Summary Basis for Regulatory Action

Date:	May 30, 2025
From:	Joseph M. Kulinski, PhD, Review Committee Chair, OVRR/DRMRR
BLA STN:	125835/0
Applicant:	ModernaTX, Inc.
Submission Receipt Date:	September 30, 2024
PDUFA* **Action Due Date:**	May 30, 2025
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	MNEXSPIKE
Indication (Proposed by Applicant):	Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have been previously vaccinated with any COVID-19 vaccine.

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR/DVP) • Facilities review (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Alena Dabrazhynetskaya, PhD – **OVRR/DVP** Christian Sauder, PhD – **OVRR/DVP** Swati Verma, PhD **– OVRR/DVP** Ou (Olivia) Ma, PhD **– OCBQ/DMPQ** Alla Kachko, PhD **– OCBQ/DMPQ** Karla Garcia **- OCBQ/DBSQC** Most Nahid Parvin, PhD **- OCBQ/DBSQC** Sang Hyuk Lee, PhD **- OCBQ/DBSQC** Marie Anderson, MS, PhD **- OCBQ/DBSQC**
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • Bioresearch Monitoring (BIMO)	Timothy Brennan, MD **– OVRR/DCTR** Brittany Shepherd, MD **– OVRR/DCTR** Stefanie Rodwell, MD **– OBPV/DPV** Haecin Chun, MS **– OCBQ/DIS**
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Ross Peterson, PhD – **OBPV/DB** Xinxin Sun, PhD – **OBPV/DB**
Non-clinical/Pharmacology/Toxicology • Toxicology/Developmental toxicology (Product Office) • Animal pharmacology	Nabil Al-humadi, PhD – **OVRR/DCTR** Alena Dabrazhynetskaya, PhD – **OVRR/DVP** Christian Sauder, PhD **- OVRR/DVP**
Clinical Pharmacology	Stefanie Rodwell, Ph.D. – **OPBV/DPV**
Labeling • Promotional (OCBQ/APLB) • Container and Carton/Package Insert Review(OVRR)	Oluchi Elekwachi, PharmD – **OCBQ/APLB** Daphne Stewart - **OVRR/DRMRR** Sylvia Park, PharmD - **OVRR/DRMRR** Donna Elhindi, PharmD- **OVRR/DRMRR** Charu Mullick, MD - **OVRR/DCTR**
Other Review(s) not captured above categories • Data Standards • Devices • DHT • Human Factors • PMR/PMC Coordinator • Regulatory Project Management	Brenda Baldwin, PhD – **OVRR/DRMRR** Andrea Gray, PhD – **ORO/DROP** Aneesha Sahu, PhD – **OBPV/DABRA** Neha Kumar, PhD – **CDER/OSE/OMEPRM/DMEPA** Helen Gemignani – **OVRR/DRMRR** Sylvia Park, PharmD – **OVRR/DRMRR** Donna Elhindi, PharmD – **OVRR/DRMRR**

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1. Introduction

ModernaTX, Inc. submitted an original Biologics License Application (BLA) STN 125835/0 for COVID-19 Vaccine, mRNA (proprietary name: MNEXSPIKE) on September 30, 2024. MNEXSPIKE is a vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have been previously vaccinated with any COVID-19 vaccine. MNEXSPIKE is administered as a single 0.2 mL dose at least 3 months after the last dose of COVID-19 vaccine.

MNEXSPIKE (also referred to in this document as “mRNA-1283 vaccine”) contains a nucleoside-modified *in vitro*-transcribed messenger RNA (mRNA) encoding the N-terminal domain (NTD) and receptor binding domain (RBD) of the S protein linked to a transmembrane domain of the influenza hemagglutinin (HATM) that is encapsulated in lipid nanoparticles (LNPs) composed of four lipids: SM-102, polyethylene glycol [PEG]

2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]. The NTD and RBD sequences are linked together with a 7-amino acid (aa) flexible linker, and the linked NTD-RBD polypeptide is attached via a (b) (4) linker to a 23-aa HATM. The RBD and NTD domains of the S protein are known to contain key sites of neutralization and a high proportion of T-cell epitopes. The HATM domain promotes fusion of the polypeptide to cell membrane and anchoring to the cell surface for antigen presentation. The mode of action is based on delivery of the mRNA-LNPs into host cells to allow expression of the NTD-RBD-HATM antigen. The vaccine elicits an immune response, which protects against COVID-19.

MNEXSPIKE is provided as a sterile, clear, (b) (4) suspension for intramuscular injection, and is supplied in a single-dose 1-mL cyclic olefin copolymer (COC) prefilled syringe (PFS). Each 0.2 mL vaccine dose is targeted to contain 10 µg of mRNA, 200 µg of total lipids, 0.09 mg tromethamine, 0.51 mg tromethamine hydrochloride, and 17 mg sucrose. The vaccine does not contain preservatives, antibiotics, adjuvants, and human- or animal-derived materials. MNEXSPIKE is stored frozen between -40°C to -15°C but can be stored refrigerated between 2° to 8°C for up to 90 days prior to first use.

The expiry for MNEXSPIKE supplied in single-dose 1-mL COC PFS is 12 months from the date of manufacture when stored at -40°C to -15°C. The date of manufacture is defined as the date of final sterile filtration of the formulated drug product (DP). Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the FDA.

2. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA zoonotic coronavirus that emerged in late 2019 and is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, but many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older, and individuals with certain underlying co-morbid conditions[2], may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome. In some cases, this may lead to multiorgan failure and/or death. In the U.S., more than 1.2 million deaths from COVID-19 have been reported to the CDC[3], with a cumulative COVID-19-associated hospitalization rate of 71.2 per 100,000 people for the 2024-2025 season, as of August 24, 2024[3]. Individuals 65 years of age and older accounted for 76% of deaths[4], while individuals 18 years of age and younger represent less than 0.2% of deaths[4].

SARS-CoV-2 no longer has a worldwide pandemic classification but continues to exhibit an endemic pattern characterized by waxing and waning of attack rates over the course of a year and with continued evolution of viral sub-lineages. Infection with SARS-CoV-2 continues to be an ongoing global health challenge. As of May 12, 2025, SARS-CoV-2 infection has resulted in over 777 million cases of COVID-19 and over 7 million deaths worldwide[1], and has caused significant societal, economic, and healthcare system disruptions, which were particularly severe in 2020 and 2021.

SARS-CoV-2 evolution is complex and remains unpredictable. Although acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. Intrinsic viral

factors, such as mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals.

COVID-19 vaccination has proven to be a cornerstone of the pandemic response, as vaccines have provided protection against COVID-19. COVID-19 vaccines based on the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as ancestral, reference, or original strain) were made available in the U.S, starting in December 2020 under an emergency use authorization (EUA) issued by FDA. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 Omicron variants. Omicron XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023. By September 2024, circulating Omicron variants worldwide included XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant Omicron variant in the U.S. in September 2024 was KP.3.1.1. It was one of many currently co-circulating JN.1-derived variants that overtook KP.3 and continued to increase in proportion. As of April 12, 2025, the dominant variants in the U.S. were Omicron LP.8.1 and XEC.

Spikevax (COVID-19 Vaccine, mRNA) and Comirnaty (COVID-19 Vaccine, mRNA) are mRNA-based vaccines manufactured by Moderna and Pfizer for BioNTech, respectively, that are currently approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The 2024-2025 Formula of both products contain nucleoside-modified mRNA, encoding pre-fusion stabilized full-length Spike S protein of the SARS-CoV-2 Omicron variant KP.2. NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is an FDA-approved COVID-19 vaccine based on recombinant spike (rS) protein of SARS-CoV-2. Each 0.5 mL dose of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) 2024 – 2025 Formula contains 5 mcg of rS protein (based on Omicron variant lineage JN.1 sequence) and 50 mcg Matrix-M adjuvant.

Several antiviral therapies, including a protease inhibitor (nirmatrelvir/ritonavir), an RNA-dependent RNA polymerase inhibitor (remdesivir), and immune modulators (baricitinib and tocilizumab) have been approved by FDA as treatments for COVID-19.

