic diary prompts, which were performed biweekly. If the participants had one of the pre-specified symptoms, they had an unscheduled visit for collection of respiratory samples for SARS-CoV-2 PCR. The PCR samples were analysed centrally. This is acceptable. RT-PCR results were shared with the DSMB in two blinded sessions. For the evaluation of immunogenicity, participants had blood collection at baseline, Day 29, Day 91, Day 181, and Day 365. Blood samples were analysed in a central laboratory. Additionally, the Applicant provided a well-structured schedule of activities, which is endorsed.

The primary rVE endpoint was the demonstration of a non-inferior vaccine efficacy of mRNA-1283 compared to mRNA-1273 in preventing the first event of COVID-19 starting 14 days after study injection. The chosen design (no placebo group) cannot inform about the absolute efficacy of mRNA-1283. This would have been informative, but it is understood that such a study might not have been feasible considering the availability of safe and efficacious vaccines against COVID-19 and the pre-existing immunity in the population.

The non-inferiority margin for the rVE was changed from -20% to -15% with the protocol amendment 1 and from -15% to -10% with the protocol amendment 3. The applicant has not provided a clear

clinical rationale for the specified non-inferiority margin of -10% for rVE. It was noted that the margin was set based on regulatory feedback received from FDA, which was confirmed. As the margin was requested by FDA and as there is no further benefit in justifying it post-hoc, the issue was not pursued further.

The primary efficacy endpoint rVE is considered acceptable. The estimand description is not fully understandable (e.g. the targeted strategies are not well explained). It is also noted that the target population is defined as the PPSE. The inclusion in the analysis population is based on post randomisation events, which are, however, not treated as intercurrent events with an adequate strategy but simply removed from the analysis set. Given that all subjects in the FAS were or were at least planned to be vaccinated and hence are subject to the vaccination routines and potential side effects and given that protocol violations might be potentially impacted by the vaccine received, this estimand in the FAS is considered crucial and clinically more relevant than the biological activity of the vaccine if patients are vaccinated and compliant. The assumption that there is no systematic differences between subjects who complete the allocated vaccine schedule in each randomised group might not hold in this case. It is acknowledged that the estimated rVE in the PPSE and the FAS were very similar, which reduces the practical implications of the estimand discussion in the given case.

The primary immunogenicity endpoints used in conjunction with the set NI margins are acceptable and have been agreed upon in scientific advice. No estimands for the immunogenicity endpoints were prespecified. Upon request the applicant provided a post hoc description of the targeted estimands.

Overall, the analysis model for the primary efficacy endpoint rVE and the tested NI-hypothesis is considered acceptable. However, in the protocol, the applicant stated that "SARS-CoV-2 status at pre-injection, number of prior injections, and type of prior vaccine could be included in the Cox model, if applicable". This is not supported as the primary analysis of the primary endpoint should be clearly and unambiguously pre-defined. In the SAP this was removed from the primary analysis but a sensitivity analysis was defined. This was provided for the updated analysis (data base cutoff 23 Feb 2024) only. The analysis models of the immunogenicity analyses and tested hypotheses are considered acceptable.

With Protocol Amendment 3 (dated 20 December 2023), i.e., very late in the conduct of the study, the applicant fundamentally changed the study design. The NI-margin for rVE was changed from -15% to -10%. This is considered acceptable as it is conservative. It was justified by a request from the FDA as discussed above. To accommodate this change and likely also driven by a lower than anticipated incidence rate and newly emerging variants, the applicant changed the sample size assumptions to maintain a power ≥ 80% and additionally introduced an adaptive design. An interim analysis after at least 700 confirmed COVID-19 events was added to allow the assessment of early efficacy, futility and to re-assess the sample size based on a conditional power approach. If needed, additional subjects were to be enrolled in a new Study Part 2, which was to use a new variant sequence against Omicron XBB.1.5 for both vaccine arms.

This newly added adaptive design is seen critical for various reasons:

- The design change was very late in an ongoing single pivotal trial. No clear rationale was given for this amendment. It was rather stated that the amendment was made to increase the sample size. This is not a justification but rather a description of a factual change. Upon request, the Applicant stated that these changes were not based on data from the study. This is not fully credible, given that the adaptive design was implemented together with changes in the sample size assumptions pertaining to an increase in the targeted rVE from 0% to 3%, a change in the assumed COVID-19 incidences, and a change in the assumed dropout rate. Taken together, this shows that the changes were either not well justified or based on accruing *monitoring* information from the trial. Overall, this issue is not further pursed.

- The Applicant was further asked to provide the FDA meeting interaction times and minutes. From the provided documentation it is obvious that FDA requested clinical efficacy data to support the authorisation of mRNA-1283.222, as immunogenicity data were not regarded sufficient for authorisation of mRNA-1283.222. Additionally, the -10 % NI margin was also introduced based on advice received from FDA. The explanations provided by the Applicant are acknowledged; the FDA seems to have been the main driving force for the -10 % NI margin which then influenced the protocol amendments.
- Documents such as the Study Data Blinding Plan and information on the DSMB meetings (timing and meeting minutes) were not submitted by the Applicant. Upon initial request, these documents were only partially provided (data blinding plans, DSMB meeting minutes for two out of 5 meetings). For three DSMB meetings (initial orientation meeting, a meeting asking for feedback on the planned adaptive design, and the preparation meeting for the rVE interim analysis) no minutes (or other documentation) were provided as, according to the Applicant, these were not generated. After the request was reiterated, the Applicant could share meeting minutes for all five DSMB meetings together with the presentation slides shared in these meetings. This shows that the Applicant has some issues with the proper documentation of the study. No further issues are derived here.
- The Applicant was further asked to clarify which data have been shared with the DSMB at the DSMB data review meeting #1 (27 Jul 2023) and to provide the presentation shared with the DSMB members. The Applicant pointed out that demographics and baseline characteristics, solicited adverse reactions, unsolicited adverse events and RT-PCR test results for SARS-CoV-2 were shared with the DSMB during that meeting. However, from the provided slides, it is unclear which information regarding RT-PCR test results for SARS-CoV-2 has been shared with the DSMB, as the respective table cited to in the minutes was not found in the presentation. It is considered very odd that information, which was mentioned in the minutes and also explicitly referred to in the responses of the Applicant to the CHMP request, is lacking in the submitted documents. This raises concerns on the quality control and the capability of the Applicant to manage the study well. However, no further issue is raised, as the unblinded data seem to have been shared during the closed session of the meeting, where the Sponsor did not take part. Additionally, according to the data blinding plan, an independent unblinded biostatistician would have been allowed to share unblinded analysis for the DSMB. Thus, the issue is not further pursued.
- It is noted that the first Data Blinding Plan (DBP) was finalized on 27 Nov 2023, after 3 previous DSMB meetings (23 May 2023, 27 June 2023 and 1 Nov 2023). The Applicant clarified that although the adaptive design has been discussed with the DSMB on 1 Nov 2023, ~1 month before the finalization of the first DBP V1 (27 Nov 2023), the DBP V1 did not include wording on the adaptive design, as it has not been contained in the protocol effective at that time. The protocol version 3, which included the adaptive design element, was finalized on 20 Dec 2023. This explanation is considered acceptable. The DBP V2, which introduced the adaptive design and which was the first document to clearly state the plan to conduct the (interim) rVE analyses based on events accrued through 31 January 2024 was finalized very late (23 February 2024). At this time the cut-off date had already passed. In both DBP V1 and V2 the purpose was described as laying out the roles and responsibilities in receiving access to unblinded data during the clinical study. The Applicant provided an overview of the key events related to DSMB meeting, DBP, and interim analysis, which is acknowledged. The Applicant did not justify the late finalization of DBP V2. It was only clarified that although the DBP v2 was finalized on 23 Feb 2024, after the Jan 31 cut-off date, the Sponsor was not aware of any

interim unblinded efficacy data. As this argument can be followed when reviewing the provided documentation which presented only blinded data, the issue is not further pursued.

- The criterion to trigger the interim analysis was very vague ("more than 700 confirmed COVID-19 cases") and was strongly exceeded with 1177 confirmed cases at the interim analysis (= 168% of target event rate of 700 events). Upon request, the Applicant provided the effect through 21 Nov 2023, the date of the 700th case, when a total of 707 cases had accumulated. Applying the O'Brien-Fleming alpha spending approach as pre-specified for the interim analysis, this analysis showed an rVE of 14.42% with a multiplicity adjusted 95% CI of (-13.31%, 35.35%).
  The average effect is in line with the observed results in the finally conducted analysis (or even better than that), however would not have been significant at that time. The confidence interval for the HR was crossing the NI margin of -10%. The Applicant did not provide a justification for the large overrunning. It was rather explained that the timing of the interim analysis was chosen as 31 Jan 2024, based on the expectation that more than 1,044 events—representing 50% information fraction—would be reached by that time. If this was the projected target, it is unclear and not understandable, why a protocol amendment from the same time (dated 20 Dec 2023) did not communicate this expectation together with the rather meaningless lower limit for the number of targeted events. The (at least) 700 events were reached already one month prior to the protocol amendment. Further evidence that the targeted information fraction was pre-specified as 50% (1044 cases) was requested but not provided. It might be that the increased information fraction at interim was triggered by the input from the DSMB, which recommended "an interim analysis with a considerable information fraction (higher than the one proposed in the examples presented)". The examples presented to the DSMB used information fractions of 30% to 40%. This was not verified by the Applicant, though. The issue was not further pursued as the impact is overall considered minor given the rather high rVE, which was also aligned over time.

Overall, the uncertainties regarding the blinding procedures (e.g. late specification of blinding and communication plans) and issues with the conduct of study (including the late definition of the adaptive design and uncertainties regarding the timing) impact the reliability of the results to some extent. It is acknowledged that one driver of the design change were FDA requirements to show non-inferiority with a -10% NI-margin. It is considered that due to the magnitude of the rVE effect and the limited impact of the observed issues, non-inferiority was demonstrated.

A blinded sample size re-assessment was planned to be conducted by the DSMB. While in principle also a blinded sample size re-assessment might lead to a type 1 error increase in non-inferiority trials (see e.g. Friede and Kieser, 2011, doi: 10.3414/ME09-01-0063) this was not an issue here as a combination test (CHW test, Cui L 1999; Lehmacher 1999) was to be used to combine Parts 1 and 2. This is established to preserve the type one error rate. Furthermore, in practice, this had no impact at all as actually no sample size re-assessment was conducted as early efficacy was shown.

The applicant made a country-specific protocol amendment to establish P301-Japan, a sub-study to evaluate the safety and immunogenicity of mRNA-1283.815 (XBB.1.5 variant) in a cohort of 692 Japanese participants aged 12 years and older. The comparator vaccine in this study was the approved mRNA-1273.815 (full-length Spike protein of the XBB.1.5 variant). The study was initiated on 15 Mar 2024. An interim analysis based on a data cutoff date of 02 May 2024 (at least 29 days follow-up for each participant) is provided. However, due to the early cut-off, most of the secondary endpoint analyses were not yet available. The Applicant explained that the final CSR from the P301-Japan study is under preparation and will be submitted as a variation procedure post-approval, which is regarded acceptable (**REC**).

Study P201 was a dose-ranging study to investigate the safety, reactogenicity, and immunogenicity of a single booster dose with mono/bi-valent mRNA-1283 vaccines in participants ≥18 years of age previously vaccinated with mRNA-1273. Part A of study P201 was a randomised, observer-blinded study that examined mRNA-1283 (monovalent; original SARS-CoV-2 [D614G]; 2.5, 5 or 10 µg) and mRNA-1283.211 (bivalent; D614G and Beta variant; 5 or 10 µg) in comparison to mRNA-1273 (monovalent full-length S; D614G; 50 µg). Part B was an open-label study that investigated the safety, reactogenicity, and immunogenicity of mRNA-1283.529 (5 or 10 µg; encoding BA.1) without a comparator group and is therefore considered rather uninformative. A total of 340 and 200 participants were randomised to the vaccination groups in Part A Part B, respectively. Overall, the design and conduct study P202 can be considered acceptable.

Study P101 was the first-in-human study of mRNA-1283 and evaluated the safety, reactogenicity, and immunogenicity of different dose levels in comparison to mRNA-1273 SARS-CoV-2 vaccine in 105 SARS-CoV-2 seronegative healthy adults, 18 to 55 years of age. The primary objective of study P101 was to evaluate the safety and reactogenicity of 3 dose levels (10, 30, and 100 µg) of mRNA-1283 and 1 dose level of mRNA-1273 (100 µg), each administered as 2 doses (28 days apart) and 1 high-dose level of mRNA-1283 administered as a single dose (placebo + 100 µg). The secondary objective investigated the immunogenicity (neutralising and binding antibody titres) of the different dose levels of mRNA-1283 in comparison to mRNA-1273. Cell-mediated immune responses were investigated as exploratory objective. Comparisons were only descriptive. No formal hypothesis was tested. Overall, design and conduct of this first-in-human study are acceptable.

Efficacy data and additional analyses

Study mRNA-1283-P301 is a pivotal Phase 3 randomised, observer-blind, active-controlled, single dose, multicentre study to evaluate the safety, immunogenicity, and rVE of mRNA-1283 (mRNA-1283 vs mRNA-1273) in medically-stable individuals ≥12 years and older for the prevention of COVID-19.

Dose Selection

Based on the previous evaluation of mRNA-1283 and mRNA-1283.211 in studies P101 and P201, the applicant has selected the 10-µg booster dose for the mRNA-1283.222 bivalent vaccine (contains equal amount of the ancestral SARS-CoV-2 and Omicron BA.4/5 variant) as a dose with a favourable safety and reactogenicity profile for pivotal study P301.

For dose selection studies P101 and P201 no results are discussed that conclusively support the choice of 10 µg dose for the pivotal study P301. The CSRs for studies P101 and P201 provide immunogenicity results for the respective doses. It should be noted that in studies P101 and P201 only the dose of 10µg was in common. While immunogenicity results from study P101 do not demonstrate a dose response with increasing doses (10 µg, 30 µg, 100 µg), immunogenicity results from study P201 favour the 10-µg dose for mRNA-1283. Again, in study P201, immunogenicity results for mRNA-1283.211 do not show a clear dose response at an increase from 5 µg to 10 µg. The applicant further justified the choice of the 10-µg dose mRNA-1283 and its derivatives in the application for MA based on a balance of reactogenicity and immunogenicity results.

The development plan in principle supports the proposed indication.

Participant Flow

The number and reasons for drop-outs are overall similar in both vaccine groups. However, it is noted that in tendency more intercurrent events / drop-outs occurred in the mRNA-1283 arm across all categories. This sums up to 55 subjects difference between the arms. Given the overall sample size

this is a very small fraction of 0.5% of all randomised subjects. Despite these systematic differences a meaningful impact is hence not expected.

The study vaccine for study P301 aligned with the 2022/2023 variant formulation recommended by the US FDA and by the WHO (original SARS-CoV-2: Omicron BA.4/BA.5 bivalent) because study enrollment occurred March through August 2023.

Participants were randomised 1:1 to receive mRNA-1283.222 10 µg (original SARS-CoV-2: Omicron BA.4/BA.5) or mRNA-1273.222 50 µg (original SARS-CoV-2: Omicron BA.4/BA.5) as a single dose. Randomisation was stratified by age groups. The essential demographics were balanced.

For the primary rVE analysis, COVID-19 was defined based on the virologic confirmation via PCR of SARS-CoV-2 infection together with the presence of at least 1 clinical symptom consistent with COVID-19 (CDC 2024).

The primary rVE objective in Study P301 to demonstrate the noninferiority of the vaccine efficacy of mRNA-1283 compared to mRNA-1273 in preventing the first event of COVID-19 starting 14 days after study vaccination (the null hypothesis H_0: rVE ≤-10%) is acceptable.

Overall non-inferiority of mRNA-1283.222 in terms of rVE (9.31 (95% CI: -6.58, 22.83)) could be demonstrated.

An analysis of rVE was also performed using the secondary protocol defined COVID-19 case definition (at least two clinical symptoms and PCR confirmed SARS-CoV-2 infection). Based on this definition, there were 498 COVID-19 cases (8.8%) in the mRNA-1283 group, and 556 cases (9.8%) in the mRNA-1273 group through 31 Jan 2024. The relative vaccine efficacy based on the hazard ratio was 10.5% with the 95% CI being (-1.01, 20.69). An analysis based on cases with the secondary COVID-19 definition through 23 Feb Jan 2024 (546 COVID-19 cases in the mRNA-1283 group, and 599 cases in the mRNA-1273 group) yielded similar results with an rVE of 8.92% (95% CI:-2.27, 18.9). Thus, similar results were achieved with both COVID-19 definitions, which is reassuring.

The relevance and interpretability of the relative vaccine efficacy between mRNA-1283 and mRNA-1273 was questioned. As the Applicant proposed to include rVE data in the SmPC section 5.1, an estimate of vaccine efficacy of the test vaccine mRNA-1283.222 was requested to interpret rVE and contextualize corresponding margins. The Applicant provided a plot depicting cumulative enrolment by arm, cumulative case accrual, and predominantly circulating variants over calendar time. The enrolment by arm was nearly identical over time. Further, from the provided case accrual over time it does not seem that a specific circulating variant led to a disproportional increase in cases. This indicates that the used vaccines were similarly efficacious independent of predominantly circulating SARS-CoV-2 variants. Additionally, the Applicant provided a correlate of protection model based on the mRNA-1283-P301 study. From the provided CoP report, the Applicant calculated a predicted vaccine efficacy of 37.1% (30.3%, 44.2%) by the PsV-nAb against BA.4/BA.5 and 44.4% (38.7%, 50.7%) by the PsV-nAb against XBB.1.5 for the mRNA-1273.222 vaccine. The provided report does not allow a direct comparison of the expected efficacy of the .222 vaccine and the .815 vaccine, as the latter was not included in the report. However, the predicted vaccine efficacy by PsV-nAb against BA.4/BA.5 and XBB.1.5 was similar, indicating that the .222 vaccine would have provided relevant protection against XBB-lineage variants, which were pre-dominant during the study period. Furthermore, the Applicant provided literature describing the vaccine effectiveness of bivalent mRNA COVID-19 vaccine in three observational studies to further contextualize the rVE data generated in study mRNA-1283-P301. From the provided publications (Link-Gelles et al. 2023; Plumb et al. 2024; DeCuir et al. 2024), it can be assumed that the bivalent mRNA-1273.222 vaccine provided relevant protection against symptomatic XBB/XBB.1.5 infection and COVID-19 associated hospitalization at the time the mRNA-1283-P301

study was conducted. Thus, it is acceptable that the derived rVE efficacy data from study mRNA-1283-P301 can be depicted in the SmPC.

Whenever the FAS is not the primary analysis set, there should be a pre-planned secondary analysis conducted in all randomised subjects who received at least one dose of assigned treatment (EMEA/CHMP/VWP/164653/05 Rev. 1). An analysis based on the FAS with an rVE of 7.47% (95% CI: -3.28, 17.09) also showed consistent results supporting the primary rVE analysis.

As per the SAP, a sensitivity analysis was foreseen according to which early COVID-19 cases (starting after study injection to <14 Days after injection) were to be considered as event. The Applicant provided upon request, this sensitivity analysis including early COVID-19 events (starting after study injection to <14 Days after injection) which is less pronounced but consistent with the primary analysis of rVE. This analysis supports the primary analysis.

The Applicant performed several pre-defined rVE subgroup analyses. Subgroup analyses by age revealed that the rVE based on hazard ratio was -29.17% (95% CI: -123.27, 25.27) in the ≥12 to <18 years group, 9.66% (95% CI: -3.75, 21.34) in the ≥18 to <65 years group and 13.54% (95% CI: -7.67, 30.57) in the ≥65 years group. Thus, the rVE seems to be lower in the youngest age group compared to the other age groups. However, this might also be due to the lower number of subjects in this age group (491 subjects in the mRNA-1283 and 490 subjects in the mRNA-1273 groups) and the lower number of infections in this age group (29 cases (5.9%) in the mRNA-1283 group and 23 cases (4.7%) in the mRNA-1273 group). Of note, the immunogenicity results for all subgroups are convincing.

It is considered unlikely that adolescents do not benefit from vaccination with mRNA-1283.222 as vaccination with mRNA-1273.222 already provides substantial protection in adolescents.

Subgroup analyses based on prior SARS-CoV-2 infection revealed that the rVE based on the hazard ratio was 6.53% (95% CI: -8.09, 19.16) in participants with a history of prior SARS-CoV-2 infection and 18.88% (95% CI: 1.85, 32.95) in participants without a history of prior SARS-CoV-2 infection. Thus, the rVE seems to be higher in the subjects with a prior COVID-19 infection. However, in both subgroups, the non-inferiority criteria applied for the primary analysis would have been met and no concern arises.

The evaluation of severe COVID-19 as a secondary endpoint was only foreseen for part 2 of Study P301. However, as it is stated in the protocol, clinical information was collected to evaluate the severity of the clinical case and thus information should be available. Therefore, the applicant was asked to provide an analysis on the incidence of severe COVID-19 for both groups in part 1 of the study, similar as it would have been foreseen for part 2 of the study. The applicant provided the requested analysis on severe COVID-19 disease for Part 1 of the study. Until 31 Jan 2024 there have been 55 severe COVID-19 cases, with 21 severe cases in the mRNA-1283 group and 34 cases in the mRNA-1273 group. The calculated rVE of mRNA-1283 versus mRNA-1273 against severe COVID-19 was 38.06% (-6.7%, 64.05%). An analysis with a later data cutoff (23 Feb 2024) yielded similar results.

For the analyses of the co-primary immunogenicity endpoints of the GMR at Day 29, participants' data due to major protocol deviations and evaluability issues were excluded. Upon request, the applicant performed a multiple imputation approach under MAR assumption in addition to tipping-point analyses, to include all subjects in the immunogenicity subset, considering a wide range of penalties (reductions) for the mRNA-1283 group or inflations (additions) for the imputed values in the mRNA-1273 group. Tipping-point analyses supported the primary conclusions.

Further, the secondary immunogenicity endpoints "Omicron BA.4/5 and ancestral SARS-CoV-2 D614G GMs at all planned timepoints (Days 91, 181, 365)" were requested. The applicant provided the GMC

of the neutralising antibodies against Omicron BA.4/5 and ancestral SARS-CoV-2 D614G for day 91 and day 181. Compared to day 29, there was a decline in antibody titres over time. However, the GMCs were well above baseline and the mRNA-1283.222/ mRNA-1273.222 ratio was similar for all time points. This is reassuring. The applicant further stated that the day 365 immunogenicity results will be presented with the final CSR post-approval. This is acceptable.

Further subgroup analysis, based on number of booster doses prior to entry, showed that the relative vaccine efficacy seems to be lower in the participants with 1 prior booster dose. In participants with 1 prior booster dose the hazard ratio-based rVE was -8.77% (95% CI: -34.60, 12.11), in participants with 2 prior booster doses the hazard ratio-based rVE was 19.00% (95% CI: 2.31, 32.84) and in participants with ≥3 prior booster doses the hazard ratio-based rVE was 11.59% (95% CI: -8.19, 27.75). Again, as immunogenicity results for all subgroups are convincing, no concern arises from these analyses.

Phase 3 study P301 – Japan specific amendment

The Applicant made country-specific protocol amendment to evaluate the safety and immunogenicity of mRNA-1283.815 (XBB.1.5 variant) in a cohort of 692 Japanese participants aged 12 years and older. The comparator vaccine in this study was the approved mRNA-1273.815 (full-length Spike protein of the XBB.1.5 variant). The study was initiated on 15 Mar 2024. An interim analysis based on a data cutoff date of 02 May 2024 (at least 29 days FU for each participant) is provided. However, due to the early cut-off, most of the secondary endpoint analyses were not yet available. The Applicant explained that the final CSR from the P301-Japan study is under preparation and will be submitted as a variation procedure post-approval, which is regarded acceptable.

The immune responses measured in the pivotal study P301 and its local sub study P301-Japan (supportive) show a better GM increase of the new vaccine compared to the originally authorised vaccine. The baseline GMs against each strain variant are similar in the vaccination groups but the new vaccine not only formally fulfils the NI but often shows a significantly higher fold-increase than the comparator. With the new vaccine all age groups show similar immune responses, especially the elderly age group shows now even better immune responses than the younger adults. Adolescents show the highest immune responses compared to the adult age groups. The fold-increases are similar across all vaccine strain variants tested (D614G, BA4/5 and XBB1.5).

2.5.7. Conclusions on the clinical efficacy

For study mRNA-1283-P301 the co-primary objectives on rVE and immunogenicity have overall been met. Uncertainties regarding the blinding procedures (e.g. late specification of blinding and communication plans) and issues with the conduct of study (including the late definition of the adaptive design and uncertainties regarding the timing) impact the reliability of the results to some extent. Overall, it is considered that due to the magnitude of the effect and the limited impact of these issues non-inferiority was demonstrated.

Descriptive Phase 1/2 studies showed that vaccination with 10 µg of mRNA-1283 (monovalent D614G) or mRNA1283.211 (bivalent D614G and Beta) elicits neutralising GMTs against D614G, Beta and Omicron BA.1 that are comparable to titres after vaccination with the full-length spike comparator vaccine mRNA-1273.

In the randomised, observer-blind, multicentre, active-controlled, 2-arm, Phase 3 study mRNA-1283-P301, it has been shown that mRNA-1283.222 (bivalent ancestral and Omicron BA.4/5 vaccine) is non-inferior to mRNA-1273.222 in terms of relative efficacy and immunogenicity. Further, in the Japan specific amendment of the Phase 3 study, it has been shown that the immune response elicited by

mRNA-1283.815 (monovalent XBB.1.5 vaccine) is non-inferior to the immune response generated by mRNA-1273.815.

2.5.8. Clinical safety

Safety data is based primarily on results from 1 pivotal study (Study P301) and 2 supportive studies (Study P201 and P101). It includes a safety database of over 6200 participants who have received at least 1 injection of mRNA-1283 (including the original and 3 variant formulations: mRNA-1283.211, mRNA-1283.222, or mRNA-1283.529) at any dose.

The key source of safety data was the pivotal active-controlled Phase 3 safety and efficacy Study P301, based on analysis performed after all participants had a minimum of 6 months follow-up time on study (data cutoff date of 23 Feb 2024). In this multicentre study (US, UK, Canada), the majority of participants were enrolled in the US (N=8664), followed by the UK (N=2575) and Canada (N=215).

Pooled summaries were not provided as they would differ only marginally from the Study P301 safety analyses. Additionally, pooling of safety data has not been provided due to differing vaccine formulations, dosing schedules, and study populations across the 3 clinical studies.

Solicited ARs were collected via eDiary up to Day 7 post-injection, using standard definitions. Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to the grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Four in-person follow-up visits after Day 1 were planned (Day 29, Day 91, Day 181, and Day 365) as well as 3 scheduled safety phone calls. For safety assessments unsolicited AEs were recorded up to 28 days after injection. MAAEs, AESIs, and AEs leading to discontinuation were recorded from Day 1 through the end of study. In Study P301, SAEs were collected from informed consent through the end of study while in Study P101 and Study P201, SAEs were collected from Day 1 and throughout available follow-up in all studies.

In the event of an off-study COVID-19 vaccine use during the study, participant AE data were censored after the off-study COVID-19 vaccination. Among those participants who received off-study vaccines and had reported adverse events, the off-study vaccines were administered between Day 61 and Day 291 relative to the study vaccine. All AEs occurring after off-study vaccinations were reported between Day 76 and Day 306 after study vaccine. Numbers of AEs in this report are based on the censored data, unless otherwise stated.

An ongoing phase 3 Japan-specific study in Japanese participants 12 years and older is included in the submission (CSR Addendum P301). Vaccine-variant is Omicron XBB.1.5 (mRNA-1283.815) as recommended for the 2023/2024 vaccination season. Reactogenicity and Safety are Primary Objectives, and an Interim-Report for at least 29 days of follow-up has been provided. 689 Participants were vaccinated: 343 received mRNA-1283.815 and 346 received mRNA-1273.815.

2.5.8.1. Patient exposure

In Study P301, 11,417 participants received a single study injection in the primary analysis with 5706 participants receiving mRNA-1283.222 10 µg and 5711 participants receiving mRNA-1273.222 50 µg (Table 23).

Table 23. Patient Exposure

Study	Placebo	Active Comparator mRNA-1273	Active Comparator mRNA-1273.222	mRNA-1283 ≤5 µg	mRNA-1283 10 µg	mRNA-1283 30 µg	mRNA-1283 100 µg	mRNA-1283.529 ≤5 µg	mRNA-1283.529 10 µg	mRNA-1283.211 5 µg	mRNA-1283.211 10 µg	mRNA-1283.222 10 µg	Total
mRNA-1283-P301 (23 Feb 24)													
			5711									**5706**	**5706**
mRNA-1283-P201													
Part A		57		121[a]	56					52	54		283
Part B								103	97				200
mRNA-1283-P101													
First vaccination	18	22			21	22	21						64
Second vaccination		(20)[b]			(19)[b]	(20)[b]	(21)[b] +15						15
Total (any dose)	**18**	**79**	**5711**	**121[a]**	**77**	**22**	**36**	**103**	**97**	**52**	**54**	**5706**	**6268**

Abbreviations: COVID-19 = coronavirus disease 2019; CSR = clinical study report; mRNA = messenger ribonucleic acid.
NOTE: For ease of review, refer to Module 2.2 for an overall Summary of mRNA-1283 Products (COVID-19 strains and Corresponding mRNA-1283 Components and Process by Study) used during the development of mRNA-1283. Further, Module 2.2 includes a Summary of the Applicant's Variant Monitoring Program.
[a.] Includes 57 participants who received mRNA-1283 2.5 µg and 63 participants who received mRNA-1283 5 µg.
[b.] Booster doses were not counted in the total column when they were a second exposure to mRNA-1283.
Source: Study P301 CSR Table 14.1.1.5, Study P201 CSR Table 14.1.2.1.1 and Table 14.1.2.1.2, Study P101 CSR Table 14.1.6.

The median follow-up duration for the pivotal study P301 follow-up was 8.772 months, with 11114 (97.3) having at least 6 months of follow-up and 7862 (68.9) having 8 months. Participant's age-distribution is presented in 5 age-groups. 91.3% of participants are adults, 8.7% of participants are between 12 and 18 years of age. The age-group ≥75 years represents 5.6% and 4.7% of participants. A summary of study duration and participants characteristics as of the data cutoff date (23 Feb 2024) is presented below Table 24.

Table 24. Characteristics and Follow-up of Participants Exposed to Study Vaccine (Safety Set)

	mRNA-1283 10 µg (N= 5706)	mRNA-1273 50 µg (N=5711)	Total (N=11417)
Age (years) Mean (SD)	51.1 (18.58)	51.2 (18.32)	51.2 (18.45)
Median	56.0	55.0	56.0

Q1, Q3	38.0, 66.0	39.0, 66.0	38.0, 66.0
Min, Max	12, 96	12, 90	12, 96
Age group, n (%) ≥12 to <18 years	497 (8.7)	495 (8.7)	992 (8.7)
≥18 Years	5209 (91.3)	5216 (91.3)	10425 (91.3)
≥18 to <65 years	3575 (62.7)	3576 (62.6)	7151 (62.6)
≥65 years	1634 (28.6)	1640 (28.7)	3274 (28.7)
≥75 years	322 (5.6)	269 (4.7)	591 (5.2)
Body Mass Index (kg/m^2)			
N	5644	5645	11289
Mean (SD)	29.45 (7.167)	29.50 (7.331)	29.47 (7.249)
Median	28.30	28.30	28.30
Q1, Q3	24.40, 33.30	24.40, 33.30	24.40, 33.30
Min, Max	14.4, 81.9	14.6, 76.7	14.4, 81.9
Body Mass Index Group, n (%)			
<30 kg/m^2	3338 (58.5)	3372 (59.0)	6710 (58.8)
≥30 kg/m^2	2306 (40.4)	2273 (39.8)	4579 (40.1)
≥40 kg/m^2	451 (7.9)	489 (8.6)	940 (8.2)
Missing	62 (1.1)	66 (1.2)	128 (1.1)
Time on study (months)[a] Mean (SD)	8.505 (1.5200)	8.546 (1.4589)	8.526 (1.4899)
Median	8.772	8.772	8.772
Q1, Q3	7.688, 9.528	7.721, 9.528	7.688, 9.528
Min, Max	0.07, 10.68	0.23, 11.01	0.07, 11.01
Number of participants, n (%) ≥28 Days since injection	5695 (99.8)	5703 (99.9)	11398 (99.8)
≥3 Months since injection	5629 (98.7)	5654 (99.0)	11283 (98.8)
≥6 Months since injection	5540 (97.1)	5574 (97.6)	11114 (97.3)
≥8 Months since injection	3908 (68.5)	3954 (69.2)	7862 (68.9)
≥10 Months since injection	878 (15.4)	896 (15.7)	1774 (15.5)
Person-years from injection[b]	4044.12	4067.29	8111.41

Person-months from injection[b]	48529.41	48807.49	97336.90

Abbreviations: Q = quartile; SD = standard deviation.
Note: Numbers were based on actual study injection received and percentages were based on the number of participants in the Safety Set.
Time on study in months was defined as [end of study date for discontinued participants or data cutoff date for ongoing study participants – study drug injection date +1]/30.4375.
Person-years was defined as the total years (months) of participants' time on study. One year=365.25 days.
Source: Summary Module 2.7.4.