The regulatory history of MNEXSPIKE is summarized in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	Not held
2. IND submission	01/25/2021
3. Pre-BLA meeting	7/10/2024
4. BLA 125835/0 submission	09/03/2024
5. BLA filed	11/26/2024
6. Mid-Cycle communication	Cancelled by applicant
7. Late-Cycle meeting telecon	03/31/2025
8. Action Due Date	05/30/2025

3. Chemistry Manufacturing and Controls (CMC)

In the original BLA 125835/0 submission, CMC and nonclinical information pertained to mRNA encoding the N-terminal domain (NTD) and receptor-binding domain (RBD) of the Spike protein of the SARS-CoV-2 Omicron variant lineage XBB.1.5, which is the RNA component of COVID-19 Vaccines (2023-2024 Formula) and not the updated COVID-19 vaccines (2024-2025 Formula) for use in the United States (U.S.) that began in fall 2024 (see: https://www.fda.gov/vaccines-blood-biologics/updated-covid-19-vaccines-use-united-states-beginning-fall-2024).

Additional CMC and nonclinical data were subsequently submitted by the applicant to support the use of an Omicron subvariant lineage JN.1 (2024-2025 Formula) of mRNA-1283 to align with the recommendation for COVID-19 vaccine (2024-2025 Formula).

a. Product Quality

Description of Active Ingredient and its Development

MNEXSPIKE is an mRNA-based vaccine indicated for active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 12 years of age and older who have been previously vaccinated with any COVID-19 vaccine. The mRNA in MNEXSPIKE is called mRNA-1283 and is comprised of the N-terminal domain (NTD) and receptor-binding domain (RBD) of the SARS-CoV-2 Spike (S) glycoprotein. The NTD and RBD sequences are linked together with a 7-amino acid (aa) flexible linker (NTD-RBD). The linked NTD-RBD polypeptide is attached via a (b) (4) linker to a 23-aa influenza hemagglutinin transmembrane domain (HATM), which anchors the linked NTD-RBD antigen to the host cell membrane. The mRNA also contains four regulatory elements: 5' and 3' untranslated regions (UTRs) which increase translational fidelity and confer robust protein expression, a 3' poly(A) tail sequence which promotes mRNA stability, and a 5' cap structure ((b) (4)) which mediates efficient translation. The mRNA is transcribed using N1-methyl-pseudoruridine instead of uridine nucleoside to minimize indiscriminate recognition of exogenous mRNA by pathogen-associated cellular receptors and to reduce the overall reactogenicity of synthetic mRNA. The in vitro transcribed single-stranded mRNA is encapsulated in a lipid nanoparticle ((b) (4)) composed of four lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; cholesterol, and DSPC. MNEXSPIKE is supplied as a frozen suspension that does not contain a preservative and must be thawed prior to administration.

Manufacturing Overview

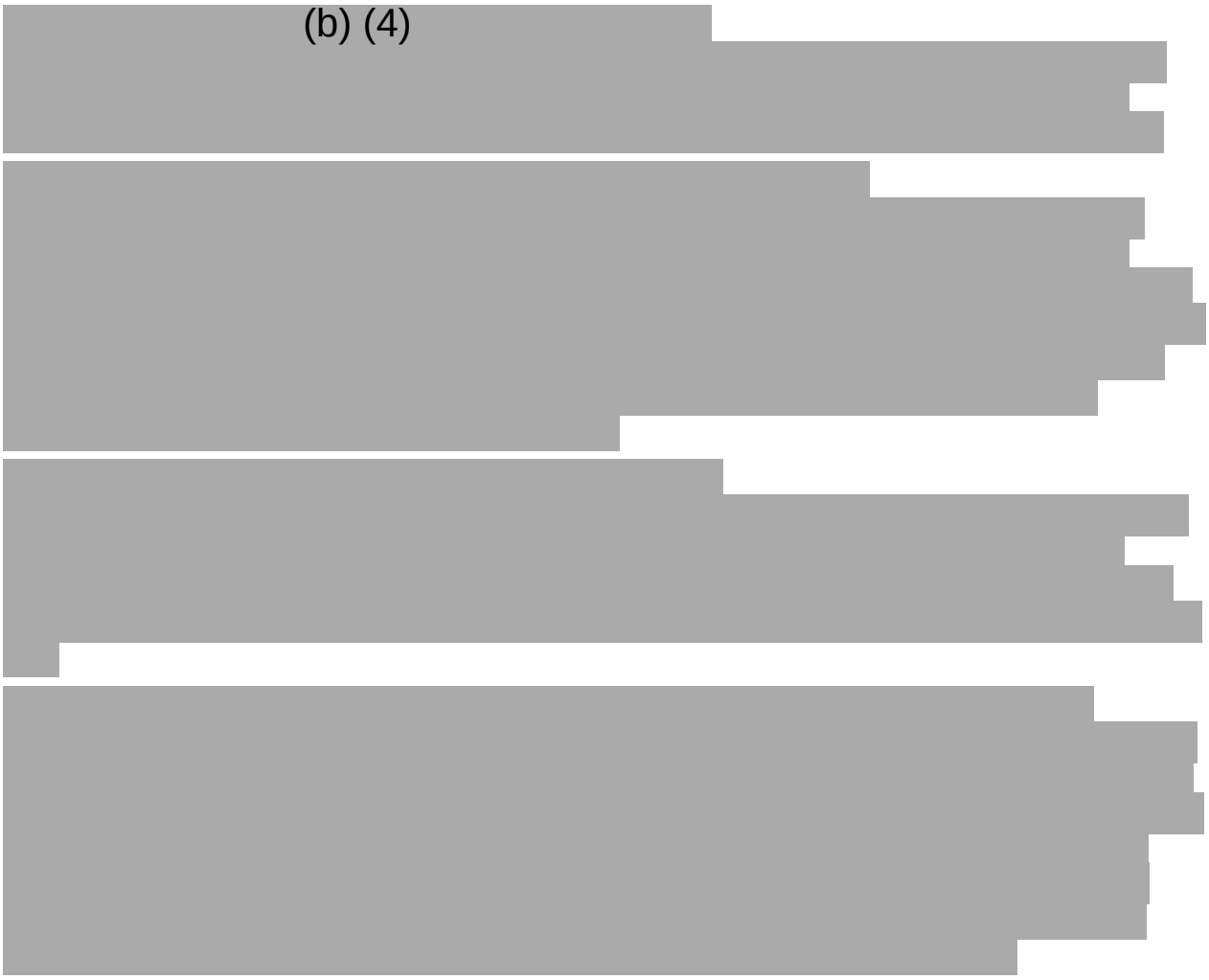
The manufacturing process for the mRNA-1283 drug substance (DS) consists of (b) (4) main steps: (b) (4)

The mRNA-1283 DP is manufactured by adjusting the concentration of the (b) (4) to the target RNA dose, formulating with a cryoprotectant, and sterile filtration, followed by filling into syringes, labeling, and packaging.

DRUG SUBSTANCE

(b) (4)

2 pages have been determined to be not releasable: (b)(4)



DRUG PRODUCT– mRNA-1283 {UDP-(b) (4) /LDP-(b) (4) }

The mRNA-1283 drug product (DP) is an mRNA-lipid complex consisting of an mRNA encapsulated in lipid nanoparticles (lipid (b) (4)). The mRNA-1283 DP is a sterile, preservative-free, white to off-white suspension containing 0.05 mg/mL RNA-(b) (4), 1.0 mg/mL (b) (4), and (b) (4) g/L sucrose in (b) (4) mM Tris buffer (pH (b) (4) The Final DP is supplied as a sterile, single-dose, ready-to-use liquid solution in a 1-mL COC prefilled syringe (PFS) for intramuscular (IM) administration.

Each PFS is intended to deliver a 0.2 mL dose containing 10 µg of RNA and 200 µg of total lipids. Composition and properties of the mRNA-1283 DP in PFS are shown in **Table 2**.