2.5.8.2. Adverse events

Reactogenicity

Study P301

Solicited Adverse Reactions were similar for mRNA -1283 10µg and mRNA-1273 50µg with 80.2 vs 83.8% affected participants, overall, with slightly lower numbers for mRNA-1283.

Local ARs were reported in 70.3 vs 78.4% of participants in the mRNA-1283 and mRNA-1273 groups respectively. In decreasing frequency, Injection site pain (68.5 vs 77.5%), Axillary swelling/tenderness (19.7 vs 18.4%), Erythema (2.2 vs 3.9%) and Swelling/Hardness (3.6 vs 6.3%) were reported.

Frequency of systemic solicited ARs was overall 64.4 vs 64.2% of participants in the mRNA-1283 and mRNA-1273 groups respectively. At the PT level, the frequency of events was higher in the mRNA-1283-222 group. In decreasing frequency, Fatigue (50.4 vs 49.0%), Headache (44.2 vs 41.2%), Myalgia (38.2 vs 37.0%), Arthralgia (29.7 vs 27.6%), Chills (22.7 vs 19.8%), Nausea/Vomiting (12.1 vs 11.0%), and Fever (5.6 vs 4.5%) were reported. A summary of solicited ARs within 7 days of injection is provided in Table 25.

Most frequent onset was within 1 or 2 days, duration was short and between 1 and 4 days, similar for both cohorts. Only 1.4% persisted beyond 7 Days in the mRNA-1283 group compared to 1.3% in the mRNA-1273 group. A summary of day of onset for solicited ARs is presented in Table 26 , and a summary of the duration of solicited ARs within 7 days after study vaccination is presented in Table 27. Most of the solicited ARs were of Grade 1 and Grade 2 intensity in both groups. Grade 3 events were infrequent (approximately 0.1–8% for all PTs) and Grade 4 events were absent in the mRNA-1283-222 group.

Table 25. Summary of Participants with Solicited Adverse Reactions Within 7 Days After Injection by Grade (Solicited Safety Set)

	Number (%) of Participants	
Solicited Adverse Reactions Category Grade	**mRNA-1283 10 µg (N=5702)**	**mRNA-1273 50 µg (N=5706)**
Solicited Adverse Reactions - N1	**5702**	**5706**
Any Solicited Adverse Reactions	4571 (80.2)	4781 (83.8)
95% CI	(79.1, 81.2)	(82.8, 84.7)
Grade 1	2133 (37.4)	2235 (39.2)
Grade 2	1982 (34.8)	2149 (37.7)
Grade 3	456 (8.0)	396 (6.9)
Grade 4	0	1 (0.02)
Solicited Local Adverse Reactions-N1	**5701**	**5705**
Any Solicited Local Adverse Reactions	4007 (70.3)	4473 (78.4)
95% CI	(69.1, 71.5)	(77.3, 79.5)

	Number (%) of Participants	
Solicited Adverse Reactions Category Grade	**mRNA-1283 10 µg (N=5702)**	**mRNA-1273 50 µg (N=5706)**
Grade 1	2816 (49.4)	2829 (49.6)
Grade 2	1099 (19.3)	1522 (26.7)
Grade 3	92 (1.6)	122 (2.1)
Grade 4	0	0
Pain - N1	5701	5705
Any	3905 (68.5)	4419 (77.5)
Grade 1	2847 (49.9)	2902 (50.9)
Grade 2	998 (17.5)	1442 (25.3)
Grade 3	60 (1.1)	75 (1.3)
Grade 4	0	0
Erythema (Redness) - N1	5701	5705
Any	123 (2.2)	225 (3.9)
Grade 1	76 (1.3)	123 (2.2)
Grade 2	36 (0.6)	78 (1.4)
Grade 3	11 (0.2)	24 (0.4)
Grade 4	0	0
Swelling (Hardness) - N1	5701	5705
Any	206 (3.6)	359 (6.3)
Grade 1	128 (2.2)	223 (3.9)
Grade 2	62 (1.1)	104 (1.8)
Grade 3	16 (0.3)	32 (0.6)
Grade 4	0	0
Axillary Swelling or Tenderness – N1	5701	5705
Any	1123 (19.7)	1047 (18.4)
Grade 1	826 (14.5)	780 (13.7)
Grade 2	278 (4.9)	248 (4.3)
Grade 3	19 (0.3)	19 (0.3)
Grade 4	0	0
Solicited Systemic Adverse Reactions – N1	**5702**	**5706**
Any Solicited Systemic Adverse Reactions	3672 (64.4)	3664 (64.2)
95% CI	(63.1, 65.6)	(63.0, 65.5)
Grade 1	1521 (26.7)	1637 (28.7)
Grade 2	1743 (30.6)	1697 (29.7)
Grade 3	408 (7.2)	329 (5.8)
Grade 4	0	1 (0.02)
Fever - N1	5697	5699
Any	317 (5.6)	254 (4.5)
Grade 1	187 (3.3)	165 (2.9)
Grade 2	97 (1.7)	60 (1.1)
Grade 3	33 (0.6)	28 (0.5)
Grade 4	0	1 (0.02)
Headache - N1	5702	5705
Any	2519 (44.2)	2349 (41.2)

	Number (%) of Participants	
Solicited Adverse Reactions Category Grade	**mRNA-1283 10 µg (N=5702)**	**mRNA-1273 50 µg (N=5706)**
Grade 1	1346 (23.6)	1354 (23.7)
Grade 2	1026 (18.0)	877 (15.4)
Grade 3	147 (2.6)	118 (2.1)
Grade 4	0	0
Fatigue - N1	5701	5705
Any	2876 (50.4)	2798 (49.0)
Grade 1	1256 (22.0)	1319 (23.1)
Grade 2	1357 (23.8)	1260 (22.1)
Grade 3	263 (4.6)	219 (3.8)
Grade 4	0	0
Myalgia - N1	5701	5706
Any	2178 (38.2)	2114 (37.0)
Grade 1	1021 (17.9)	1065 (18.7)
Grade 2	952 (16.7)	900 (15.8)
Grade 3	205 (3.6)	149 (2.6)
Grade 4	0	0
Arthralgia - N1	5701	5705
Any	1696 (29.7)	1577 (27.6)
Grade 1	889 (15.6)	860 (15.1)
Grade 2	687 (12.1)	628 (11.0)
Grade 3	120 (2.1)	89 (1.6)
Grade 4	0	0
Nausea/Vomiting - N1	5701	5706
Any	691 (12.1)	625 (11.0)
Grade 1	503 (8.8)	474 (8.3)
Grade 2	182 (3.2)	141 (2.5)
Grade 3	6 (0.1)	10 (0.2)
Grade 4	0	0
Chills - N1	5701	5705
Any	1293 (22.7)	1127 (19.8)
Grade 1	677 (11.9)	615 (10.8)
Grade 2	574 (10.1)	481 (8.4)
Grade 3	42 (0.7)	31 (0.5)
Grade 4	0	0

Abbreviations: CI = confidence interval; N1 = Number of exposed subjects who submitted any data for the event.
Note: Any = Grade 1 or higher.
Note: Percentages are based on the number of exposed subjects who submitted any data for the event (N1).
Note: 95% CI is calculated using the Clopper-Pearson method.
Source: Summary Module 2.7.4 Table 14

Table 26. Study P301: Summary of Day of Onset of Solicited Adverse Reactions (Solicited Safety Set)

Solicited Adverse Reactions	Number (%) of Participants	
Category	mRNA-1283.222 10 µg	mRNA-1273.222 50 µg
Statistics	(N=5702)	(N=5706)
Any solicited adverse reactions - N1	**5702**	**5706**
Any, n (%)	4571 (80.2)	4781 (83.8)
Day of onset		
Mean (SD)	1.7 (0.84)	1.6 (0.77)
Median	2.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7
Any solicited local adverse reactions - N1	**5701**	**5705**
Any, n (%)	4007 (70.3)	4473 (78.4)
Day of onset		
Mean (SD)	1.8 (0.78)	1.6 (0.68)
Median	2.0	2.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 6
Any solicited systemic adverse reactions - N1	**5702**	**5706**
Any, n (%)	3672 (64.4)	3664 (64.2)
Day of onset		
Mean (SD)	2.0 (1.03)	1.9 (1.08)
Median	2.0	2.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7

Abbreviations: CSR = clinical study report; N1 = Number of exposed participants who submitted any data for the event; n = Number of exposed participants who reported the event on any day within 7 days of the first injection; Q = quartile; SD = standard deviation.
Percentages were based on the number of exposed participants who submitted any data for the event (N1).
Source: Study P301 CSR Table 14.3.1.1.3.1.

Table 27. Duration of Solicited Adverse Reactions Within 7 Days After Study Vaccination (Solicited Safety Set)

Solicited Adverse Reactions Category Statistics	mRNA-1283.222 10 µg (N=5702)	mRNA-1273.222 50 µg (N=5706)
Any Solicited Adverse Reactions - N1	5702	5706
Any, n (%)	4571 (80.2)	4781 (83.8)
Duration (Days)		
Mean (SD)	3.7 (5.71)	3.6 (3.77)
Median	3.0	3.0
Q1, Q3	2.0, 5.0	2.0, 5.0
Min, Max	1, 203	1, 155
Persisted Beyond 7 Days, n (%)	81 (1.4)	75 (1.3)
Any Solicited Local Adverse Reactions - N1	5701	5705
Any, n (%)	4007 (70.3)	4473 (78.4)
Duration (Days)		
Mean (SD)	2.7 (1.82)	2.8 (1.75)
Median	2.0	3.0
Q1, Q3	1.0, 4.0	2.0, 4.0
Min, Max	1, 38	1, 52
Persisted Beyond 7 Days, n (%)	27 (0.5)	23 (0.4)
Any Solicited Systemic Adverse Reactions -N1	5702	5706
Any, n (%)	3672 (64.4)	3664 (64.2)
Duration (Days)		
Mean (SD)	3.3 (6.26)	3.1 (4.15)
Median	2.0	2.0
Q1, Q3	1.0, 4.0	1.0, 4.0
Min, Max	1, 203	1, 155
Persisted Beyond 7 Days, n (%)	59 (1.0)	59 (1.0)

Abbreviations: N1 = Number of exposed participants who submitted any data for the event; n = Number of exposed participants who reported the event on any day within 7 days of the first study vaccination; Q = quartile; SD = standard deviation.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Duration is calculated as the last day – the first day + 1 when the solicited adverse reaction was reported starting within the 7 days of study vaccination; for solicited adverse reactions not resolved, duration is calculated using the earlier of (Date of study vaccination + 28, data cutoff date, end of study date, date of off-study COVID-19 vaccine use or death).
Source: Study P301 CSR Table 14.3.1.1.3.1

Japanese-Study (P301 Addendum Japan)

Solicited Adverse Reaction were similar for mRNA -1283 10µg and mRNA-1273 50µg with 89.5 vs 95.7% affected participants, overall.

Local ARs were reported in 86.3 vs 95.1%. In decreasing frequency, Injection site pain (84.8 vs 94.5%), Axillary swelling/tenderness (24.5 vs 26.0%), Swelling/Hardness (9.3 vs 14.7%), and Erythema (3.8 vs 11.0%) were reported.

Frequency of systemic solicited ARs was overall 59.8 vs 76.9%. In decreasing frequency, Fatigue (51.0 vs 63.6%), Headache (42.6 vs 56.1%), Myalgia (35.0 vs 39.9%), Arthralgia (31.8 vs 36.1%), Chills (21.0 vs 31.5%), Nausea/Vomiting (7.9 vs 9.0%), and Fever (7.0 vs 12.7%) were reported.

Most frequent onset was within 1 or 2 days, duration was between 2 and 4 vs 5 days, similar for both cohorts.

Unsolicited Adverse Events

Study P301

Unsolicited AEs were also similar for mRNA -1283 10µg and mRNA-1273 50µg, with an overall frequency of 12.3 vs 11.9% within 28 day, and 36.8 vs 35.8% until data cutoff.

Most frequently reported AEs until 28 days and until data cutoff were in the infections and infestations SOC (refer to Table 30). Although less frequent, 16 reports (2 related) of "immune system disorders", 59 nervous system disorders (7 related) are considered to be of interest. Urticaria was reported in five participants in the mRNA-1283 group versus one in the control group.

In the SOC "Reproductive system and breast disorders" up to 28 days post-injection 11 events (0.2%) were reported in the mRNA-1283 group compared with 7 events (0.1%) in the other.

A summary of unsolicited AEs up to 28 days after study injection is presented in Table 28.

Table 28. Study P301: Summary of Unsolicited Adverse Events Up to 28 Days After Study Injection (Safety Set)

	mRNA-1283.222 10 µg (N=5706)		**mRNA-1273.222 50 µg (N=5711)**	
	Any	Related	Any	Related
All	701 (12.3)	45 (0.8)	680 (11.9)	51 (0.9)
Serious	13 (0.2)	1 (0.02)	18 (0.3)	1 (0.02)
Fatal	0	0	1 (0.02)	1 (0.02)
Medically Attended	425 (7.4)	9 (0.2)	422 (7.4)	12 (0.2)
Leading to Study Discontinuation	0	0	1 (0.02)	1 (0.02)
Severe	13 (0.2)	3 (0.05)	18 (0.3)	2 (0.04)

Abbreviations: CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Numbers were based on actual vaccine received and percentages were based on the number of participants in the Safety Set.
MedDRA version 26.1.
Source: Study P301 CSR Table 14.3.1.2.1.1.

Table 29. Study P301: Overall Summary of Unsolicited Adverse Events Up to Data Cutoff Date (Safety Set)

	mRNA-1283.222 10 µg (N=5706)		**mRNA-1273.222 50 µg (N=5711)**	
	Any	Related	Any	Related
All	2100 (36.8)	48 (0.8)	2046 (35.8)	52 (0.9)
Serious	156 (2.7)	2 (0.04)	151 (2.6)	1 (0.02)
Fatal	5 (0.09)	0	10 (0.2)	1 (0.02)
Medically Attended	1932 (33.9)	12 (0.2)	1883 (33.0)	13 (0.2)
Leading to Study Discontinuation	8 (0.1)	0	12 (0.2)	1 (0.02)
Severe	129 (2.3)	4 (0.07)	133 (2.3)	2 (0.04)

Abbreviations: CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Numbers were based on actual vaccine received and percentages were based on the number of participants in the Safety Set.
MedDRA version 26.1.

Source: Study P301 CSR Table 14.3.1.2.1.2.