Table 2. mRNA-1283 Drug Product Composition

Component	Unit Formula (mg/mL)	Unit Formula (µg/dose) (0.2 mL dose)
RNA- (b) (4)	0.05	10
SM-102	(b) (4)	(b) (4)
Cholesterol	(b) (4)	(b) (4)
DSPC	(b) (4)	(b) (4)
mPEG2000-DMG	(b) (4)	(b) (4)
Tris	0.45	90
Tris-HCl	2.6	510
Sucrose	(b) (4)	17 mg
Water for injection	q.s. to 1.0 mL	q.s. to 0.2 mL

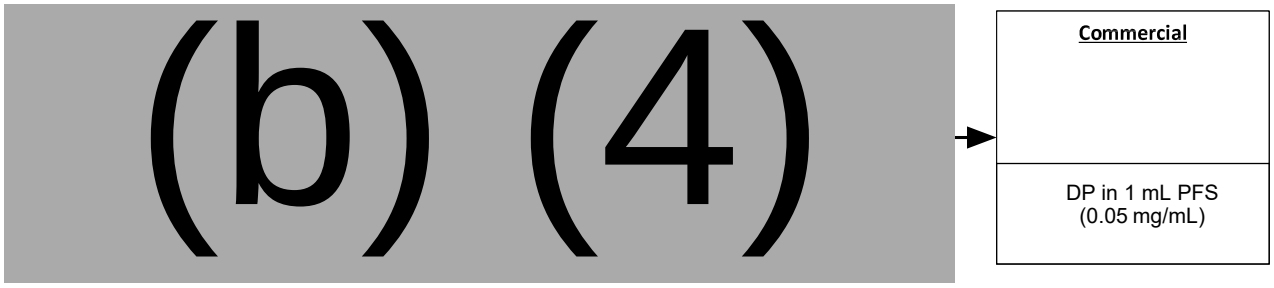
RNA - ibonucleic acid; LNP - lipid nanoparticle; SM-102 - (b) (4) ; DSPC - 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG - 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000;

Manufacture of mRNA-1283 DP

The mRNA-1283 DP is manufactured by adjusting the concentration of the (b) (4) to the target mRNA dose and formulating with a cryoprotectant, followed by sterile filtration, filling into syringes, labeling, and packaging.

Manufacturing Process Development

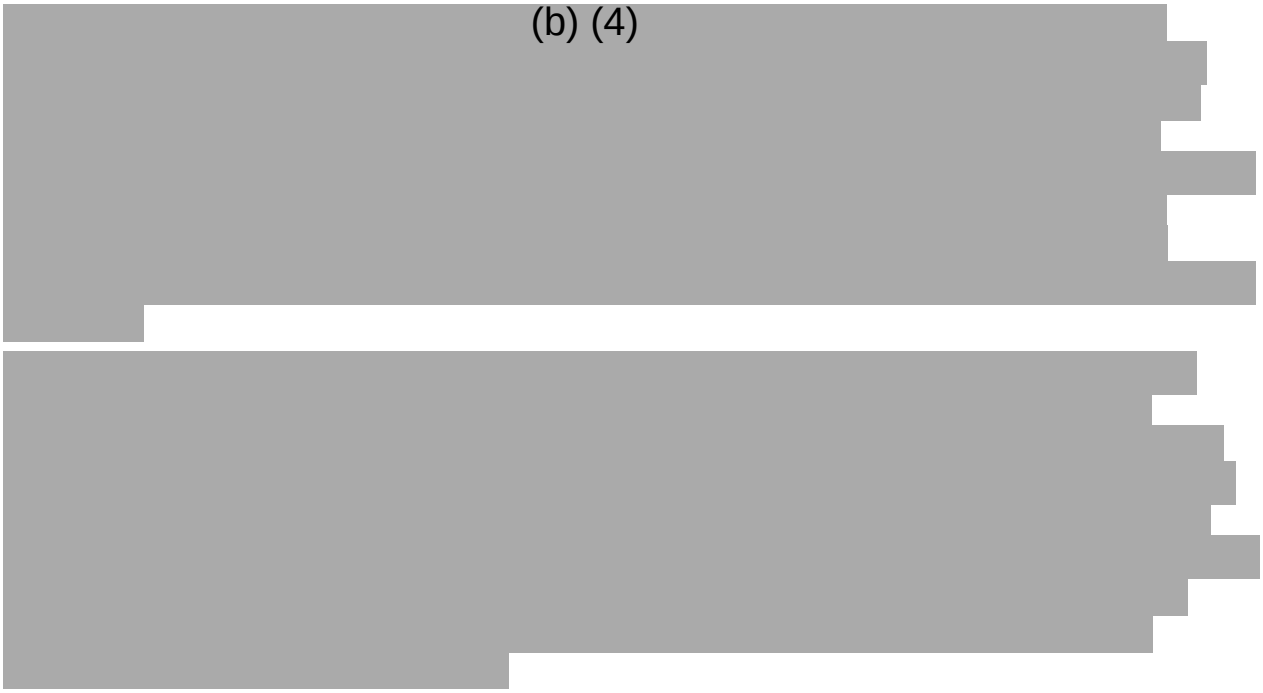
Manufacturing process development for mRNA-1283 DP progressed to support clinical development and commercial registration as shown in the scheme below.



The Version A manufacturing process is a (b) (4) -batch process, developed to supply early-phase clinical studies, mRNA-1283-P101 and mRNA-1283-P201, and pivotal clinical study mRNA-1283-P301 Part 1. The Version B manufacturing process is a (b) (4) DP process, developed to supply pivotal clinical studies and is representative of the intended commercial-scale process. The commercial process was developed to achieve the target strength, safety, and product quality attributes in a scaled-up production, ensuring comparability with the previously manufactured clinical DP.

Comparability Assessment

Comparability assessment was performed to ensure that the quality attributes of the DP, from the Version B process for the pivotal mRNA-1283-P301 clinical studies to the commercial-scale PPQ lots, remain consistent throughout the implemented manufacturing process changes.



Stability Summary and Conclusion

An initial shelf life of 12 months is proposed for the mRNA-1283 DP lots stored in the commercial container-closure system at the recommended long-term storage condition of -40°C to -15°C. The proposed shelf life may include up to 90 days of storage at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25ºC) to support administration of the vaccine at the point-of-care site.

b. Testing Specifications

The specifications for release testing of MNEXSPIKE are shown in **Table 3**.

Table 3. The release and shelf-life specifications for MNEXSPIKE

Test Method	Sample	Release Acceptance Criteria	Shelf-Life Acceptance Criteria
Appearance by Visual Inspection	(b) (4)	White to off-white dispersion. May contain visible, white or translucent product related particulates	White to off-white dispersion. May contain visible, white or translucent product related particulates
Identity by (b) (4)		(b) (4)	N/A
Total RNA Content by (b) (4)		(b) (4)	
mRNA Purity by (b) (4)			
Product-related Impurities by (b) (4)			
% RNA (b) (4) by (b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
Lipid Identity by (b) (4) SM-102 Cholesterol		(b) (4)	N/A

Test Method	Sample	Release Acceptance Criteria	Shelf-Life Acceptance Criteria
DSPC PEG2000-DMG	(b) (4)		
Lipid Content by (b) (4) SM-102 Cholesterol DSPC PEG2000-DMG		(b) (4)	
Lipid-related Impurities by (b) (4)			
Particulate Matter by (b) (4)			
(b) (4)			
(b) (4)		(b) (4)	N/A
Bacterial Endotoxins by (b) (4)		(b) (4)	(b) (4)
Sterility by (b) (4)		No Growth	No Growth
Deliverable Volume by (b) (4)		For each of the (b) (4) yringes: (b) (4) 0.2 mL	For each of the (b) (4) syringes: (b) (4) 0.2 mL
(b) (4)		(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)
Container Closure Integrity		N/A	PASS

Abbreviations: (b) (4) JP = Japanese Pharmacopoeia; LDP = Labeled Drug Product; N/A = not applicable; PFS = pre-filled syringe; Ph. Eur. = European Pharmacopoeia; (b) (4) UDP = Unlabeled Drug Product; USP = U.S. Pharmacopeia

The analytical methods and their validation and/or qualification for (b) (4) DP were found to be adequate for release testing and stability monitoring.

c. CBER Lot Release

Moderna submitted an LRP template in BLA 125835 on September 30, 2024. This template was reviewed by OVRR/DVP, OCBQ/DBSQC and OCBQ/DMPQ/PRB with comments. A response and revised LRP template were submitted in amendment 125835/0.11 on January 10, 2025. This response and LRP template were reviewed by OCBQ/DBSQC and found to be acceptable for use for future lot release submissions.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of COVID-19

Vaccine, mRNA are listed in Table 4. The activities performed and inspectional histories are noted in the table.