Table 30. Study P301: Incidence of Unsolicited Adverse Events by System Organ Class and Preferred Term up to 28 Days After Study injection Occurring in ⩾0.1% of Participants (Safety Set)

System Organ Class	mRNA-1283.222 10 µg (N=5706)		mRNA-1273.222 50 µg (N=5711)	
Preferred Term	Any	Related	Any	Related
Number of participants reporting an unsolicited AE	701 (12.3)	45 (0.8)	680 (11.9)	51 (0.9)
Number of unsolicited AEs	909	56	911	53
Infections and infestations	238 (4.2)	0	229 (4.0)	4 (0.07)
Upper respiratory tract infection	81 (1.4)	0	88 (1.5)	1 (0.02)
Urinary tract infection	14 (0.2)	0	19 (0.3)	0
Viral upper respiratory tract infection	14 (0.2)	0	6 (0.1)	0
Nasopharyngitis	11 (0.2)	0	16 (0.3)	0
Respiratory tract infection viral	10 (0.2)	0	4 (0.07)	0
Bronchitis	6 (0.1)	0	6 (0.1)	0
Conjunctivitis	6 (0.1)	0	3 (0.05)	0
Ear infection	6 (0.1)	0	4 (0.07)	0
Rhinitis	6 (0.1)	0	2 (0.04)	0
Blood and lymphatic system disorders	9 (0.2)	4 (0.07)	10 (0.2)	5 (0.09)
Lymphadenopathy	5 (0.09)	4 (0.07)	8 (0.1)	5 (0.09)
Immune system disorders	16 (0.3)	2 (0.04)	9 (0.2)	0
Seasonal allergy	9 (0.2)	0	9 (0.2)	0
Psychiatric disorders	27 (0.5)	1 (0.02)	23 (0.4)	0
Anxiety	8 (0.1)	0	7 (0.1)	0
Attention deficit hyperactivity disorder	6 (0.1)	0	1 (0.02)	0
Depression	6 (0.1)	0	3 (0.05)	0
Nervous system disorders	59 (1.0)	7 (0.1)	67 (1.2)	8 (0.1)
Headache	15 (0.3)	1 (0.02)	25 (0.4)	1 (0.02)
Dizziness	9 (0.2)	1 (0.02)	8 (0.1)	2 (0.04)
Migraine	2 (0.04)	1 (0.02)	6 (0.1)	0
Cardiac disorders	13 (0.2)	1 (0.02)	11 (0.2)	1 (0.02)
Palpitations	7 (0.1)	1 (0.02)	2 (0.04)	1 (0.02)
Vascular disorders	19 (0.3)	0	25 (0.4)	1 (0.02)
Hypertension	16 (0.3)	0	22 (0.4)	1 (0.02)
Respiratory, thoracic and mediastinal disorders	74 (1.3)	3 (0.05)	76 (1.3)	3 (0.05)
Oropharyngeal pain	21 (0.4)	1 (0.02)	22 (0.4)	1 (0.02)
Cough	13 (0.2)	2 (0.04)	24 (0.4)	1 (0.02)
Nasal congestion	11 (0.2)	1 (0.02)	12 (0.2)	0
Respiratory disorder	7 (0.1)	0	2 (0.04)	0
Rhinorrhoea	6 (0.1)	0	15 (0.3)	0
Asthma	5 (0.09)	0	6 (0.1)	0
Gastrointestinal disorders	52 (0.9)	7 (0.1)	57 (1.0)	7 (0.1)
Diarrhoea	18 (0.3)	6 (0.1)	17 (0.3)	4 (0.07)
Gastroesophageal reflux disease	8 (0.1)	0	4 (0.07)	0
Nausea	6 (0.1)	1 (0.02)	2 (0.04)	0

System Organ Class Preferred Term	mRNA-1283.222 10 µg (N=5706) Any	 Related	mRNA-1273.222 50 µg (N=5711) Any	 Related
Skin and subcutaneous tissue disorders	36 (0.6)	9 (0.2)	41 (0.7)	2 (0.04)
Rash	7 (0.1)	2 (0.04)	7 (0.1)	1 (0.02)
Dermatitis contact	2 (0.04)	0	6 (0.1)	0
Musculoskeletal and connective tissue disorders	85 (1.5)	1 (0.02)	81 (1.4)	4 (0.07)
Arthralgia	20 (0.4)	0	16 (0.3)	1 (0.02)
Back pain	16 (0.3)	0	14 (0.2)	0
Osteoarthritis	9 (0.2)	0	7 (0.1)	0
Pain in extremity	9 (0.2)	0	4 (0.07)	0
Myalgia	6 (0.1)	0	5 (0.09)	1 (0.02)
General disorders and administration site conditions	52 (0.9)	12 (0.2)	45 (0.8)	10 (0.2)
Fatigue	11 (0.2)	2 (0.04)	14 (0.2)	0
Pyrexia	6 (0.1)	0	3 (0.05)	0
Investigations	18 (0.3)	4 (0.07)	15 (0.3)	2 (0.04)
Blood pressure increased	7 (0.1)	1 (0.02)	7 (0.1)	2 (0.04)
Injury, poisoning and procedural complications	59 (1.0)	0	61 (1.1)	0
Fall	8 (0.1)	0	5 (0.09)	0
Arthropod bite	6 (0.1)	0	6 (0.1)	0
Contusion	6 (0.1)	0	2 (0.04)	0

Abbreviations: AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Numbers were based on actual vaccine received and percentages were based on the number of participants in the Safety Set.
MedDRA version 26.1.
Source: Study P301 CSR Table 14.3.1.2.2.1.1.

No events of "Polymenorrhagia", "Menometrorrhagia" or "Polymenorrhea" were reported. Fourteen (14) participants had unsolicited AEs of "Vaginal haemorrhage" (3 events), "Dysmenorrhea" (2 events), "Intermenstrual bleeding" (1 event), "Heavy menstrual bleeding" (6 events), and "Menstruation irregular" (2 events). All 14 events were non-serious, and 11 of the 14 events were medically attended.

Japanese-Study (P301 Addendum Japan)

Unsolicited AEs were similar for mRNA -1283 10µg and mRNA-1273 50µg, with an overall frequency of 7.0% vs 6.9% within 28 days.

Most frequently reported AEs until 28 days and until data cutoff were in the infections and infestations SOC.

Related unsolicited adverse events

At least 1 unsolicited AE assessed as related to the study intervention by the investigator was reported in 0.8% of participants in the mRNA-1283.222 group (48 events) and 0.9 % of participants in the mRNA-1273.222 group (52 events).

The applicant classified rash as an ADR as up to 28 days after study vaccination in Study P301, and events of rash were reported by 4/5706 participants in the mRNA-1283-222 group and 1/5711 participant in the mRNA-1273.222 group. All 5 events were considered related by the Investigator. The events, all of which were non-serious, included 2 events of rash, 1 event of rash macular, and 1 event of rash papular for participants in the mRNA-1283.222 group, and 1 event of rash for the participant in

the mRNA-1273.222 group. Furthermore, there were three related cases of pruritus in the mRNA-1283 group versus none related in the control group. Additionally, one case of treatment related chronic urticaria was observed in the mRNA-1283 group.

One case of irregular menstruation was observed in the mRNA-1283 group and was judged to be related by the investigator. The participant (52 years of age) had a relevant medical history of post-menopausal haemorrhage, relevant co-medication of Spironolacton (which can cause menstrual bleeding disorders) and obesity. It appears from the high-level medical information, that the female participant experienced post-menopausal haemorrhage after each COVID-19 vaccination in the past with different vaccine products, of note including others than Spikevax or mNEXSPIKE (2 doses of COVID-19 Vaccine (recombinant, adjuvanted) (Nuvaxovid) and 1 dose of Tozinameran).

Japanese-Study (P301 Addendum Japan)
Unsolicited AEs assessed as related to study vaccine by the Investigator were reported in 3/343 (0.9%) participants in the mRNA-1283.815 group (headache, urticaria, and injection site bruising) and 2/346 (0.6%) participants in the mRNA-1273.815 group (myalgia, and injection site discomfort) These events occurred within 28 days of study injection and were nonserious.

2.5.8.3. Serious adverse event/deaths/other significant events

Adverse events of special interest

Study P301

The number of participants reporting an AESI in Study P301 are the same in both groups (60 participants, 1.1%). There were no AESIs of myocarditis or pericarditis reported for mRNA-1283. Up to 28 days of study vaccination, no AESIs of new onset of worsening neurologic disease were reported in either group. Beyond 28 days of study vaccination, new onset of or worsening of neurologic disease had similar reporting incidence for both groups (4 participants in the mRNA-1283-group [1 event each of seizure, epilepsy, Bell's palsy, and narcolepsy] and 2 participants in the mRNA-1273-group [1 event each of viral meningoencephalitis and Bell's palsy]). All events were assessed by the Investigator as not related to study vaccination. All cases of Ageusia/anosmia were reported beyond 28 days of vaccination and were assessed to be not related with mRNA-1283, which is acknowledged. Two cases of Guillain-Barre syndrome were found in the mRNA-1283 group starting on Study Day 269 and Study Day 164, which were censored after receiving off-study vaccination. Both were judged to be not related. Within 28 days on, no coagulation disorder AESIs were reported in either group. Beyond 28 days of study vaccination, coagulation disorder AESIs had similar reporting incidence in both groups (7 participants in the mRNA-1283, and 13 participants in the mRNA-1273-group). A small imbalance can be seen in the PT Appendicitis (6 events in the mRNA-1283 group versus 0 in the mRNA-1273 group).

Investigator-assessed AESIs up to data Cutoff of vaccination are presented below.

Table 31. Study P301: Incidence of Adverse Events of Special Interest by System Organ Class and Preferred Term Up to Data Cutoff Date (Safety Set)

System Organ Class	mRNA-1283.222 10 µg (N=5706)		mRNA-1273.222 50 µg (N=5711)	
Preferred Term	**Any**	**Related**	**Any**	**Related**
Number of participants reporting an unsolicited AESI	60 (1.1)	1 (0.02)	60 (1.1)	0
Number of unsolicited AESI	74	1	77	0

System Organ Class	mRNA-1283.222 10 µg (N=5706)		mRNA-1273.222 50 µg (N=5711)	
Preferred Term	**Any**	**Related**	**Any**	**Related**
Infections and infestations	6 (0.1)	0	1 (0.02)	0
Appendicitis	5 (0.09)	0	0	0
Appendicitis perforated	1 (0.02)	0	0	0
Meningoencephalitis viral	0	0	1 (0.02)	0
Blood and lymphatic system disorders	0	0	1 (0.02)	0
Thrombocytopenia	0	0	1 (0.02)	0
Immune system disorders	1 (0.02)	1 (0.02)	0	0
Anaphylactic reaction	1 (0.02)	1 (0.02)	0	0
Nervous system disorders	29 (0.5)	0	22 (0.4)	0
Ageusia	18 (0.3)	0	12 (0.2)	0
Anosmia	15 (0.3)	0	16 (0.3)	0
Bells palsy	1 (0.02)	0	1 (0.02)	0
Cerebrovascular accident	1 (0.02)	0	2 (0.04)	0
Epilepsy	1 (0.02)	0	0	0
Narcolepsy	1 (0.02)	0	0	0
Seizure	1 (0.02)	0	0	0
Transient ischaemic attack	1 (0.02)	0	1 (0.02)	0
Cardiac disorders	15 (0.3)	0	24 (0.4)	0
Myocardial infarction	4 (0.07)	0	5 (0.09)	0
Acute myocardial infarction	3 (0.05)	0	2 (0.04)	0
Atrial fibrillation	3 (0.05)	0	10 (0.2)	0
Cardiac failure congestive	3 (0.05)	0	1 (0.02)	0
Cardiac arrest	2 (0.04)	0	1 (0.02)	0
Acute coronary syndrome	1 (0.02)	0	2 (0.04)	0
Cardiomyopathy	1 (0.02)	0	0	0
Sinus node dysfunction	1 (0.02)	0	1 (0.02)	0
Atrial flutter	0	0	1 (0.02)	0
Bundle branch block left	0	0	1 (0.02)	0
Coronary artery occlusion	0	0	1 (0.02)	0
Myocardial ischaemia	0	0	1 (0.02)	0
Pericarditis	0	0	1 (0.02)	0
Sinus tachycardia	0	0	1 (0.02)	0
Ventricular tachycardia	0	0	1 (0.02)	0
Vascular disorders	2 (0.04)	0	6 (0.1)	0
Deep vein thrombosis	1 (0.02)	0	4 (0.07)	0
Thrombosis	1 (0.02)	0	1 (0.02)	0
Superficial vein thrombosis	0	0	1 (0.02)	0
Respiratory, thoracic and mediastinal disorders	4 (0.07)	0	3 (0.05)	0
Pulmonary embolism	3 (0.05)	0	3 (0.05)	0
Respiratory failure	1 (0.02)	0	0	0
Hepatobiliary disorders	0	0	1 (0.02)	0
Hypertransaminasaemia	0	0	1 (0.02)	0
Musculoskeletal and connective tissue disorders	1 (0.02)	0	1 (0.02)	0
Fibromyalgia	1 (0.02)	0	1 (0.02)	0

System Organ Class	mRNA-1283.222 10 µg (N=5706)		mRNA-1273.222 50 µg (N=5711)	
Preferred Term	**Any**	**Related**	**Any**	**Related**
Renal and urinary disorders	0	0	1 (0.02)	0
Acute kidney injury	0	0	1 (0.02)	0
General disorders and administration site conditions	1 (0.02)	0	0	0
Chronic fatigue syndrome	1 (0.02)	0	0	0
Investigations	1 (0.02)	0	0	0
Liver function test abnormal	1 (0.02)	0	0	0
Injury, poisoning and procedural complications	0	0	1 (0.02)	0
Chillblains	0	0	1 (0.02)	0

Abbreviations: AESI = adverse event of special interest; CSR = clinical study report; mRNA = messenger ribonucleic acid.
Note: Numbers were based on actual vaccine received and percentages were based on the number of participants in the Safety Set.
Source: Study P301 CSR Table 14.3.1.6.1.2.

Standard MedDRA Queries (SMQs)

Study P301

All reported unsolicited AEs (regardless of Investigator assessment as AESI) were queried using MedDRA SMQs (narrow + broad scope) to identify AEs of interest.

Hypersensitivity

Narrow Scope Events Up to 28 Days After Study Injection

In Study P301, up to 28 days after study injection, the proportion of participants with events in the narrow scope hypersensitivity SMQ was 34/5706 (0.6%) in the mRNA-1283.222 group and 26/5711 (0.5%) in the mRNA-1273.222 group.

The most frequently reported PTs were rash (7/5706 [0.1%] participants in the mRNA-1283.222 group and 7/5711 [0.1%] participants mRNA-1273.222 group), dermatitis contact (2/5706 [0.04%] participants in the mRNA-1283.222 group and 6/5711 [0.1%] participants mRNA-1273.222 group), rhinitis allergic (5/5706 [0.09%] participants in the mRNA-1283.222 group and 2/5711 [0.04%] participants in the mRNA-1273.222 group), and urticaria (5/5706 [0.09%] participants in the mRNA-1283.222 group and 1/5711 [0.02%] participants in the mRNA-1273.222 group).

Of the total participants with events in the hypersensitivity SMQ within 28 days, 7 participants in the mRNA-1283.222 group and 1 participant in the mRNA-1273.222 group had events that were assessed as related to study injection by the Investigator. In the mRNA-1283.222 group, these included 1 participant with hypersensitivity, 1 urticaria chronic, and 4 cases of rash and related terms, which are all presented below. The remaining 1 participant in the mRNA-1283.222 group had a possible delayed anaphylactic reaction and is described in the SAE section.

Narrow/Broad Scope Events Up to 28 Days After Study Injection

Up to 28 days after study injection, the incidence of events in the narrow and broad scope hypersensitivity SMQ was 60/5706 (1.1%) in the mRNA-1283.222 group and 50/5711 (0.9%) in the mRNA-1273.222 group.

Pruritus was reported in 3/5706 [0.05%] participants in the mRNA-1283.222 group and 3/5711 [0.05%] participants in the mRNA-1273.222 group. All 3 participants with events of pruritus in the mRNA-1283.222 group were assessed by the Investigator as related to study injection.

Up to data cutoff (including events within 28 days), the incidence of events in the narrow and broad scope hypersensitivity SMQ was balanced between groups (150/5706 [2.6%] participants in the mRNA-1283.222 group and 131/5711 [2.3%] participants in the mRNA-1273.222 group).

All the events beyond 28 days were assessed by the Investigator as not related to study injection.

Angioedema

All events in the angioedema SMQ were assessed as not related to study injection by the Investigator. Events of urticaria were also included under this SMQ, with 7/5706 [0.1%] participants in the mRNA-1283.222 group and 3/5711 [0.05%] participants in the mRNA-1273.222 group.

Cardiomyopathy

Up to 28 days after study vaccination, no events in the narrow scope of the cardiomyopathy SMQ were reported in either group. Up to the data cutoff date, 2 participants had events in the narrow scope cardiomyopathy SMQ in the mRNA-1283.222 group. Both events were assessed by the Investigator as not related to study injection. Syncope occurred in 5/5706 (0.09%) participants in the mRNA-1283.222 group and 2/5711 (0.04%) participants in the mRNA-1273.222 group in the first 28 days after study injection.

Cardiac Events Including Ischemic Heart Disease, Cardiac Arrhythmia, and Cardiac Failure

No cardiovascular safety concerns were identified by the applicant based on review of narrow and broad scope cardiac SMQs for ischemic heart disease, cardiac arrhythmia, and cardiac failure.

Up to 28 days after study injection and up to the data cutoff, the incidence of participants with events was balanced across groups in the cardiac SMQs for narrow scope events.

There was one event of myocardial infarction in an 85-year-old participant in the evening of the day of vaccination with mNEXSPIKE. The participant also experienced concomitant pneumonia.

All events were assessed as not related to study injection by the Investigator and the Sponsor.

Peripheral Neuropathy

No peripheral neuropathy safety concerns were identified by the Applicant based on review of the narrow and broad scope SMQs for peripheral neuropathy.

<u>Narrow Scope Up to 28 Days After Study Injection</u>

Two events were in the narrow scope peripheral neuropathy SMQ in the mRNA-1283.222 group, and none were in the mRNA-1273.222 group up to 28 days following study injection. Both events were nonserious neuralgia and were assessed as not related to study injection by the Investigator.

<u>Narrow Scope Up to The Data Cutoff Date</u>

In Study P301, there were no imbalances in the events reported in both groups in the narrow scope peripheral neuropathy SMQ up to the data cutoff date (including events within 28 days) (Study P301 CSR Table 14.3.1.7.1.1). All events in both groups were assessed by the Investigator as not related to study injection.

<u>Narrow/Broad Scope up to 28 Days After Study Injection</u>

There were no imbalances in the events reported in both groups in the narrow and broad scope peripheral neuropathy SMQ up to 28 days after study injection (6 versus 5 cases). Of these, 1 participant in each group had an event of hypoaesthesia judged as related to study injection by the Investigator.

Narrow/Broad Scope Up to The Data Cutoff Date

The incidence of events in the peripheral neuropathy narrow and broad scope SMQ up to the data cutoff date (including events up to 28 days) was similar for both groups (12/5706 [0.2%] in the mRNA-1283.222, and 20/5711 [0.4%] in the mRNA-1273.222 group). All of the events occurring beyond 28 days were assessed by the Investigator as not related to study injection in both groups.

Immune-mediated/Autoimmune Disorders

Narrow Scope Events Up to 28 Days After Study Injection

The incidence of events in the narrow scope autoimmune disorder SMQ up to 28 days after study injection was 2/5706 (0.04%) in the mRNA-1283.222 group and 3/5711 (0.05%) in the mRNA-1273.222 group. One event reported in the mRNA-1273.222 group was an exacerbation of alopecia areata starting on Day 16 and was assessed by the Investigator as related to the study injection.

Narrow Scope Events Up to The Data Cutoff Date

Up to the data cutoff date, events reported in the narrow scope immune-mediated/autoimmune disorders SMQ was 14/5706 (0.2%) in the mRNA-1283.222 group and 18/5711 (0.3%) in the mRNA-1273.222 group. None of the events reported for the mRNA-1283.222 group were assessed as related to study injection by the Investigator. No new events were reported beyond 28 days of study injection that were considered related by the Investigator.

Narrow/Broad Scope Events Up to 28 Days After Study Injection

In Study P301, up to 28 days after study injection, events reported in the narrow/broad scope immune-mediated/autoimmune disorders SMQ was 13/5706 (0.2%) in the mRNA-1283.222 group and 18/5711 (0.3%) in the mRNA-1273.222 group.

Up to 28 days after study injection, 5 participants in the mRNA-1283.222 group had a worsening of an underlying condition (2x arthritis, 1x lichen planus, 1x lichen sclerosus, 1x hypothyroidism). Of these, 1 event was assessed by the Investigator as related to study injection (Lichen planus).

In the mRNA-1273.222 group, 3 participants had worsening of a preexisting condition within 28 days. All events were assessed as not related to study injection by the Investigator.

Narrow/Broad Scope Events Up to The Data Cutoff Date

In Study P301, the incidence of events in the narrow and broad autoimmune disorders SMQ up to the data cutoff (including events within 28 days) was 69/5706 (1.2%) in the mRNA-1283.222 group and 92/5711 (1.6%) in the mRNA-1273.222 group.

Of the broad scope autoimmune disorder SMQ events reported beyond 28 days of study injection, 4 participants in the mRNA-1283.222 group had a worsening of a pre-existing condition with onset occurring between Day 52 and Day 176. In the mRNA-1273.222 group, 12 participants had a worsening of a pre-existing condition with onset occurring between Day 36 and Day 253; all of these events in both groups were assessed as not related to study injection by the Investigator.

The other 2 events assessed by the Investigator as related to study injection in the mRNA-1283.222 participant were an SAE of acute aseptic arthritis (verbatim: left knee swelling - possible acute aseptic arthritis) and nonserious arthritis (verbatim: left knee inflammatory arthritis).

Hearing and Vestibular Disorders

The proportion of events in the narrow scope hearing and vestibular disorders SMQ up to 28 days after study injection was 12/5706 (0.2%) in the mRNA-1283.222 group and 4/5711 (0.07%) in the mRNA-1273.222 group.

Up to 28 days in the broad scope SMQ of hearing and vestibular disorders, dizziness was reported as related to study injection in 1 participant in the mRNA-1283.222 group and 2 participants in the mRNA-1273.222 group. All 3 events were nonserious, and onset was on Day 1 or Day 2 after study injection.

All of the events occurring beyond 28 days after study injection in the hearing and vestibular disorders SMQ were assessed by the Investigator as not related to study injection.

Convulsions

Up to the data cutoff date, 4 participants in the mRNA-1283-group had an event in the narrow scope. All events were assessed as not related by the Investigator.
One participant had 2 events that were reported as SAEs: partial seizures (verbatim: provoked localized focal seizures) and postictal paralysis (verbatim: possible Todd's paralysis) on Day 240 which occurred 1 day after a craniotomy for removal of a meningioma. Two participants each had an event of epilepsy, and 1 participant had an event of seizure. In 2 of these 3 cases, the participants had predisposing risk factors (a history of epilepsy and history of syncopal episodes and blackouts). The onset of the events ranged from Day 169 and Day 240. One report in the narrow/broad scope described a non-related event of worsening of narcolepsy on day 176.

Demyelinating Disease of Central Nervous System

In Study P301, no events were reported in the narrow scope demyelinating disease of CNS SMQ up to the data cutoff date.

Up to 28 days after study injection in the narrow and broad scope demyelinating disease of CNS SMQ, 1/5706 (0.02%) participant in the mRNA-1283.222 group had an event (Trigeminal neuralgia) that was assessed by the Investigator as related to study injection; no events were reported for participants in the mRNA-1273.222 group.

One event occurred beyond 28 days after study injection in the mRNA-1273.222 group and was assessed by the Investigator as not related to study injection.

Serious Adverse Events

One SAE in each group has been assessed to be related according to the investigator within 28 days after study vaccination. SAEs until data cut-off as presented in Table 32 are balanced between mRNA-1283 and mRNA-1273. The proportions of participants reporting any SAE are very similar (2.7% vs. 2.6%). Events judged as related were very rare in both groups (0.04% for mRNA-1283 vs. 0.02% for mRNA-1273).

Table 32. Study P301: Incidence of Serious Adverse Events by Preferred Term up to the Data Cutoff Date Occurring in ⩾2 Participants in any Group (Safety Set)

	mRNA-1283.222 10 µg (N=5706)		mRNA-1273.222 50 µg (N=5711)	
System Organ Class Preferred Term	Any	Related	Any	Related
Number of Participants Reporting Serious Adverse Event	156 (2.7)	2 (0.04)	151 (2.6)	1 (0.02)

System Organ Class Preferred Term	mRNA-1283.222 10 µg (N=5706) Any	 Related	mRNA-1273.222 50 µg (N=5711) Any	 Related
Number of serious AE	194	3	195	1
Infections and Infestations				
Appendicitis	4 (0.07)	0	0	0
Pneumonia	4 (0.07)	0	6 (0.1)	0
Urosepsis	3 (0.05)	0	0	0
Sepsis	2 (0.04)	0	1 (0.02)	0
Cellulitis	1 (0.02)	0	3 (0.05)	0
Pneumonia bacterial	1 (0.02)	0	2 (0.04)	0
Diverticulitis				
Osteomyelitis				
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	26 (0.5)	0	16 (0.3)	0
Basal cell carcinoma	2 (0.04)	0	0	0
Ovarian cancer	2 (0.04)	0	0	0
Prostate cancer	2 (0.04)	0	0	0
Colon cancer	1 (0.02)	0	2 (0.04)	0
Malignant melanoma	1 (0.02)	0	3 (0.05)	0
Oesophageal carcinoma				
Metabolism and nutrition disorders	6 (0.1)	0	7 (0.1)	0
Dehydration	3 (0.05)	0	1 (0.02)	0
Hypokalaemia	2 (0.04)	0	0	0
Psychiatric disorders	5 (0.09)	0	6 (0.1)	0
Suicidal ideation	2 (0.04)	0	0	0
Suicide attempt	1 (0.02)	0	0	0
Nervous system disorders	16 (0.3)	0	13 (0.2)	0
Transient ischaemic attack	4 (0.07)	0	3 (0.05)	0
Syncope	3 (0.05)	0	1 (0.02)	0
Cerebrovascular accident	2 (0.04)	0	2 (0.04)	0
Migraine	2 (0.04)	0	2 (0.04)	0
Ear and labyrinth disorders				
Vertigo	0	0	2 (0.04)	0
Cardiac disorders	20 (0.4)	0	22 (0.4)	0
Cardiac failure congestive	4 (0.07)	0	2 (0.04)	0
Myocardial infarction	4 (0.07)	0	6 (0.1)	0
Acute myocardial infarction	3 (0.05)	0	2 (0.04)	0
Angina pectoris	3 (0.05)	0	2 (0.04)	0
Atrial fibrillation	2 (0.04)	0	6 (0.1)	0
Cardiac arrest	2 (0.04)	0	2 (0.04)	0
Bradycardia	1 (0.02)	0	2 (0.04)	0
Vascular disorders	1 (0.02)	0	8 (0.1)	0
Deep vein thrombosis	0	0	3 (0.05)	0
Respiratory, thoracic, and mediastinal disorders				
Asthma	4 (0.07)	0	1 (0.02)	0
Pulmonary embolism	3 (0.05)	0	3 (0.05)	0

System Organ Class Preferred Term	mRNA-1283.222 10 µg (N=5706) Any	 Related	mRNA-1273.222 50 µg (N=5711) Any	 Related
Chronic obstructive pulmonary disease	2 (0.04)	0	2 (0.04)	0
Respiratory failure	1 (0.02)	0	2 (0.04)	0
Gastrointestinal disorders	11 (0.2)	0	17 (0.3)	0
Hiatus hernia	2 (0.04)	0	0	0
Upper gastrointestinal haemorrhage	2 (0.04)	0	0	0
Inguinal hernia	1 (0.02)	0	2 (0.04)	0
Abdominal pain	0	0	2 (0.04)	0
Gastrointestinal haemorrhage	0	0	3 (0.05)	0
Hepatobiliary disorders	6 (0.1)	0	5 (0.09)	0
Cholecystitis	3 (0.05)	0	3 (0.05)	0
Musculoskeletal and connective tissue disorders	12 (0.2)	1 (0.02)	8 (0.1)	0
Osteoarthritis	7 (0.1)	0	3 (0.05)	0
Renal and urinary disorders	5 (0.09)	0	3 (0.05)	0
Acute kidney injury	3 (0.05)	0	1 (0.02)	0
General disorders and administration site conditions	7 (0.1)	0	4 (0.07)	1 (0.02)
Non-cardiac chest pain	3 (0.05)	0	0	0
Chest pain	2 (0.04)	0	1 (0.02)	0
Death	1 (0.02)	0	2 (0.04)	1 (0.02)
Injury, poisoning, and procedural complications	14 (0.2)	0	18 (0.3)	0
Fall	3 (0.05)	0	0	0
Concussion	2 (0.04)	0	0	0
Ankle fracture	1 (0.02)	0	2 (0.04)	0
Hip fracture	1 (0.02)	0	2 (0.04)	0
Foot fracture	0	0	2 (0.04)	0
Patella fracture	0	0	2 (0.04)	0

Abbreviations: AE = adverse event; CSR = clinical study report; mRNA = messenger nucleic acid; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Numbers were based on actual vaccine received and percentages were based on the number of participants in the Safety Set.
MedDRA version 26.1.
Source: Modified from Study P301 CSR Table 14.3.1.2.2.4.2.

Noteworthy, is one SAE/ AESI "Anaphylactic reaction" with the following presentation:

A 41-year-old woman with baseline low blood pressure, allergies and hypothyroidism reported fever, chills, fatigue, headache, faintness, chest pain, nausea and diarrhoea 18 hours after receiving mRNA-1283.222. Symptoms resolved within hours, except diarrhoea, which lasted two days. She did not seek medical care. The investigator considered it possible delayed anaphylaxis. The AE has been reported as serious, medically important and related with the vaccination by the investigator.

Furthermore, two SAEs (1 event acute aseptic arthritis and 1 event of oligoarthritis) were reported beyond 28 days in 1 participant in the mRNA-1283-group. A 37-year-old man with reported tuberculosis exposure 10 to 14 years prior developed sudden left knee swelling on Day 56, later diagnosed as acute aseptic arthritis. Although the arthritis resolved, joint pain and swelling were ongoing. On day 108, he was hospitalised with fever, night sweats, and multiple swollen joints. A

positive QuantiFERON-TB test led to a presumptive TB arthritis diagnosis. On Day 215, he tested positive for HLA-B27, raising the suspicion of ankylosing spondylitis. The Investigator assessed the events as related to study vaccine in absence of another medical explanation.

Deaths

Study P301

In Study P301, deaths up to the data cutoff date are presented in Table 33. After the data cutoff date (23 Feb 2024) and up to the data extraction date (06 May 2024), 2 deaths occurred in the mRNA-1283.222 group and no deaths occurred in the mRNA-1273.222 group. The deaths occurred on Day 343 and Day 369, respectively, and were assessed by the Investigator as not related to study injection.

Table 33. Deaths Up to the Data Cutoff Date in Study P301 (23 Feb 2024)

Preferred Term / Verbatim Term	Start Day	End Day	Investigator Relationship to Study Vaccine
mRNA-1283.222			
Myocardial rupture / Ruptured Myocardium	Day 149	Day 149	Not Related
Respiratory failure / Respiratory failure	Day 82	Day 82	Not Related
Cardiac arrest / Cardiac arrest	Day 251	Day 254	Not Related
Death / Death by homicide	Day 248	Day 248	Not Related
Cardiac arrest / Cardiac arrest	Day 160	Day 160	Not Related
mRNA-1273.222			
Oesophageal carcinoma / Oesophageal cancer	Day 124	Day 163	Not Related
Cardiac arrest / Cardiac arrest	Day 47	Day 53	Not Related
Pulmonary embolism / Pulmonary embolism	Day 234	Day 234	Not Related
Death / Death – Cause unknown	Day 7	Day 7	Related
Gastrointestinal haemorrhage / Gastrointestinal haemorrhage	Day 259	Day 265	Not Related
Hepatic cancer / Liver Cancer	Day 274	Day 335	Not Related
Myocardial infarction / Heart Attack	Day 256	Day 256	Not Related
Toxicity to various agents / Drug intoxication	Day 43	Day 47	Not Related
Death / Death by homicide	Day 248	Day 248	Not Related
Completed suicide / Suicide	Day 236	Day 236	Not Related

Abbreviation: CSR = clinical study report.
Source: mRNA-1283-P301 CSR Table 41.

A-77-year-old participant with underlying cardiac disease died on Day 7; cause of death was reported as unknown. The participant had multiple preexisting comorbidities and the use of concomitant medications known to increase the risk of arrhythmias. The Investigator indicated the cause of death was more likely cardiopulmonary, but assessed the death as related to study injection due to temporality. The Sponsor assessed the death as not related to study injection given the participant's long-term cardiovascular history and ongoing medications including digoxin and duloxetine, and the recent initiation of diltiazem.

Japanese-Study (P301 Addendum Japan) and other studies

No SAE or AESIs occurred in the Japanese Substudy so far. None of SAEs and AESIs in Study P101 and Study P201 were judged as related.

2.5.8.4. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.5. Safety in special populations

In Study P301 with the exception of age-groups, no special populations (e.g. immunocompromised, pregnant) have been investigated.

Age

In Study P301, solicited ARs were analyzed across 3 age groups: adolescents aged ≥12 to <18 years, adults aged 18 to <65 years, and adults aged ≥65 years. Age-related analysis suggests decreasing reactogenicity with increasing age. Rates of any solicited AR are noticeably lower in adults aged ⩾65 years (71.1%) compared with adolescents (79.1%) and younger adults (84.5%) with also a lower proportion of grade 3 reactions, which is in line with other Covid vaccinations. The majority of events in older adults were of grade 1 or Grade 2 severity with only a small proportion being Grade 3 severity. No Grade 4 Reactions have been reported with the exception of one Grade 4 fever reaction in the mRNA-1273-group. In adolescents, 79.1% of those receiving mRNA-1283.222 and 85.5% receiving mRNA-1273.222 reported reactions, which were predominantly Grade 1 and Grade 2, with a slightly higher occurrence of Grade 3 events for the mRNA-1283.222. Among adults aged 18 to <65 years, overall reaction rates were 84.5% for mRNA-1283.222 and 86.7% for mRNA-1273.222, with similar patterns in severity. A similar trend was seen in the older group (Table 34).

Table 34. Summary of Participants with Solicited Adverse Reactions Within 7 Days After Injection by Grade (by Age Groups) (Solicited Safety Set)

	≥12-<18 Years		≥18-<65 Years		≥65 Years	
	mRNA-1283.222 10 µg (N=497) n (%)	mRNA-1273.222 50 µg (N=495) n (%)	mRNA-1283.222 10 µg (N=3573) n (%)	mRNA-1273.222 50 µg (N=3574) n (%)	mRNA-1283.222 10 µg (N=1632) n (%)	mRNA-1273.222 50 µg (N=1637) n (%)
Any Solicited Adverse Reactions	**393 (79.1)**	**423 (85.5)**	**3018 (84.5)**	**3099 (86.7)**	**1160 (71.1)**	**1259 (76.9)**
95% CI	(75.2, 82.6)	(82.0, 88.4)	(83.2, 85.6)	(85.6, 87.8)	(68.8, 73.3)	(74.8, 78.9)
Grade 1	103 (20.7)	103 (20.8)	1376 (38.5)	1369 (38.3)	654 (40.1)	763 (46.6)
Grade 2	212 (42.7)	264 (53.3)	1350 (37.8)	1467 (41.0)	420 (25.7)	418 (25.5)
Grade 3	78 (15.7)	56 (11.3)	292 (8.2)	263 (7.4)	86 (5.3)	77 (4.7)
Grade 4	0	0	0	0	0	1 (0.06)

Source: Study P301 CSR Table 14.3.1.1.1.1.