Table 4. Manufacturing Facilities Table for MNEXSPIKE (COVID-19 Vaccine, mRNA)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
ModernaTX, Inc. One Moderna Way Norwood, MA 02062 *DS manufacturing and release testing*	3014937058	116912313	Waiver	ORA April 2024 NAI
(b) (4) *Manufacture of* (b) (4)	(b) (4)	(b) (4)	Waiver	OII (b) (4) NAI
(b) (4) *DP manufacturing*	(b) (4)	(b) (4)	Waiver	OII (b) (4) VAI
(b) (3), (b) (4) *DP* (b) (4)	(b) (3), (b) (4)	(b) (3), (b) (4)	Waiver	CBER/DMPQ (b) (3), (b) (4) Records request acceptable
(b) (4) *DP primary labeling, packaging, and release testing*	(b) (4)	(b) (4)	Waiver	ORA for CDER (b) (4) VAI
(b) (3), (b) (4) *DP release testing*	(b) (3), (b) (4)	(b) (3), (b) (4)	Waiver	MRA/(b) (3), (b) (4) (b) (3), (b) (4) Assessed by ORA: VAI
Moderna Biotech Spain S.L. Calle Julian Camarillo 31 28037 Madrid, Spain	3030155316	469713566	Waiver	AEMPS (b) (3) Equivalent to VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
DP batch release; DP release testing				

Acronym key: DS – drug substance; DP – drug product; CBER – Center for Biologics Evaluation and Research; DMPQ – Division of Manufacturing and Product Quality; CDER – Center for Drug Evaluation and Research; OII – Office of Inspections and Investigations; ORA – the former Office of Regulatory Affairs; MRA – Mutual Recognition Agreement; AEMPS - Spanish Agency of Medicines and Medical Products; NAI – No Action Indicated; VAI – Voluntary Action Indicated

ORA performed a surveillance inspection of the ModernaTX, Inc facility in April 2024. No Form FDA 483 was issued and the inspection was classified as NAI.

OII performed a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as NAI.

OII performed a surveillance inspection of the (b) (4) facility in (b) (4). A Form FDA 483 Inspectional Observations was issued at the end of the inspection. All inspectional issues have been resolved and the inspection was classified as VAI.

CBER/DMPQ reviewed the requested manufacturing site records of the (b) (3), (b) (4) facility under Section 704(a)(4). The records review was found to be acceptable.

ORA performed a pre-license inspection of the (b) (4) facility for CDER in (b) (4). A Form FDA 483 Inspectional Observations was issued. All inspectional issues have been resolved and the inspection was classified as VAI.

The (b) (3), (b) (4) performed an inspection of the (b) (3), (b) (4) facility in (b) (3), (b) (4). In accordance with the MRA between the FDA and European regulators, ORA requested and assessed the inspection report and determined the inspection was classified as VAI.

The Spanish AEMPS performed an inspection of the Moderna Biotech Spain S.L. facility in (b) (3). The AEMPS inspection report concluded that Moderna Biotech Spain S.L. facility complies with the requirements established in the European Union's Good Manufacturing Practices. The inspection appears to be equivalent to a VAI classification.

e. Container/Closure System

The prefilled syringe (PFS) container closure system consists of a 1 mL long cyclic olefin copolymer syringe barrel with a halobutyl rubber tip cap in rigid plastic cover manufactured by (b) (4), 1 mL long halobutyl rubber plunger with (b) (4) coating on the product contact surface manufactured by (b) (4), and a polypropylene plunger rod manufactured by (b) (4).

(b) (4) performed the container closure integrity testing, employing a (b) (4) test method; all acceptance criteria were met.

Human Factors Assessment
The information provided regarding the use-related risk analysis (URRA) tasks for MNEXSPIKE appear to be comprehensive and appropriate based on the design and intended use of this product. No additional use-related issues were identified, and the risks were found to be appropriately mitigated by the proposed labels and labeling. The

Applicant is leveraging the Human Factor (HF) validation study results for the SPIKEVAX, which they submitted June 9, 2023, and were found to be acceptable. Overall, the URRA and comparative analyses did not identify any new, differing, or unique risks for the proposed MNEXSPIKE PFS as compared to the SPIKEVAX PFS. As such, the Applicant's justification for not submitting HF validation study results as part of their marketing application is acceptable.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

GLP Combined Perinatal/Postnatal Developmental & Reproductive Toxicity Study
A developmental toxicity study was conducted to assess the effects of MNEXSPIKE on pregnant/lactating female rats, as well as the development of the embryo/fetus and offspring following exposure to the female to the vaccine from implantation through the end of pregnancy, with follow-up of the offspring through weaning. In this study, 0.2 mL of a vaccine formulation containing 80 mcg of nucleoside-modified mRNA per dose (which is 8 times the amount of mRNA in a full human dose of MNEXSPIKE [10 mcg of nucleoside-modified mRNA; encoding the N- terminal domain (NTD) and receptor-binding domain (RBD) of the viral spike (S) glycoprotein of SARS-CoV-2 Wuhan-Hu 1 strain]). Each dose of the vaccine formulation administered to rats also contained the following ingredients: a total lipid content of 1.8 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.48 mg tromethamine, 17 mg sucrose, and 0.1 mg sodium acetate). MNEXSPIKE was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effect on postnatal development were observed in the study. The study also revealed no evidence of effects on female fertility.

Non-GLP Repeat Dose Toxicity and Immunogenicity Study
In this study, animals were randomized and assigned to 13 different groups. Each group consisted of 10/sex/group. Animals were dosed by IM injection on study days 1 and 22. Based on the overall findings in this study, it can be concluded that in (b) (4) rats, test article [(b) (4) µg/dose mRNA-1284, (b) (4) µg/dose mRNA-1285, and (b) (4) µg/dose mRNA-1284/1285]-administered by IM injection caused significant increases in liver enzymes. Also, caused injection site inflammation, increases in hematology parameters (monocyte, basophil, LUC, neutrophils, and eosinophils), and immune responses.

Nonclinical Pharmacology Studies Supporting mRNA-1283
Comprehensive nonclinical pharmacology studies were performed to evaluate the expression and immunity derived from mRNA-1283 encoding the NTD and RBD sub-domains of the SARS-CoV-2 S protein linked to the influenza HATM domain (NTD-RBD-HATM) in comparison with the licensed SPIKEVAX vaccine (referred to as mRNA-1273) encoding the full-length S protein of the SARS-CoV-2 (S-2P). All immunogenicity studies were performed in mice, following administration of

mRNA-1283 as a primary series or as a booster dose in animals previously vaccinated with mRNA-1273 as presented in **Table 6**. Additional immunogenicity data for mRNA-1283 were obtained in two repeat-dose toxicity studies performed in (b) (4) rats. The immune response was assessed using quantitative ELISA for the full-length S protein, N-terminal domain, or receptor-binding domain, Intracellular Cytokine Staining, EliSpot and Pseudovirus Virus Neutralization Assay. All The results of nonclinical studies performed in mice demonstrated that MNEXSPIKE is well tolerated, safe, and elicits a robust and effective immune response against SARS-CoV-2.

Table 6. Summary of Nonclinical Pharmacology Studies Supporting mRNA-1283

Type of Study	Test Article and Dose (µg)[a]	Species or Cell Line, Strain or Derivative	Administration; Immunization Schedule	GLP	Report Number
Evaluation of in vitro and in vivo expression of mRNA-1273 and mRNA-1283 (SARS-CoV-2)	In vitro: mRNA encoding SARS-CoV-2 S-2P or NTD-RBD-HATM: (0.1 µg to 0.003125 µg via TransIT®-mRNA Transfection Kit) In vivo: mRNA-1273: 2 or 10 mRNA-1283: 2 or 10	In vitro: HEK293T cells, ATCC# CRL-11268 In vivo: Mouse (female), BALB/c	IM; single dose (Day 0)	No	MOD-4112
Evaluation of the immunogenicity and dynamic range of mRNA-1283 (SARS-CoV-2)	mRNA-1283: 0.000305, 0.000611, 0.001221, 0.002441, 0.004883, 0.009766, 0.019531, 0.039063, 0.078125, 0.15625, 0.3125, 0.625, 1.25, 2.5, 5, 10, or 20	Mouse (female), BALB/c	IM; prime/boost (Day 1 and Day 22)	No	MOD-4079
Evaluation of the immunogenicity of mRNA-1283 (SARS-CoV-2)	mRNA-1273: 0.1 or 1mRNA-1283: 0.1 or 1	Mouse (female), BALB/c	IM; prime/boost (Day 1 and Day 22)	No	MOD-3964 MOD-4035 MOD-4101
Evaluation of immunogenicity of mRNA-1283 primary series and matched variant-specific booster dose in mice (Stewart-Jones et al. 2023)	mRNA-1283: 0.1 or 1 mRNA-1273: 0.1 or 1 mRNA-1273.351[1]: 0.1 or 1 mRNA-1283.351: 0.1 or 1	Mouse, BALB/c	IM; primary series (Day 1 and Day 22) followed by boost (Day 57)	No	NA
Evaluation of immunogenicity of mRNA-1283 variant-specific booster dose following mRNA-1273 primary series in mice (Stewart-Jones et al. 2023)	mRNA-1283: 1.0 mRNA-1273: 1.0 Variant-specific (B.1.351) monovalent or bivalent mRNA-1273: 1.0 Variant-specific (B.1.351) monovalent or bivalent mRNA-1283: 1.0	Mouse, BALB/c	IM; primary series (Day 1 and Day 22) followed by boost (Day 57)	No	NA
(b) (4)					