In population below 18 years of age, local solicited ARs were reported in 71.4 vs 79.8% of participants in the mRNA-1283 and mRNA-1273 groups respectively. In decreasing frequency, Injection site pain (68.8 vs 78.8%), Axillary swelling/tenderness (34.6 vs 27.1), Swelling/Hardness (3.6 vs 5.1%) and Erythema (1.2 vs 2.6%) were reported. Most of the local solicited ARs were of Grade 1 and Grade 2 intensity in both groups. Grade 3 events were infrequent (approximately 3.0 versus 4.2%) and Grade 4 events were absent in both groups.

Frequency of systemic solicited ARs was overall 67.6 vs 71.1% of participants in the mRNA-1283 and mRNA-1273 groups respectively. At the PT level, the frequency of events was similar in the mRNA-1283 and mRNA-1273 groups. In decreasing frequency, Headache (54.5 vs 58.0%), Fatigue (47.3 vs 50.7%), Myalgia (39.2 vs 36.0%), Chills (31.6 vs 31.9%), Arthralgia (23.9 vs 23.6%), Nausea/Vomiting (16.1 vs 17.6%) and Fever (9.9 vs 9.3%) were reported. Most of the systemic solicited ARs were of Grade 1 and Grade 2 intensity in both groups. Grade 3 events were 14.3 vs 8.9% and Grade 4 events were absent in both groups.

Unsolicited AEs

A summary of unsolicited AEs after study injection by age group is presented in Table 35.

Table 35. Study P301: Summary of Unsolicited Adverse Events After Study Injection by Age Subgroup (Safety Set)

	≥12-<18 Years		≥18-<65 Years		≥65 Years	
	mRNA-1283.222 10 µg (N=497)	mRNA-1273.222 50 µg (N=495)	mRNA-1283.222 10 µg (N=3575)	mRNA-1273.222 50 µg (N=3576)	mRNA-1283.222 10 µg (N=1634)	mRNA-1273.222 50 µg (N=1640)
Up to 28 Days after Study injection						
All	58 (11.7)	56 (11.3)	435 (12.2)	427 (11.9)	208 (12.7)	197 (12.0)
Serious	0	0	6 (0.2)	11 (0.3)	7 (0.4)	7 (0.4)
Fatal	0	0	0	0	0	1 (0.06)
Medically Attended	40 (8.0)	35 (7.1)	246 (6.9)	239 (6.7)	139 (8.5)	148 (9.0)
Leading to Study Discontinuation	0	0	0	0	0	1 (0.06)
Severe	1 (0.2)	0	7 (0.2)	13 (0.4)	5 (0.3)	5 (0.3)
Up to the Data Cutoff Date (23 Feb 2024)						
All	175 (35.2)	150 (30.3)	1301 (36.4)	1294 (36.2)	624 (38.2)	602 (36.7)
Serious	3 (0.6)	4 (0.8)	87 (2.4)	79 (2.2)	66 (4.0)	68 (4.1)
Fatal	1 (0.2)	1 (0.2)	1 (0.03)	4 (0.1)	3 (0.2)	5 (0.3)
Medically Attended	162 (32.6)	133 (26.9)	1183 (33.1)	1179 (33.0)	587 (35.9)	571 (34.8)
Leading to Study Discontinuation	1 (0.2)	1 (0.2)	2 (0.06)	4 (0.1)	5 (0.3)	7 (0.4)
Severe	3 (0.6)	5 (1.0)	75 (2.1)	76 (2.1)	51 (3.1)	52 (3.2)

Abbreviations: CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Numbers were based on actual study injection received and percentages were based on the number of participants in the Safety Set.
MedDRA version 26.1.
Source: Study P301 CSR Table 14.3.1.2.1.1 and Table 14.3.1.2.1.2.

Unsolicited AEs were lower in the younger age groups and increased with age. One related case of Syncope was reported in the adolescent mRNA-1283 group compared to none in the control group. A 12-year-old female participant had a syncope on the evening of Day 1 after receiving the study vaccine and was taken to the emergency room. Upon arrival she had high fever, severe headache, tachycardia and myalgia. The participants symptoms resolved during observation, and she was discharged. The remaining events of syncope were assessed as not related to study vaccine by the investigator. Overall, 9/5706 (0.2%) participants had events of syncope up to the data cutoff date for mRNA-1283. Furthermore, one related Vertigo case, one related case of Hypoaesthesia and one related case of Disorientation was found in the older mRNA-1283 group.

There was a small imbalance in Number of Subjects Reporting Unsolicited AE until data cutoff in the youngest age group (35.2% vs 30.3%), probably driven by the SOC Psychiatric disorders (20 vs. 11 subjects) and Respiratory, thoracic and mediastinal disorders (16 subjects vs. 7 subjects).

Up to the data cutoff, in the subgroup of adolescents (12 to <18 years) no related serious adverse events were reported, and only one AESI (Anosmia) was reported, which was considered not related by the Investigator.

Organ transplant

A patient representative raised concerns that administration of mRNA-1283 might cause abnormalities in the immune system that could trigger organ rejection processes.

The applicant compiled scientific publications on the issue providing evidence for benefit of the COVID-vaccination for transplant recipients. Taking all the available information together, there is no confirmed safety concerns that mRNA COVID-19 vaccines cause organ rejection in transplant recipients. Reports of rejection after vaccination are rare and do not prove the vaccine was the cause. The benefits of vaccination—especially preventing severe COVID-19—outweigh potential risks for most transplant recipients. Ongoing safety monitoring continues, with extra attention for people who are recently transplanted, have known donor-specific antibodies, or are on higher levels of immunosuppression. Decisions about vaccination should always be made in partnership with the patient's transplant team.

Further, the Robert Koch-Institut (RKI) has discussed and published their views and recommendations, respectively (Epid Bull 2021;39).

Pregnancy and breast feeding

Up to the data cutoff, 10 participants had reported pregnancies, 3 participants in the mRNA-1283.222 vaccine group and 7 participants in the mRNA-1273.222 vaccine group. In the mRNA-1283.222 vaccine group all 3 pregnancies were pending the final outcome. Of the 7 pregnancies in the mRNA-1273.222 vaccine group, 3 resulted in term births without complications, 1 participant had an induced abortion on Day 37, and the final outcomes for the 3 remaining pregnancies had not yet been reported.

Safety data on breast feeding is lacking.

2.5.8.6. Laboratory findings

Study P301/ P201

Routine clinical laboratory evaluations were not performed in Study P301 and Study P201. Additionally, no clinically relevant changes were noted in the review of vital signs (diastolic and systolic blood pressure, pulse rate, respiratory rate) for either group based on assessments performed on Day 1 after vaccination and vital signs collected at other in-person visits in conjunction with a symptom-directed physical examination.

Study P101

Only in in Study P101 routine clinical laboratory evaluations were performed. Laboratory data indicate a notable decrease in haemoglobin levels across all doses of the mRNA-1283 vaccine. At Day 8 a large proportion of participants experienced AE Grade 1 haemoglobin reductions (50 to 76.2% across different doses) with some cases experiencing Grade 2 or 3 toxicity. A similar picture is seen at Day 29 and Day 36. Data coagulation laboratory data like aPTT and PT, were also provided by the applicant on request

2.5.8.7. Immunological events

Not applicable.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.5.8.9. Discontinuation due to adverse events

Up to 28 days after study vaccination, there were no discontinuations from the study due to unsolicited AEs in the mRNA-1283 group and 1 participant was discontinued in the mRNA-1273 group due to death.

Up to the data cutoff date (including events within 28 days), 8/5706 (0.1%) and 12/5711 (0.2%) participants had unsolicited AEs leading to discontinuation from the study in the mRNA-1283 group and mRNA-1273 group, respectively. Of these, 5 participants in the mRNA-1283.222 group and 10 participants in the mRNA-1273 group were discontinued from the study due to death.

The remaining non-fatal unsolicited AEs leading to discontinuation occurred beyond 28 days of study vaccination and these were all assessed as not related to study vaccine by the Investigator. In the mRNA-1283 group, the 3 unsolicited AEs leading to discontinuation were metastatic gastric cancer, polycythaemia vera, and suicide attempt (1 participant each). In the mRNA-1273 group, the 2 unsolicited AEs leading to discontinuation were oesophageal carcinoma and pancreatic carcinoma stage IV (1 participant each).

2.5.8.10. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

The safety profile is primarily based on results from one pivotal study (Study P301) and the two supportive studies (Study P101 and P201). It includes a safety database of over 6200 participants who have received at least 1 injection of mRNA-1283 (including the original and 3 variant formulations: mRNA-1283.211, mRNA-1283.222, or mRNA-1283.529) at any dose. Pooled summaries of the studies were not provided. The pivotal, randomised, observer-blind, active-controlled, phase 3 safety and efficacy Study P301 provided the main safety data from participants aged 12 years and older, with analysis conducted after each participant had at least 6 months of follow-up (data cutoff date of 23 Feb 2024). The study allowed for the inclusion of participants with stable pre-existing medical conditions, while immunocompromised and pregnant women were not enrolled.

Exposure

The safety database consists of 11417 participants, 5706 and 5711 having received mRNA-1283.222 10 µg or mRNA 1273.222 50 µg from study P301 respectively. Notably, only about 0.4% of participants of the mRNA-1283 group were excluded from the Safety Set, reflecting a very low exclusion rate, which is similar to the rate in the control group. The median follow-up duration for the pivotal study P301 follow-up was 8.772 months, with 11114 (97.3) having at least 6 months of follow-up and 7862 (68.9) having 8 months.

The size of the safety database and the overall length of the safety follow-up are considered sufficient for an evaluation of the B/R profile of mRNA-1283. The applicant seeks an indication for adults and adolescents from 12 years of age. All intended age groups are sufficiently represented in terms of numbers recruited.

Regarding patient characteristics, most baseline characteristics are evenly distributed or considered to be acceptable. Participant's age-distribution is presented in 5 age-groups. 91.3% are adults and 8.7%

are between 12 and 18 years of age. The age-group ≥75 years is small with a proportion of only 5.6% and 4.7% of participants. It is also important to note the BMI distribution. As the normal range is between 18.5 and 24.9, the presented cut-off of 30 (>40% range above 30, and are therefore categorized "obese") is considered to be high. This finding might be relevant in the context of SARS-Cov-2 infection susceptibility. However, distribution between both groups appears to be similar. Europe is represented by participants from the UK (22.5%), which is considered to be acceptable. Considering participants demographic, safety database and length of follow up duration, the patient exposure is deemed sufficient by the CHMP.

Solicited ARs were collected via eDiary until day 7 using standard definitions. For safety assessments, unsolicited AEs were recorded up to 28 days after injection, which is also standard procedure. SAEs, MAAEs, AESIs, and AEs leading to discontinuation were recorded through the end of study. In the event of an off-study COVID-19 vaccine use during the study, participant AE data were censored after the off-study COVID-19 vaccination. All AEs occurring after off-study vaccinations were reported between Day 76 and Day 306 after study vaccine. Numbers of AEs in this discussion are based on the censored data, unless otherwise stated. Overall, the safety data collection methods are standard and appear reliable.

Solicited Adverse Reactions

In Study P301 Solicited Adverse Reactions were similar for mRNA -1283 and mRNA-1273 with 80.2% vs 83.8% affected participants, overall, with slightly lower numbers for mRNA-1283. Local ARs were reported in 70.3 vs 78.4%. In decreasing frequency, Injection site pain (68.5 vs 77.5%), Axillary swelling/tenderness (19.7 vs 18.4%), Erythema (2.2 vs 3.9%) and Swelling/Hardness (3.6 vs 6.3%) were reported. Frequency of systemic solicited ARs was overall 64.4 vs 64.2%. However, at the PT level, the frequency of events was higher in the mRNA-1283 group. In decreasing frequency, Fatigue (50.4 vs 49.0%), Headache (44.2 vs 41.2%), Myalgia (38.2 vs 37.0%), Arthralgia (29.7 vs 27.6%), Chills (22.7 vs 19.8%), Nausea/Vomiting (12.1 vs 11.0%), and Fever (5.6 vs 4.5%) were reported. These are reflected accordingly in the SmPC.

The most frequent onset was within 1 or 2 days, duration was short and between 1 and 4 days, similar for both cohorts. Only 1.4% persisted beyond 7 Days in the mRNA-1283 group, similar to 1.3% in the mRNA-1273 group. Most of the solicited ARs were of Grade 1 and Grade 2 intensity in both groups. Grade 3 events were infrequent (approximately 0.1–8% for all PTs) but slightly more frequent in the mRNA-1283 group. Grade 4 events were absent in in the mRNA-1283 group.

Unsolicited Adverse Events

Unsolicited AEs were also similar for mRNA-1283 and mRNA-1273, with an overall frequency of 12.3 vs 11.9% within 28 days respectively, and 36.8 vs 35.8% until data cutoff.

The most frequently reported unsolicited AE considered to be related to mRNA-1283.222 by the investigator in 4 participants or more were diarrhoea (6/5706 [0.1%]), and lymphadenopathy (4/5706 [0.07%]), which are reflected in the SmPC with the respective frequencies.

Most frequently reported AEs until 28 days and until data cutoff were in the infections and infestations SOC. Although less frequent, 16 reports (2 related) of "immune system disorders", 59 nervous system disorders (7 related), and the AESIs are considered to be of interest. There were three related cases of pruritus in the mRNA-1283 group versus none related in the control group. Additionally, one case of treatment related chronic urticaria was observed in the mRNA-1283 group. Among cases judged as unrelated, urticaria was reported in five participants in the mRNA-1283 group versus one in the control group. Furthermore, one related case of Urticaria was found in the Japanese sub study.

In the SOC "Reproductive system and breast disorders" up to 28 days post-injection 11 events (0.2%) were reported in the mRNA-1283 group compared with 7 events (0.1%) in the control group. One case of irregular menstruation was observed in the mRNA-1283 group and was judged to be related by the investigator. The applicant discussed all cases of vaginal haemorrhage, dysmenorrhoea, intermenstrual bleeding and related PTs. Taking the provided clinical information regarding cases of menstrual bleeding disorders into account it can be agreed that an inclusion of heavy menstrual bleeding or other menstrual bleeding disorders in the SmPC is currently not justified. One case of post-menopausal haemorrhage after COVID-19 vaccination in a participant of 52 years of age remains of interest. Despite a relevant medical history of post-menopausal haemorrhage, relevant co-medication of Spironolactone (which can cause menstrual bleeding disorders) and obesity, it appears from the high-level medical information, that the female participant experienced post-menopausal haemorrhage after each COVID-19 vaccination in the past with different vaccine products, of note including others than Spikevax or mNEXSPIKE (2 doses of COVID-19 Vaccine (recombinant, adjuvanted) (Nuvaxovid) and 1 dose of Tozinameran).

The applicant agreed to follow the issue of menstrual bleeding disorders via routine pharmacovigilance (within PSURs) as adverse events of special interest (AESI). The MedDRA PTs used by the applicant to respond to the issue of irregular menstrual bleeding, i.e. "Vaginal haemorrhage," "Dysmenorrhoea," "Intermenstrual bleeding," "Heavy menstrual bleeding," "Polymenorrhagia," "Menometrorrhagia," "Polymenorrhea," and "Menstruation irregular" should be used.

Solicited Adverse Reactions in the Japanese-Study (P301 Addendum Japan) were similar for the mRNA -1283 10µg group and the mRNA-1273 50µg group with 89.5 vs 95.7% of participants reporting a solicited AE, overall. Local ARs were reported in 86.3 vs 95.1%. In decreasing frequency, Injection site pain (84.8 vs 94.5%), Axillary swelling/tenderness (24.5 vs 26.0%), Swelling/Hardness (9.3 vs 14.7%), and Erythema (3.8 vs 11.0%) were reported. Frequency of systemic solicited ARs was overall 59.8 vs 76.95%. In decreasing frequency, Fatigue (51.0 vs 63.6%), Headache (42.6 vs 56.1%), Myalgia (35.0 vs 39.9%), Arthralgia (31.8 vs 36.1%), Chills (21.0 vs 31.5%), Nausea/Vomiting (7.9 vs 9.0%), and Fever (7.0 vs 12.7%) were reported. Most frequent onset was within 1 or 2 days, duration was between 2 and 4 vs 5 days, similar for both cohorts. Overall, the reactogenicity profile of the Omicron-XBB variant appears to be similar with the bivalent (original/BA4/5) variant as used in study P301. Descriptively, the XBB variant might be slightly more reactogenic.

Unsolicited AEs were similar for the mRNA -1283 group and the mRNA-1273 group, with an overall frequency of 7.0 vs. 6.9% within 28 days. Most frequently reported AEs until 28 days and until data cutoff were in the infections and infestations SOC. Unsolicited AEs assessed as related to study vaccine by the investigator were reported in 3/343 (0.9%) participants in the mRNA-1283 group (headache, urticaria, and injection site bruising) and 2/346 (0.6%) participants in the mRNA-1273 group (myalgia, and injection site discomfort). These events occurred within 28 days of study injection and were nonserious. Up to 28 days post injection there were no reported deaths, SAEs, unsolicited events leading to study discontinuation, or severe unsolicited AEs or AESIs in either group. The Applicant will provide the Final CSR for the Japanese Study, as soon as available (**REC**).

Adverse Events of Special Interest

The number of participants reporting an AESI within 28 days of vaccination in Study P301 are the same in both groups (60 participants, 1.1%). Overall, numbers are balanced between both groups. Rare AEs might only be detected by chance in the restricted clinical-trial-setting and will primarily target the post-marketing-setting.

There were no AESIs of myocarditis or pericarditis reported for mRNA-1283. Because of rare cases of myocarditis/pericarditis detected in Spikevax in the post-marketing setting, for which

pharmacoepidemiological studies revealed the highest excess risk in younger males. It is not known whether there is a similar risk with mRNA-1283. As a result, the relevant warning in section 4.4 of the SmPC is included and the RMP includes myocarditis and pericarditis as important potential risks together with additional pharmacovigilance activities.

All cases of Ageusia/anosmia are reported beyond 28 days of vaccination and are assessed to be not related with mRNA-1283, which is acknowledged.

Within 28 days, no coagulation disorder AESIs were reported in either group. Beyond 28 days of study vaccination, coagulation disorder AESIs had similar reporting incidence in both groups (7 participants in the mRNA-1283-, and 13 participants in the mRNA-1273-group). All AESIs were assessed as not related to study vaccine by the Investigator.

Two cases of Guillain-Barre syndrome were found in the mRNA-1283 group starting on Study Day 269 and Study Day 164, which were censored after receiving off-study vaccination. Both were judged to be not related, which is supported by the CHMP. Up to 28 days of study vaccination, no AESIs of new onset of worsening neurologic disease were reported in either group. Beyond 28 days of study vaccination, new onset of or worsening of neurologic disease had similar reporting incidence for both groups All events were assessed by the Investigator as not related to study vaccination. The Applicant provided the narratives of the 4 participants in the mRNA-1283-group on request of the Agency, which confirmed that the events were most likely not related to mRNA-1283.

An imbalance can be seen in the PT Appendicitis (6 events in the mRNA-1283 group versus 0 in the mRNA-1273 group), after review of the narratives, it is found probably to be due to chance.

All other reported AESIs were with long intervals and assessed to be not related to mRNA-1283.

Serious Adverse Events and Deaths

SAEs in Study P301 are balanced between mRNA-1283 and mRNA-1273. The proportions of participants reporting any SAE are very similar (2.7% vs. 2.6%). Events judged to be related were very rare in both groups (0.04% for mRNA-1283 vs. 0.02% for mRNA-1273). One SAE in each group has been assessed to be related according to the investigator within 28 days after study vaccination. Noteworthy, is one SAE/ AESI "Anaphylactic reaction". The investigator considered it possible delayed anaphylaxis, but the applicant disagreed, citing the absence of rapid progression, skin, mucosal or respiratory symptoms. The applicant suggested food contamination as an alternative cause. The AE has been reported as serious, medically important and related with the vaccination by the investigator. Further, the clinical description of "underarm swelling on the day of vaccination", and symptoms of fever, chills, headache, fatigue and feeling faint 18 hours after vaccination, further chest pain, nausea and subsequent diarrhoea are plausible and typical signs of delayed anaphylaxis although the Brighton-criteria for Anaphylaxis/Hypersensitivity are difficult to fully apply. Thus, anaphylactic reaction has been reflected in the SmPC**.**

Furthermore, two SAEs (1 event acute aseptic arthritis and 1 event of oligoarthritis) were reported beyond 28 days in 1 participant in the mRNA-1283-group. The Investigator assessed the events as related to study vaccine in absence of another medical explanation, but the applicant attributed it to tuberculosis arthritis or HLA-B27-associated arthropathy due to long latency and other possible causes. After providing updated information on this case, an HLA-B27–associated spondyloarthropathy seems to be the most likely explanation. While biologically plausible, with the available information to date a reasonable possibility for a causal relationship between mRNA-1283 and the two AEs cannot be established.

Seven death cases are reported for mRNA-1283 until data extraction date. The applicant presented the narratives. No causal relationship with the vaccination has been established. SAE or AESIs were rare

in the Japanese Substudy so far. None of SAEs and AESIs in Study P101 and Study P201 were judged as related.

Standard MedDRA Queries (SMQs)

SMQs have been applied. Overall, no imbalances between the mRNA-1283- and the mRNA-1273-group were detected by the applicant. Up to 28 days after study vaccine, the incidence of participants with events in the narrow scope **hypersensitivity** SMQ was 34 participants in the mRNA-1283 group and 26 participants in the mRNA-1273 group). For mRNA-1283 the most frequently reported PTs were rash (7 reports) followed by dermatitis contact (2 reports). 7 participants in the mRNA-1283 group had events that were assessed as related to study injection by the Investigator. These included one participant with hypersensitivity, one urticaria chronic, and 4 cases of rash and related terms. The remaining participant with a possible delayed anaphylactic reaction, is described in the SAE section, above. In the broad scope hypersensitivity SMQ, pruritus was the only PT for which all reported events in the mRNA-1283-group were considered related to study vaccine by the investigator for three participants. Based on the available data, the applicant included rash and hypersensitivity reactions (pruritus, urticaria, chronic urticaria) in section 4.8 of the SmPC.

It is well-established that hypersensitivity or allergic (anaphylactic) reaction can be triggered by vaccines and a general warning regarding these undesirable effects of vaccines is already included in section 4.4. of the SmPC for mNEXSPIKE.

In the **Angioedema** SMQ up to 28 days after study vaccination, the incidence of events in the narrow scope was 7 events in the mRNA-1283-group, including 5 non-related events of urticaria and one related event of chronic urticaria.

The **Cardiomyopathy** SMQ for narrow scope up to 28 days was zero; until data-cutoff two participants had non-related events in the mRNA-1283 group.

In the narrow/broad scope up to 28 days of study vaccination, 7 participants in the mRNA-1283 group had events assessed by the Investigator as related to study vaccine: the most frequently reported terms were blood pressure increased (7 participants) palpitations (7 participants), and syncope (5 participants). Rare events of elevated or abnormal blood pressure assessed as related to study vaccine were noted. All participants either had pre-existing hypertension, were prescribed antihypertensives, or had risk factors for hypertension. Out of the cases of palpitations reported only one was assessed as related to study vaccine by the Investigator. The participant reported further symptoms consistent with an upper respiratory tract infection, received concomitant medications for treatment of the other symptoms, which in the case of loratadine can in rare cases cause palpitations. Therefore, the addition of palpitations in the SmPC is currently not warranted.

Syncope, was reported in 5 participants occurring up to 28 days after study vaccination. Two events were reported on Day 1 after study vaccination. One event was assessed as related to study vaccine. A 12-year-old female participant had a syncope on the evening of Day 1 after receiving the study vaccine and was taken to the emergency room. Upon arrival she had high fever, severe headache, tachycardia and myalgia. The participants symptoms resolved during observation, and she was discharged. The remaining events of syncope were assessed as not related to study vaccine by the investigator The applicant discussed, after providing a Table listing all syncopes, the inclusion of syncope in Section 4.8 of the SmPC but did not consider it to be warranted. The applicant argued in the related case of the 12 year old female participant that although fever may have been triggered by the vaccine as part of expected reactogenicity, the syncopal event was a secondary, physiologic response to fever and not indicative of a causal, product-related adverse event. The CHMP agrees with this reasoning.

Three cases with **chest pain** were reported for the mRNA-1283-group, one of these assessed as related (case of anaphylaxis as discussed, above). One further event occurred 30 minutes post

injection with subsequent admission to the Emergency Room, and Hospital, but not assessed as related. No further **Cardiac events** were reported to be related with the vaccination for the mRNA-1283-group.

In the **Peripheral Neuropathy** SMQ, one participant had an event of hypoaesthesia on day 1 post injection, assessed as related to study injection by the investigator in the mRNA-1283-group. Close temporal and anatomical relation, the assessment of the Investigator and in-line with the other mRNA-vaccines, "hypoaesthesia" is therefore added in section 4.8 of the SmPC.

In the SMQ **Arthritis,** one participant in the mRNA-1283-group had 2 SAEs (acute aseptic arthritis and oligoarthritis) and 1 nonserious unsolicited AE (arthritis), all of which occurred beyond 28 days of study vaccination that were assessed by the Investigator as related to study vaccine. While biologically plausible, with the available information to date a reasonable possibility for a causal relationship between mRNA-1283 and the two AEs cannot be established.

In the **Immune-mediated/Autoimmune Disorders-**SMQ one event reporting a worsening of a preexisting condition in the mRNA-1283-group was assessed by the Investigator as related to study injection, describing Lichen planus exacerbation. Further, 3 events in 2 participants were reported beyond 28 days and assessed by the Investigator as related to the study injection. One case of Hypoparathyoidism, one SAE of acute aseptic arthritis, and one nonserious arthritis.

In the **Hearing and Vestibular Disorders-**SMQ Vertigo (one report) and dizziness (one report) were assessed as related with the study injection. Vertigo was the most frequently reported event in this category up to 28 days after study vaccination 5 participants in the mRNA-1283-group, but with the exception one in a 74-year old participant, they were assessed as unrelated with the vaccination. Based on the hypertension, hypercholesterolaemia and vitamin B12 deficiency as a precondition This isolated report does not warrant an update of the SmPC. One Trigeminal neuralgia on day 1 in a patient with underlying Trigeminal neuralgia and Acoustic neuroma was reported to be related with mRNA-1283 due to the temporal relationship. Due to the more plausible explanation based on the patient's medical history, inclusion in section 4.8 is not warranted at this time.

Convulsions SMQ: Up to the data cutoff date, 4 participants in the mRNA-1283-group had an event in the narrow scope. All events were assessed as not related by the Investigator.

Discontinuations due to adverse events

Discontinuations due to AEs up to 28 days cover one death-case of unknown reason 7 days post injection in the mRNA-1273-group but no discontinuation in the mRNA-1283 group. Up to data-cutoff, 8/5706 (0.1%) and 12/5711 (0.2%) discontinuations were reported for mRNA-1283 group and for mRNA-1273 group, respectively. All reports are considered to be not causally related with the vaccinations.

Safety in special populations

Age

With the exception of age-groups, no special populations (e.g. immunocompromised, pregnant) have been investigated.

The data cover 3 age-groups (adolescents aged ≥12 to <18 years, adults aged 18 to <65 years, and adults aged ≥65 years). The data suggest decreasing reactogenicity with increasing age. Rates of any solicited AR are noticeably lower in adults aged ≥65 years (71.1%) compared with adolescents (ca 79.1%) and younger adults (84.5%) with also a lower proportion of grade 3 reactions, which is in line with other COVID-19 vaccinations. The majority of events in older adults were of grade 1 or Grade 2

severity with only a small proportion being Grade 3 severity. Grade 4 events were nearly absent (only one occurrence in the control group).

Unsolicited AEs were lower in the younger age groups and increased with age. One related case of Syncope was reported in the adolescent mRNA-1283 group compared to none in the control group. Furthermore, one related Vertigo case, one related case of Hypoaesthesia and one related case of Disorientation was found in the older mRNA-1283 group. No Grade 4 Reactions have been reported with the exception of one Grade 4 fever reaction in the mRNA-1273-group.

In the subgroup of adolescents (12 to <18 years) no serious adverse events were reported and only one AESI (Anosmia) was reported.

The incidence of solicited systemic adverse reactions was similar for the mNEXSPIKE group for the population overall and across all age subgroups. Assessment of unsolicited adverse events did not reveal any safety concerns for the adolescent population, and no differences of clinical concern were noted between the two vaccine groups or when compared to the adult population.

Organ transplant

There are no confirmed safety concerns that mRNA COVID-19 vaccines can cause organ rejection in transplant recipients. Ongoing safety monitoring continues, with extra attention for people who are recently transplanted, have known donor-specific antibodies, or are on higher levels of immunosuppression. Decisions about vaccination should always be made in partnership with the patient's transplant team.

Further, the Robert Koch-Institut (RKI) has discussed and published their views and recommendations, respectively (Epid Bull 2021;39).

Pregnancy and breast feeding

Pregnant women were excluded from the phase 3 trial. A total of 10 pregnancies were reported. Two deliveries without complications were documented. For 6 pregnancies the outcome of the pregnancy was unknown (pending), and the participants continued study follow-up. One participant was discontinued due to pregnancy, and another participant had an induced abortion. No conclusions derive from this information.

Safety data on breast feeding is lacking. However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast feeding woman to mNEXSPIKE active substance is negligible. Observational data from women who were breastfeeding after vaccination with elasomeran and its variants have not shown a risk for adverse effects in breastfed newborns/infants. mNEXSPIKE can therefore be used during breast-feeding.

Phase 3 study in Japan (CSR addendum)

An additional cohort was added to Study P301 through a country-specific protocol amendment to evaluate the safety and immunogenicity of mNEXSPIKE in Japanese participants (Study P301-Japan). Participants of this Japanese cohort received a monovalent formulation of mRNA-1283.815 encoding the linked N-terminal domain-receptor binding domain (NTD-RBD) of the Spike protein of the XBB.1.5 variant. Participants were randomised 1:1 to receive mRNA-1283.815 10 µg (n=343) or mRNA-1273.815 50 µg (n=346) as a single dose.

The safety reporting of solicited and unsolicited AEs was comparable to the main study.

Preliminary results show slightly lower incidence of **solicited local reactions** in the mRNA-1283-group (86.3%) compared with the mRNA-1273 group (95.1%), also with respect to grade 3 local ARs (2.9% vs 6.6%), potentially due to the lower injection volume, in line with the results from the main study.

Incidence of **solicited local reactions** was slightly lower in the mRNA-1283-group (86.3%) than in the mRNA-1273 group (95.1%), also with respect to grade 3 local ARs (2.9% vs 6.6%), potentially due to the lower injection volume.

No SAEs or deaths were reported in either group until the data cutoff of the interim report.

It is unclear to what extent the lower reactogenicity of mRNA-1283 vs mRNA-1273 was influenced by the monovalent formulation, the different population, the lower sample size, or the longer mean time interval to previous vaccination against COVID-19 in this Japanese cohort of the Phase 3 trial.

Following the agency's request, the Applicant provided a comparative safety analysis of Studies P301 and P301-Japan showed that the safety profiles were comparable between the two studies and did not give rise to any new safety concerns. The applicant committed to update the Module 2 documents with the safety data from the Study P301 Addendum Japan when submitting the final Study P301 CSR (**REC**). The CHMP considers this to be acceptable.

Study P101

In the phase 1 Study P101, three dose levels (10, 30, and 100 µg) of mRNA-1283 (Arms 1 through 3) and 1 dose level (100 µg) of mRNA-1273 (Arm 5) were evaluated in a 2-dose regimen, with the doses administered 28 days apart. One dose level (100 µg) of mRNA-1283 was evaluated in a single-dose regimen (Arm 4). Approximately 125 participants were randomised in a 1:1:1:1:1 ratio, with approximately 25 participants randomised to each study arm.

After 2 injections, no strong and consistent dose-dependent effect on reactogenicity was noticeable, except for a trend for lower incidences in the 10 and 30 µg groups compared to the 100µg group.

Study P201

Study P201 was a phase 2a dose-ranging study to assess the immunogenicity and safety of mRNA-1283 vaccines given as a single dose, in healthy adult participants previously vaccinated with mRNA-1273. The study consisted of 2 parts. Part A was an observer-blind study of a single injection of mRNA-1283 (2.5, 5, 10 µg), mRNA-1283.211 (5 and 10 µg), or the active comparator mRNA-1273 (50 µg). Individuals who previously had a primary series of mRNA-1273 were randomised in a 1:1:1:1:1:1 ratio. Part B was an open-label study that sequentially enrolled participants who had previously received primary series and a booster to receive mRNA-1283.529 as a 5 µg or 10 µg injection.

Considering that the data from Part A suggested a lower or comparable reactogenicity of mRNA-1283 to mRNA1273, the Applicant's **choice** of the **10µg dose** seems reasonable from a safety perspective.