Type of Study	Test Article and Dose (µg)[a]	Species or Cell Line, Strain or Derivative	Administration; Immunization Schedule	GLP	Report Number
Evaluation of the protection of monovalent mRNA-1283 against WA1/2020 D614G or B.1.1.529 (BA.1; Omicron) challenge (Stewart-Jones et al. 2023)	mRNA-1283: 0.1 or 5 mRNA-1273: 0.1 or 5	Mouse, K18-hACE2 C57BL/6 J	IM; prime/boost (Day 1 and Day 22)	No	NA
Evaluation of in vivo immunogenicity of mRNA-1283.222 in BALB/c mice	mRNA-1283.222-v2[3]: 0.4 mRNA-1283.222[3]: 0.4	Mouse, BALB/c	IM; prime/boost (Day 1 and Day 22)	No	MOD-5814-1283
(b) (4)					
Evaluation of immunogenicity of monovalent SARS-CoV-2 XBB-containing mRNA-1283 vaccine boosters in mice	Primary series mRNA-1273: 0.5 Booster dose mRNA-1273.116[4]: 1.0 mRNA-1283.815[5]: 1.0 mRNA-1283.116[4]: 1.0 mRNA-1283.222[3]: 1.0	Mouse, BALB/c	IM primary series (Day 1 and Day 22) followed by boost (Day 106)	No	MOD-5972.1283
Evaluation of the Immunogenicity of JN.1-containing mRNA-1283 vaccine in BALB/c Mice following a 2-dose primary series administration	2-dose primary series mRNA-1283.167[6]	Mouse, BALB/c	IM primary series (Day 1 and Day 22)	No	MOD-7153-1283.167

GLP - Good Laboratory Practice; HATM - hemagglutinin transmembrane domain; HEK - human embryonic kidney; IM - intramuscular(ly); mRNA - messenger ribonucleic acid; NA - not applicable; NTD - N-terminal domain; PBS - phosphate-buffered saline; RBD - receptor-binding domain; S-2P - spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2.

[a] Dose refers to the total dose of mRNA encapsulated in the administered LNP.

1 - mRNA-1283.351 and mRNA-1273.351: Monovalent, Omicron B.1.351 (Beta) variant.

2 - mRNA-1283.214 and mRNA-1273.214: Bivalent (mRNA-1283 + mRNA-1283.529), Original and Omicron B.1.1.519 [BA.1] variant.

3 - mRNA-1283.222 and mRNA-1283.222: Bivalent (mRNA-1283 + mRNA-1283.045), Original and Omicron BA.4/BA.5 variant.

4 - mRNA-1283.116 and mRNA-1273.116: Monovalent (Omicron XBB.1.16 subvariant).
5 - mRNA-1283.815: Monovalent (Omicron XBB.1.5/XBB.1.9.1 subvariant. Note: S protein of XBB.1.9.1 is identical to XBB.1.5).
6 - mRNA-1283.167: Monovalent (Omicron JN.1 subvariant).

5. Clinical Pharmacology

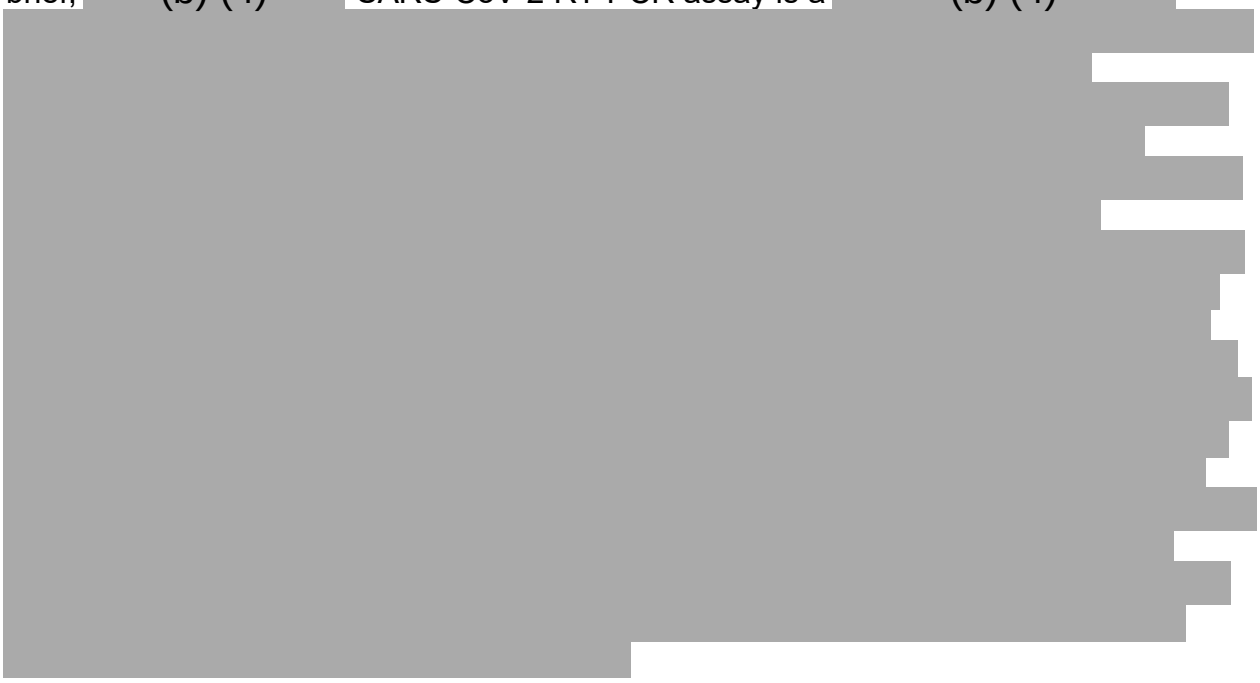
The nucleoside-modified mRNA in MNEXSPIKE is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the N-terminal domain (NTD) and receptor-binding domain (RBD) of the Spike (S) glycoprotein of SARS-CoV-2. The vaccine elicits an immune response which protects against COVID-19.

6. Clinical/Statistical

Clinical Diagnostic Assays Used to Support Clinical Endpoints

RT-qPCR Assay by (b) (4) for the Quantification of SARS-CoV-2 RNA

(b) (4) SARS CoV-2 specific RT-PCR assay was used at (b) (4) for baseline SARS CoV-2 serostatus determination and at (b) (4) for the COVID-19 case confirmation for primary efficacy endpoint analysis in Study P301. The assay is an FDA Emergency Use Authorized In Vitro Diagnostic test for the qualitative detection of SARS CoV-2 nucleic acid in nasal and nasopharyngeal swabs from infected people. In brief, (b) (4) SARS-CoV-2 RT-PCR assay is a (b) (4)



Immunogenicity Assays

Pseudotype Virus Neutralization Assays (PsVNA)

- A proprietary Anti-Spike (D614G), and Omicron (BA.1) serological assay developed, qualified, and validated by the "Neutralizing Antibody Core" Laboratory at the Duke University Medical Center was used to measure neutralizing antibody titers against SARS-CoV-2 in sera from clinical study participants after vaccination in studies P101 and P201.
- A proprietary Anti-Spike Ancestral (D614G) VAC62, Omicron (BA.4/BA.5) VAC137 and XBB.1.5 VAC150 variant serological assay developed, qualified, and validated by (b) (4) was used to assess the clinical study P301 – Japan substudy.

Based on the review of the validation data, the SARS-CoV-2 Omicron BA.1 variant-specific, prototype D614G and variant-specific BA.4/BA.5 and XBB.1.5 pseudovirus assays were adequately validated and appropriate for its intended purpose to measure the neutralizing antibodies to SARS CoV-2 virus and variants.

Live Virus Microeutralization (MN) Assay

A live virus microneutralization (MN) assay was developed to quantify the SARS-CoV-2 neutralizing antibodies in serum or plasma samples from individuals who have received

a SARS-CoV-2 vaccine in study P101. The assay was developed, qualified, and successfully validated at the (b) (4) and is appropriate for its intended purpose of quantifying the SARS-CoV-2 neutralizing antibodies in vaccine recipients.

Elecsys N protein IgG Assay

The assay is a commercially available kit from Roche Diagnostics that has been authorized by the FDA under an Emergency Use Authorization. Elecsys® Anti-SARS-CoV-2 immunoassay is intended for the qualitative detection of antibodies to SARS-CoV-2 in human serum and plasma. The same assay was used during the original BLA approval of SPIKEVAX and was also reviewed at the time of licensure. The assay is fit for its intended purpose and (b) (4) has demonstrated adequate assay performance in their lab.

a. Clinical Program

Overview of Clinical Studies

The application includes data from four ongoing clinical studies summarized in **Table 7** below. The primary focus of the review is Study mRNA-1283-P301, a multi-center, Phase 3 randomized, blinded, placebo-controlled study evaluating the safety, immunogenicity, and efficacy of mRNA-1283. Study mRNA-1283-P301-Japan Addendum is a randomized, observer-blinded, active-controlled study assessing the safety and immunogenicity study of the Omicron XBB.1.5 monovalent formulation, based on the 2023-2024 strain selection. Study mRNA-1283-P201 is a dose-ranging study to assess the safety and immunogenicity of a single dose mRNA-1283 in participants previously vaccinated with mRNA-1273. Phase 1 mRNA-1283-P101 evaluated the safety and reactogenicity of 3 dose levels of mRNA-1283 and 1 dose level of mRNA-1273, each administered as 2 doses, 28 days apart, as well as a single high-dose level of mRNA-1283.

Table 7. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the mRNA-1283 Vaccine

Study Number	Type of Study	Participants Randomized (N)	Study Design, Type of Control	Dose Levels Assessed	Study Status
P301	Efficacy, safety, immunogenicity	11,454	Phase 3, randomized, observer-blind, placebo-controlled study	10 µg	Ongoing
P301-Japan	Safety, immunogenicity	692	Phase 3, randomized, observer-blind, placebo-controlled study	10 µg	Ongoing
P201	Safety, immunogenicity	540	Phase 2 randomized, observer-blind, placebo-controlled dose-ranging study	2.5 µg, 5 µg, 10 µg	Completed

Study Number	Type of Study	Participants Randomized (N)	Study Design, Type of Control	Dose Levels Assessed	Study Status
P101	Safety, reactogenicity, immunogenicity	105	Phase 1 randomized, placebo-controlled dose-ranging study	2 dose regimen 28 days apart: 10µg, 30µg, 100µg 1 dose regimen: 100µg	Completed

Study mRNA-1283-P301

Study mRNA-1283-P301 is an ongoing randomized, stratified, observer-blind study evaluating the safety, immunogenicity, and relative vaccine efficacy (rVE) of a single dose of mRNA-1283.222 compared with a previously authorized COVID-19 vaccine, Moderna COVID-19 Vaccine, Bivalent, in healthy adolescents and adults ≥12 years of age who have previously received a COVID-19 vaccine primary series according to the locally authorized or approved regimen. Both the investigational and the comparator vaccines used were aligned with 2022-2023 Formula for COVID-19 vaccines recommended by FDA and the World Health Organization (WHO; bivalent Wuhan + Omicron BA.4/BA.5). Study enrollment occurred between March and August of 2023. Participants (N=11,454) were randomized 1:1 to receive mRNA-1283.222 10 µg (n=5728) or Moderna COVID-19 Vaccine, Bivalent 50 µg (n=5726) as a single dose. Participants were stratified by age groups (12 to <18, 18 to <65, and ≥65 years), with a goal to enroll approximately 1000 adolescents (12 to <18 years old) and approximately 30% of participants in the ≥65 years of age group. The planned follow-up time for all participants is 12 months. As of the data cutoff date, the median duration of follow-up after study vaccination was 8.8 months in both groups, with most (>97%) of participants in both groups having at least 6 months of follow-up postvaccination.

Objectives

Primary efficacy objective:

To demonstrate noninferior rVE of mRNA-1283 compared with mRNA-1273 to prevent the first event of COVID-19 starting 14 days after study injection.

Primary Immunogenicity objectives:

- To demonstrate a noninferior neutralizing antibody response of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent against Omicron BA.4/BA.5 based on geometric mean concentration (GMC) ratio and seroresponse rate (SRR) percentage difference at Day 29.
    - GMC ratio, defined as GMCs against SARS-CoV-2 Omicron BA.4/BA.5 elicited by mRNA-1283.222 divided by the GMCs against SARS-CoV-2 Omicron BA.4/BA.5 elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29.
    - Difference in seroresponse rates against Omicron BA.4/BA.5, defined as percentage of participants with seroresponse at Day 29 who received mRNA-1283.222 minus percentage of participants with seroresponse at Day 29 who received Moderna COVID-19 Vaccine, Bivalent.
- To demonstrate a noninferior neutralizing antibody response of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent against the ancestral SARS-CoV-2 D614G based on GMC ratio and SRR percentage difference at Day 29.

- GMC ratio, defined as GMCs against ancestral SARS-CoV-2 D614G elicited by mRNA-1283.222 divided by the GMCs against ancestral SARS-CoV-2 D614G elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29.
- Difference in seroresponse rates against Omicron BA.4/BA.5, defined as percentage of participants with seroresponse at Day 29 who received mRNA-1283.222 minus percentage of participants with seroresponse at Day 29 who received Moderna COVID-19 Vaccine, Bivalent.

Secondary Objectives:

- To assess SARS-CoV-2 infection regardless of symptoms (mRNA-1283 and mRNA-1273 ([variant formulations]).
  - SARS-CoV-2 infection (symptomatic or asymptomatic).
  - Asymptomatic SARS-CoV-2 infection is defined as absence of symptoms and:
    - A positive RT-PCR test on a respiratory sample, or
    - A positive serologic test for anti-nucleocapsid antibody for those participants with negative SARS-CoV-2 status at baseline[1].

Study Results

Analyses of Primary Efficacy Endpoint

The BLA submission includes data from the pre-specified interim analysis of the primary efficacy endpoints (considered the primary analysis) which includes cases of first episode of COVID-19 starting 14 days after study vaccination through the data cutoff date of 31 January 2024. The primary efficacy analysis was based on the Per-Protocol Set for Efficacy (PPSE), which consisted of all participants in the full analysis set (FAS) who received the planned dose of study vaccine and had no major protocol deviations that impacted vaccine efficacy data ([99.1%] in the mRNA-1283.222 group and [99.3%] in the Moderna COVID-19 Vaccine, Bivalent group). The primary efficacy objective was to demonstrate the noninferior relative vaccine efficacy (rVE) of mRNA-1283.222 relative to Moderna COVID-19 Vaccine, Bivalent in preventing the first episode of COVID-19 starting 14 days after study vaccination, with a noninferiority margin of 10%.

The primary efficacy analysis demonstrated a rVE against COVID-19 occurring at least 14 days after the study vaccination of 9.31% (99.4% CI: -6.58, 22.83), which met the pre-specified noninferiority success criterion of the lower bound (LB) of the 99.4% CI being >-10% (**Table 8**). The case split was 560 COVID-19 cases in the mRNA-1283.222 group and 617 cases of COVID-19 in the Moderna COVID-19 Vaccine, Bivalent group.

rVE was also calculated with a nominal 95% CI as well as using incidence rates rather than hazard ratios with results consistent with those obtained in the primary analysis rVE outcome.

Table 8. Analysis of Primary Efficacy Endpoint of Relative Vaccine Efficacy (rVE) to Prevent COVID-19, Starting 14 Days Postvaccination, PPSE, Data Cutoff 31 Jan 2024, Study mRNA-1283-P301

1 SARS-CoV-2 status at baseline is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1. Positive SARS-CoV-2 status is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1. Negative status is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid on or before Day 1.