Clinical laboratory

Study P101 included routine clinical laboratory evaluations, while in Study P301 listed some laboratory related AEs but showed no safety issue. In Study P101, notable haemoglobin reductions across all doses of the mRNA-1283 vaccine were observed with 50 to 76.2% of participants experiencing Grade 1 reductions by Day 8, and some reaching Grade 2 or 3 toxicity. Similar trends were seen at Day 29 and Day 36. One event of decreased haemoglobin in the 100 µg group was judged as related by the investigator. It is understood that the haemoglobin decreases were in normal range in most cases. The Applicant discussed the consistent trend of decreased haemoglobin after receiving this vaccination to be small, within normal ranges, clinically silent, and reversible. The few cases meeting higher grade thresholds did not manifest as clinical anaemia. No concerning trends were observed from the CSR for Study P101, which included coagulation laboratory data (aPTT and PT).

2.5.10. Conclusions on the clinical safety

Based on the available evidence, one dose of 10 µg mRNA-1283 demonstrates an acceptable safety profile comparable to the already approved mRNA-1273 (Spikevax), characterised by respective transient and predominantly mild to moderate ARs. The most frequently reported solicited local ARs were pain at the injection site, axillary swelling or tenderness, arthralgia, chills and nausea/vomiting and the most commonly reported solicited systemic adverse reactions across dose groups were fatigue, headache and myalgia. With increasing age reactogenicity decreased, as expected but also the youngest age group ≥12-<18 Years showed lower reactogenicity compared to adults. Most unsolicited AEs were of mild to moderate severity and the numbers of SAEs and deaths were comparable to the control group. No causal relationship was established between the vaccine and the fatal cases.

No new safety issues have been identified based on the submitted safety data.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Myocarditis Pericarditis
Missing information	Use in pregnancy

2.6.2. Pharmacovigilance plan

Study Number, Title, and Categories (Status)	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
mRNA-1283-P901 Post-marketing safety of the mRNA-1283 vaccine in the United States (Planned)	Primary Objectives: • Estimate the incidence of myocarditis and pericarditis among recipients of mRNA-1283 and among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously	Myocarditis Pericarditis	Protocol submission: Final report:	31 Mar 2026 30 Sep 2029

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
mRNA-1283-P902 An observational cohort study to assess maternal and infant outcomes following exposure to mRNA-1283 during pregnancy (Planned)	Primary Objectives: • Describe the utilisation of the mRNA-1283 vaccine in routine clinical practice and estimate incidence rates of pregnancy complications (gestational hypertensive disorders and gestational diabetes), adverse pregnancy outcomes (medically attended spontaneous abortion, stillbirth, and preterm birth), and infant major congenital malformations among mRNA-1283 vaccine recipients using large-scale administrative claims data in the US. • Upon accrual of a sufficient number of exposed pregnancies: ○ Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of pregnancy complications. ○ Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of adverse pregnancy outcomes. ○ Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased prevalence of infant MCM.	Use in pregnancy	Final report:	15 Dec 2032
mRNA-1283-P904 Long-term outcomes of myocarditis following administration of the mRNA-1283 vaccine (Planned)	Primary Objectives: • Characterise the presentation and clinical course of vaccine-associated myocarditis • Characterise potential long-term outcomes following vaccine-associated myocarditis	Myocarditis	Final report:	31 Mar 2034
mRNA-1283-P906 Post-marketing safety of the mRNA-1283 vaccine in Europe (Planned)	Primary Objectives: • Monitor the distribution of mRNA-1283 in Europe. • Describe the uptake of mRNA-1283, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them. • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received a COVID-19 vaccine within the past 90 days.	Myocarditis Pericarditis	Final report:	30 Sep 2030

Abbreviations: COVID-19 = coronavirus disease 2019; MCM = major congenital malformation; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; US = United States.

2.6.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis (Important potential risk)	Routine risk minimisation measures: • *Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4* • *Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4* • *Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2* • *Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P901* • *mRNA-1283-P904* • *mRNA-1283-P906*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis (Important potential risk)	Routine risk minimisation measures: • *Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4* • *Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4* • *Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2* • *Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P901* • *mRNA-1283-P906*
Use in pregnancy (Missing information)	Routine risk minimisation measures: • *SmPC Section 4.6* • *SmPC Section 5.3* • *Precautionary guidance to avoid the use of mNEXSPIKE during pregnancy in SmPC Section 4.6* • *Guidance for the user to tell their doctor, nurse or pharmacist if they are pregnant or think they may be pregnant before they receive this vaccine in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P902*

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. 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. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 30.05.2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

the Group granted a labelling exemption to replace the full excipient name (IUPAC name) "heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate" with the acronym "SM-102" on the outer carton due to space constraints.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, mNEXSPIKE (COVID-19 mRNA Vaccine) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by SARS-CoV-2, that spread worldwide during 2020 causing WHO to declare a pandemic on 11 March 2020. Globally, as of 2 November 2025, 281,593,874 COVID-19 cases and 2,281,733 deaths had been reported. On 5 May 2023, given that the disease was well established and ongoing, WHO considered that COVID-19 no longer met the definition of a Public Health Emergency of International Concern. COVID-19 is no longer a pandemic, but the virus is still present.

The clinical manifestation of COVID-19 is non-specific and variable. It can range from no symptoms (asymptomatic) to severe pneumonia and death. The disease burden is highest amongst individuals with increased age; however, all age groups are susceptible. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease,

immune compromised status, cancer, and obesity are considered risk factors for developing severe COVID-19.

COVID-19 remains a global health threat that still places a burden on healthcare systems, and due to new birth cohorts, waning immunity and antigenic evolution of the virus, there is a recognised need for periodic COVID-19 vaccination.

3.1.2. Available therapies and unmet medical need

Intervention for SARS-CoV-2 infection includes prophylactic vaccination, supportive care for symptomatic infection, and treatments for the viral infection, including antivirals, immune modulators, and monoclonal antibodies.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase 3 multicentre, randomised, observer-blind study to demonstrate non-inferiority of mRNA-1283.222 (mNEXSPIKE) in adolescents and adults 12 years of age and older in terms of relative vaccine efficacy (rVE) and immunogenicity as compared to approved mRNA-1273.222 (Spikevax original/BA.4-5).

3.2. Favourable effects

Overall, non-inferiority (NI) of mRNA-1283.222 versus approved mRNA-1273.222 (bivalent Spikevax original/Omicron BA.4-5) in terms of rVE (9.31, multiplicity adjusted 95% CI: -6.58, 22.83) could be demonstrated.

The immune responses measured in the pivotal study P301 and its local sub study P301-Japan (supportive) show a better geometric mean (GM) increase of the new vaccine compared to an authorised vaccine (Spikevax). The baseline GMs against each strain variant are similar in the vaccination groups but the new vaccine not only formally fulfils the NI but often shows a significantly higher fold-increase than the comparator. With the new vaccine all age groups show similar immune responses, especially the elderly age group shows better immune responses than the younger adults. Adolescents show the highest immune responses compared to the adult age groups. The fold-increases are similar across all vaccine strain variants tested (D614G, BA4-5 and XBB1.5).

3.3. Uncertainties and limitations about favourable effects

Uncertainties regarding the blinding procedures (e.g. late specification of blinding and communication plans) and issues with the conduct of study (including the late definition of the adaptive design and uncertainties regarding the timing) impact the reliability of the results to some extent. It is acknowledged that one driver of the design change were FDA requirements to show non-inferiority with a -10% NI-margin. Overall, it is considered that due to the magnitude of the rVE effect and the limited impact of the observed issues, non-inferiority was demonstrated.

Formally, non-inferiority in adolescents from 12 – 17 years of age could not be demonstrated. However, the study was conducted when SARS-CoV-2 variant XBB.1.5 became the pre-dominantly circulating variant. On the other hand, nAb titres in the adolescent age group 12 – 17 years of age exceeded the titres from other age groups and were comparable for both treatment groups. Incidence rates in the adolescent groups were lower as compared to the adult groups.

In study mRNA-1283-P301 no subjects from special populations such as immunocompromised or pregnant women have been enrolled.

3.4. Unfavourable effects

The clinical safety profile of mRNA -1283 was mainly derived from data obtained in study P301 which represents a major part of the overall exposure to the mRNA-1283.222 vaccine (5 706 participants vs 5 711). The median safety follow-up in study P301 was 8.8 months.

Additionally, Day 29 interim analysis safety results are available for Study P301-Japan as summarised in the Study P301-Japan CSR Addendum.

Reactogenicity: The incidence of any solicited adverse reaction (AR) was 80.2% in the mRNA-1283 group and 83.8% in the control group. Solicited local ARs were reported in 70.3% versus 78.4% of participants, while systemic ARs were observed in 64.4% and 64.2% of participants in the mRNA-1283 group and mRNA-1273 group, respectively. Injection site pain was the most frequently reported local AR, affecting 68.5% of participants of the mRNA-1283 compared to 77.5% in the mRNA-1273 group, followed by axillary swelling/tenderness (19.7 vs 18.4%). Fatigue was the most common systemic AR (50.4% vs. 49.0%), followed by headache (44.2% vs. 41.2%), myalgia (38.2% vs. 37.0%), and arthralgia (29.7% vs. 27.6%). Grade 3 solicited ARs were reported in 8.0% of participants in the mRNA-1283 group and in 6.9% of participants in the mRNA-1273 group. Grade ≥3 local reactions were infrequent occurring in 1.6% and 2.1% of participants in the mRNA-1283 group and mRNA-1273 group, respectively, with injection site pain being the most frequent. Grade ≥3 systemic reactions were observed in 7.2% versus 5.8% of participants in the mRNA-1283 group and mRNA-1273 group, respectively, with fatigue being the most frequent severe systemic event. Only a small proportion of participants (1.4% vs. 1.3%) experienced solicited ARs that persisted for more than 7 days.

Unsolicited AEs: Unsolicited AEs were reported in 12.3% and 11.9% of participants in the mRNA-1283 group and mRNA-1273 group respectively, within the first 28 days post injection. The most frequently reported unsolicited AEs were of the SOCs "Infections and Infestations", "Nervous System Disorders" and "Respiratory, Thoracic, and Mediastinal Disorders". The incidence of Grade ≥3 unsolicited AEs was 0.2% and 0.3%. AEs considered to be related were observed in 0.8% versus 0.9% of participants.

AESIs: In study P301 AESIs until data cut-off were reported by 0.1% of participants in both the mRNA-1283 group and the mRNA-1273 group. No cases of myocarditis/ pericarditis were reported in the mRNA-1283 group.

SAE: SAEs were rare, occurring in 0.2% vs. 0.3% of participants in the first 28 days. Up to the data cut-off date, the incidence of SAEs was balanced between groups 2.7% in the mRNA-1283 group and 2.6% in the mRNA-1273 group. None of the SAE considered related to the vaccine was reported by more than 1 participants.

3.5. Uncertainties and limitations about unfavourable effects

Despite the rather large phase 3 trial, potential rare adverse events might not have been detected.

Post-marketing data for Spikevax revealed ADRs, which were not detected in initial clinical trials. This includes rare cases of myocarditis/pericarditis, for which pharmacoepidemiological studies revealed the highest excess risk in younger males. It is not known whether there is a similar risk for cardiac inflammation with mRNA-1283. As a result, the relevant warning in section 4.4 of the SmPC is

included. The RMP includes myocarditis and pericarditis as important potential risks together with additional pharmacovigilance activities.

Individuals with congenital or acquired immunodeficiency or immune-mediated disease requiring treatment were excluded from the trial. Taking all the available information together, there is no confirmed safety concern that mRNA COVID-19 vaccines might cause organ rejection in transplant recipients. Of note, there were cases of exacerbations of pre-existing autoimmune (but also other) conditions.

No safety data are available for frail individuals with unstable medical conditions.

There are no data on the use in pregnant women since they were not included in the clinical development program. However, the applicant is planning and conducting studies, which will assess the safety in this population.

Effects Table

Table 36. Effects Table for mNEXSPIKE, indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older

Effect	Short Description	Unit	mRNA-1283 (mNEXSPIKE)	mRNA-1273 (Spikevax)	Uncertainties/ Strength of evidence	References
Favourable Effects						
rVE	Non-inferiority of mRNA-1283.222 vs. mRNA-1273	Incidence rate per 100 person-months (95% CI)	1.373 (1.262, 1.492)	1.513 (1.396, 1.637)	Uncertainties in conduct of study and blinding	P301
		rVE based on Hazard Ratio, % (99.4% CI)	9.31 (-6.58, 22.83)			
nAbs	NI for GMR and SRR difference (lower bound of the GMR 95% CI needed to be >0.667 and lower bound of the SRR difference 95% CI needed to be above -10%) on D29	BA.4-5 SRR n (%) 95% CI	496 (79.9) (76.5, 83.0)	372 (65.5) (61.4, 69.4)	SoE: Primary objective met	P301
		BA.4-5 SRR difference % (95% CI)	14.4 (9.3, 19.4)			
		BA.4-5 GMR (95% CI)	1.335 (1.194, 1.492)			
		D614G- SRR n (%) 95% CI	519 (83.6) (80.4, 86.4)	414 (72.9) (69.0, 76.5)		
		D614G SRR difference % (95% CI)	10.7 (6.0, 15.4)			
		D614G GMR (95% CI)	1.240 (1.128, 1.362)			
nAbs	NI for GMR (lower bound of the GMR 95% CI needed to be >0.667) on D29	XBB.1.5 GMR (95% CI)	1.20 (1.03, 1.39)		SoE: Primary objective met consistent with P301 results	P301 - Japan

Effect	Short Description	Unit	mRNA-1283 (mNEXSPIKE)	mRNA-1273 (Spikevax)	Uncertainties/ Strength of evidence	References
	SSR on D29	XBB.1.5 SRR n % (95% CI)	92.2 (88.8, 94.9)	86.8 (82.7, 90.3)		
		XBB.1.5 SRR difference % (95% CI)	5.4 (0.8, 10.2)			
Unfavourable Effects						
Solicited adverse reactions						
solicited ARs		%	80.2	83.8		P301
solicited local ARs		%	70.3	78.4		
solicited systemic ARs		%	64.4	64.2		
Injection site pain		%	68.5	77.5		
Fatigue		%	50.4	49.0		
Headache		%	44.2	41.2		
Myalgia		%	38.2	37.0		
Arthralgia		%	29.7	27.6		
Local ARs Grade ≥3		%	1.6	2.1	Mostly inj. site pain	
Systemic ARs Grade ≥3		%	7.2	5.8	Mostly fatigue	
ARs Persisted >7 days		%	1.4	1.3		
Unsolicited adverse events <28 days						
Any AE		%	12.3	11.9		P301
Severe/≥Grade 3 AEs		%	0.2	0.3		
SAEs		%	0.2	0.3		

Abbreviations: AEs: Adverse Events, ARs: Adverse Reactions, CI: confidence intervals, GM: geometric mean, GMR: geometric mean ratios, NI: noninferiority, rVE: relative vaccine efficacy, nAb: neutralising antibodies, SAEs: Serious AEs, SRR: seroresponse rate.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Study mRNA-1283-P301 demonstrated overall rVE of mRNA-1283.222 as compared to approved mRNA-1273.222 (Spikevax bivalent original/Omicron BA.4/5). Immunogenicity results also favoured mRNA-1283 versus mRNA-1273.

The overall documented safety exposure is considered sufficient to assess the safety profile of the mRNA-1283. The safety profile is acceptable and mainly characterised by reactogenicity reactions. The most frequently reported adverse events were injection-site pain, fatigue, myalgia, headache and arthralgia, and these reactions were mostly mild to moderate, transient, and self-limited. SAEs and AESIs were infrequent. Some aspects will remain open for the routine postmarketing setting.

No immunocompromised participants were included in the studies, and safety information for frail patients with unstable conditions is lacking. However, it is not anticipated that mRNA-1283 will show a principally different safety profile than the authorised comparator in these sub-populations. Pregnant women were also excluded from the study, however, the applicant is planning and conducting studies,

which will assess the safety in this population. Myocarditis and pericarditis remain important potential risks to be further monitor post-authorisation via additional pharmacovigilance and routine pharmacovigilance activities.

3.6.2. Balance of benefits and risks

Study mRNA-1283-P301 demonstrated non-inferiority of mRNA-1283.222 in the overall study population as compared to mRNA-1273.222 (Spikevax bivalent original/Omicron BA.4-5) in relative efficacy, and in the immunogenicity in terms of GMR and SRR.

The mRNA-1283 vaccine is mildly reactogenic and generally well-tolerated in the intended target population.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable

3.7. Conclusions

The overall benefit/risk balance of mNEXSPIKE is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of mNEXSPIKE is favourable in the following indication(s):

> *mNEXSPIKE is indicated for active immunisation to prevent COVID 19 caused by SARS-CoV-2 in individuals 12 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the N-terminal domain and receptor-binding domain of the viral spike (S) protein of SARS-CoV-2 (XBB.1.5) is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0365/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.