Age Group	mRNA-1283.222 Cases[a]/N (%) Incidence Rate Per 100 Person-Months[b]	Moderna COVID-19 Vaccine, Bivalent Cases[a]/N (%) Incidence Rate Per 100 Person-Months[b]	Relative Vaccine Efficacy[c] % (99.4% CI)[d]
All participants 12 years of age and older	560/5679 (9.9) 1.4	617/5687 (10.8) 1.5	9.3 (-6.6, 22.8)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.2.1.2.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; N=number of participants in the per-protocol set for efficacy; PPSE=per-protocol set for efficacy.
a. Cases are based on CDC COVID-19 definition: the presence of at least 1 CDC listed symptom; and positive RT-PCR test on a respiratory sample. Listed symptoms are 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 diarrhea.
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. rVE=1-hazard ratio (mRNA-1283.222 vs Moderna COVID-19 Vaccine, Bivalent), hazard ratio and CI are estimated using a stratified Cox proportional hazard model (stratified by age group per randomization) 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-1283.222 vs Moderna COVID-19 Vaccine, Bivalent]).

These data demonstrating the noninferior relative vaccine efficacy of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent support the clinical benefit of mRNA-1283.

Analyses of Primary Immunogenicity Endpoints

The primary immunogenicity objective was to demonstrate noninferior neutralizing antibody (nAb) responses of mRNA-1283.222 relative to Moderna COVID-19 Vaccine, Bivalent. The four co-primary endpoints were Day 29 GMC ratio and seroresponse rate (SRR) percentage differences against both Omicron BA.4/BA.5 and ancestral D614G strains after vaccination with mRNA-1283.222 or Moderna COVID-19 Vaccine, Bivalent. The pre-specified primary immunogenicity subset (PPIS) was randomly generated when approximately 8000 participants were enrolled. The PPIS consisted of a random sample of adult trial participants (n=1090) and all dosed adolescents who were enrolled by end of July 2023 (n=210). Results for the co-primary endpoint of GMC ratio (mRNA-1283.222/Moderna COVID-19 Vaccine, Bivalent) against Omicron BA.4/BA.5 and D614G are displayed in **Table 9** below. The GMC ratio against Omicron BA.4/BA.5 was 1.3 (95% CI: 1.2, 1.5), which met the pre-specified noninferiority success criteria of the lower bound of the 95% CI >0.667. The GMC ratio against D614G was 1.2 (95% CI: 1.1, 1.4), which also met the pre-specified noninferiority success criteria.

Table 9. Analyses of Primary Immunogenicity Endpoints of Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against the D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, PPIS, Study mRNA-1283-P301

Strain	mRNA-1283.222 GMC (95% CI)[a] N=621	Moderna COVID-19 Vaccine, Bivalent GMC (95% CI)[a] N=568	GMC Ratio (mRNA-1283.222/Moderna COVID-19 Vaccine, Bivalent) (95% CI)[a]
D614G	10631.9 (9960.2, 11348.9)	8576.5 (8012.5, 9180.1)	1.2 (1.1, 1.4)
Omicron BA.4/BA.5	2340.9 (2167.0, 2528.8)	1753.8 (1618.2, 1900.7)	1.3 (1.194, 1.492)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.1.1.1.2. Data cutoff 23 Feb 2024.
Abbreviations: N=total number of participants in the specified group; ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=coronavirus disease 2019; GLSM=geometric least square mean; GMC=geometric mean concentration; LLOQ=lower limit of quantification; LS=least squares; 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. VAC137 Neutralizing Antibody against BA.4/BA.5 (AU/mL) (LLOQ: 103, ULOQ: 28571) VAC62 Neutralizing Antibody against Ancestral SARS-CoV-2 D614G (AU/mL) (LLOQ: 10, ULOQ: 111433)
a. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.222 vs Moderna COVID-19 Vaccine, Bivalent) as fixed effect, adjusted by SARS-CoV-2 status at pre-booster, 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 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.

Results for the co-primary endpoint of SRR percentage difference (mRNA-1283.222 - Moderna COVID-19 Vaccine, Bivalent) against Omicron BA.4/BA.5 and D614G are displayed in **Table 10** below. Seroresponse was defined as the value change from baseline as follows:

- below the lower limit of quantification (LLOQ) to ≥4 x 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.

SRR percentage difference against Omicron BA.4/BA.5 was 14.4% (95% CI: 9.3, 19.4), which met the pre-specified noninferiority success criteria of the lower bound of the 95% CI >-10%. The SRR percentage difference against D614G was 10.7% (95% CI: 6.0, 15.4), which also met the pre-specified noninferiority success criteria.

A descriptive analysis was also performed using a secondary seroresponse definition, 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. Using this secondary seroresponse definition, the noninferiority criterion of the lower bound of the 95% CI with the SRR difference >-10% would also have been met for both Omicron BA.4/BA.5 and D614G.

Table 10. Analyses of Primary Immunogenicity Endpoints of Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, PPIS, Study mRNA-1283-P301

Strain	mRNA-1283.222 Seroresponse Rate % [95% CI][C] N1=621	Moderna COVID-19 Vaccine, Bivalent Seroresponse Rate % [95% CI][c] N1=568	Difference in SRR (mRNA1283.222− Moderna COVID-19 Vaccine, Bivalent) % (95% CI)[d]
D614G	83.6 [80.4, 86.4]	72.9 [69.0, 76.5]	10.7 (6.0, 15.4)
Omicron BA.4/BA.5	79.9 [76.5, 83.0]	65.5 [61.4, 69.4]	14.4 (9.3, 19.4)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.1.1.1.3, Table 14.2.1.1.1.4. Data cutoff 23 Feb 2024.
Abbreviations: N1=Number of participants with non-missing data at baseline and the corresponding timepoint.; CI=confidence interval; COVID-19=coronavirus disease 2019; 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 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
VAC137 Neutralizing Antibody against BA.4/BA.5 (AU/mL) (LLOQ: 103, ULOQ: 28571)
VAC62 Neutralizing Antibody against Ancestral SARS-CoV-2 D614G (AU/mL) (LLOQ: 10, ULOQ: 111433)
a. Seroresponse 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 pre-booster.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) method.

Noninferiority of Ab responses based on GMC ratio and difference in SRR percentages were demonstrated for both strains encoded for in mRNA-1283.222 (Omicron BA.4/BA.5 and D614G) as compared with Moderna COVID-19 Vaccine, Bivalent.

Study mRNA-1283-P301 – Japan

Study mRNA-1283-P301-Japan Substudy (hereafter referred to as P301-Japan) is a Phase 3, randomized observer-blind, active controlled study conducted in Japan to evaluate the safety and immunogenicity of mRNA-1283.815 (monovalent vaccine encoding the NTD and RBD of the S glycoprotein from SARS-CoV-2 variant lineage XBB.1.5) compared with Spikevax (2023-2024 formula; hereafter referred to as Spikevax), in COVID-19 vaccine experienced participants ≥12 years of age. Participants were randomized 1:1 to receive either a single dose of mRNA-1283.815 (10 µg) or Spikevax (50 µg). Participants are followed for 12 months after vaccination. The study was initiated on March 15, 2024, and the data submitted to the BLA consists of results from an interim analysis with a median follow-up of 35 days (data cutoff: May 2, 2024). Study mRNA-1283-Japan data support the review of the overall safety and effectiveness of mRNA-1283 because a monovalent XBB.1.5 formulation (mRNA-1283.815) was assessed.

Objectives

Primary immunogenicity objective:

To demonstrate a noninferior neutralizing antibody response of mRNA-1283.815 compared with the antibody response of Spikevax based on geometric mean concentration (GMC) ratio at Day 29 after the study injection.

- Ratio of Omicron XBB.1.5 GMC in participants who received mRNA-1283.815 divided by the Omicron XBB.1.5 GMC in participants who received Spikevax at Day 29 after the study injection.

Primary safety objective (Descriptive):

To evaluate the safety and reactogenicity of mRNA-1283.815

- Solicited local and systemic reactogenicity during the 7-day follow-up period after study injection
- Unsolicited adverse events (AEs) during the 28-day follow-up period after the study injection
- SAEs, MAAEs, and AEs leading to withdrawal, as well as AESIs from Day 1 to end of study

Secondary objective (descriptive):

To characterize the antibody response against Omicron XBB.1.5 and the ancestral SARS-CoV-2 D614G (mRNA-1283.815) at all study timepoints.

- Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G GM levels at all planned timepoints
- Seroresponse rate against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G at all planned timepoints

Study Results

Analyses of Primary Immunogenicity Endpoint

The primary immunogenicity objective was to demonstrate the noninferior neutralizing antibody (nAb) responses of mRNA-1283.815 compared with Spikevax based on

geometric mean concentration (GMC) ratio against Omicron XBB.1.5 at 29 days after vaccination. Results of the primary endpoint are displayed in **Table 11** below. The GMC ratio was 1.2 (95% CI: 1.0, 1.4), which met the pre-specified noninferiority success criterion of the lower bound of the 95%CI >0.667.

Table 11. Analyses of Primary Immunogenicity Endpoint of Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against Omicron XBB.1.5 at 28 Days Postvaccination, PPIS, Study mRNA-1283-P301-Japan Substudy

mRNA-1283.815 GMC [95% CI][a] N=334	SPIKEVAX GMC [95% CI][a] N=334	GMC Ratio (mRNA-1283.815/SPIKEVAX) [95% CI][a]
1757.2 [1580.1, 1954.3]	1470.4 [1322.4, 1635.0]	1.195 [1.028, 1.389]

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan substudy Clinical Study Report, Table 14.2.1.1.1.2. Data cutoff 2024-05-02.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=coronavirus disease 2019; FAS=full analysis set; GMC=geometric mean concentration; 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; N=number of participants in the specified group.
PPIS consists of all participants in the FAS who receive the planned dose of study vaccination, have baseline and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody against XBB.1.5 data and have no major protocol deviations that impact vaccine immunogenicity data.
VAC150 Neutralizing Antibody Against XBB.1.5 (AU/mL) (LLOQ: 38, ULOQ: 6960).
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. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.815 vs SPIKEVAX) as fixed effect, adjusted by SARS-CoV-2 status at Baseline, 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). LS means are based on the observed margins. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

Analysis of the Secondary Objective

The secondary immunogenicity objective evaluated the seroresponse rate (SRR) against Omicron XBB.1.5 at 28 days after mRNA-1283.815 compared with Spikevax. SRR was assessed by two seroresponse definitions. The primary seroresponse definition was based on an antibody value change from baseline level below LLOQ to ≥4×LLOQ, or at least a 4-fold rise if baseline level is ≥LLOQ and <4×LLOQ, or at least a 2-fold rise if baseline level is ≥4×LLOQ, where baseline level refers to pre-dose. The secondary seroresponse definition was based on an antibody value change from baseline below the LLOQ to ≥4×LLOQ, or at least a 4-fold rise if baseline level is ≥LLOQ. A higher percentage of participants in the mRNA-1283.815 group achieved seroresponse compared with the Spikevax group, irrespective of the seroresponse definition used. Although the secondary analyses evaluating seroresponse are descriptive without pre-specified hypothesis testing, the results suggest that the conventional noninferiority criterion of a lower bound of the 95% CI for difference in SRR percentage (mRNA-1283.815 – Spikevax) >-10% would have been met using either the primary or secondary SRR definition.

Study P201 (Parts A and B)

Study P201 is a Phase 2, randomized, observer-blind, stratified dose-finding study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1283 vaccine candidates, and the active comparator Spikevax, in healthy adults 18 years of age and older who were previously vaccinated with Spikevax. The study enrolled 340 participants in Part A consisting of participants who have previously received a 2-dose primary series of Spikevax. Participants were randomized 1:1:1:1:1:1 to receive a single mRNA-1282

(2.5 µg, 5 µg, 10 µg), mRNA-1283.211 (5 µg, 10 µg), or Spikevax (50 µg). Part B was an open-label study evaluating mRNA-1283.529 (5 µg, 10 µg) in participants who have received the 2-dose primary series of Spikevax and one booster dose. A total of 200 participants were enrolled in Part B, with 103 participants receiving 5 µg pf mRNA-1283.529 and 97 participants receiving 10 µg of mRNA-1283.529, respectively.

The immunogenicity objectives for Part A and B were to evaluate the neutralizing and binding antibody titers against SARS-CoV-2 D614G and variants, including Omicron BA.1 for both study parts and Beta (B.1.351) for Part A only at Day 29 postvaccination. All participants were followed for solicited adverse reactions through 7 days after each vaccination. Unsolicited AEs were collected through 28 days after each vaccination. SAEs and MAAEs will be collected through the end of the study (12 months after vaccination).

Study Objectives/Endpoints Relevant to the BLA - Part A

Primary safety objective: To evaluate the safety and reactogenicity of a single dose of mRNA-1283 (2.5 µg, 5 µg, 10 µg) and mRNA-1283.211 (5 µg, 10 µg), compared with Spikevax (50 µg).

Primary immunogenicity objective: To evaluate the immune responses against the original SARS-CoV-2 (D614G) and variants, including Beta (B.1.351) and Omicron BA.1, after a single dose of mRNA-1283 (2.5 µg, 5 µg, 10 µg), mRNA-1283.211 (5 µg, 10 µg), compared with Spikevax (50 µg) at Day 29.

Secondary immunogenicity objective: To evaluate the immune responses against the original SARS-CoV-2 (D614G) and against SARS-CoV-2 variants, including Beta (B.1.351) and Omicron BA.1, after a single dose of mRNA-1283 (2.5 µg, 5 µg, 10 µg), mRNA-1283.211 (5 µg, 10 µg), compared with Spikevax (50 µg) all immunogenicity time points.

Study Objectives/Endpoints Relevant to the BLA - Part B

Primary safety objective: To assess the safety and reactogenicity of mRNA-1283.529 booster vaccine candidate (5 µg, 10 µg).

Primary immunogenicity objective: To assess the immune responses elicited against the original SARS-CoV-2 (D614G) and against SARS-CoV-2 variants, including Beta (B.1.351) and Omicron BA.1, after a single dose of mRNA-1283.529 (5 µg, 10 µg) as the second booster dose at Day 29.

Secondary immunogenicity objective: To assess the immune responses elicited against the original SARS-CoV-2 (D614G) and against SARS-CoV-2 variants, including Beta (B.1.351) and Omicron BA.1, after a single dose of mRNA-1283.529 (5, 10 µg) as the second booster dose at all immunogenicity time points.

Study Results

Immunogenicity Analysis

mRNA-1283 (2.5µg, 5µg and 10µg) and mRNA-1283.211 (5µg and 10µg) induced similar or higher nAb GMTs against D614G, Beta, and Omicron BA.1 compared with Spikevax. The 10-µg dose of mRNA-1283 elicited the highest GMTs and SRRs. Antibody responses persisted through Day 366. *(Part A)*

mRNA-1283.539 (5 µg and 10 µg) induced elicited high nAb GMTs against D614G and Omicron BA.1 at Day 29 and the antibody responses persisted through Day 366. *(Part B)*

Study P101

Study P101 was a Phase 1, randomized, observer-blind, dose-ranging study in 105 healthy COVID-19 vaccine-naïve adults 18 through 55 years of age in the U.S. Participants were randomized 1:1:1:1:1 into five study groups:

- mRNA-1283 (2-dose series, 28 days apart): 10 µg (Group 1), 30 µg (Group 2), 100 µg (Group 3)
- mRNA-1283 (single dose): 100 µg (Group 4)
    - Participants in this group received placebo on Day 1 and study vaccine on Day 29
- Spikevax (2-dose series, 28 days apart): 100 µg (Group 5)

Participants were followed for 13 months with optional study visits at 18 months post last vaccination and 24 months after last vaccination. An interim analysis occurred after Day 57 visits.

Objectives

Primary Safety Objective

To evaluate the safety and reactogenicity of a 2-dose series of mRNA-1283 (10 µg, 30 µg, 100 µg), a 2-dose series of Spikevax (100 µg), and a single dose of mRNA-1283 (100 µg).

Primary Safety Endpoints:

- Frequency and severity of solicited local and systemic ARs through 7 days after each vaccination
- Frequency and severity of unsolicited AEs through 28 days after each vaccination
- Frequency of SAEs, MAAEs, and AESIs through study end
- Safety laboratory abnormalities through 7 days after each vaccination

Secondary Immunogenicity Objective

To evaluate humoral immune responses following a 2-dose series of mRNA-1283 (10 µg, 30 µg, 100 µg), a 2-dose series of Spikevax (100 µg), and a single dose of mRNA-1283 (100 µg).

Secondary Immunogenicity Endpoints

- GMT, GMFR, and SRR of SARS-CoV-2 specific neutralizing antibodies and binding antibodies at all timepoints at Days 29, 57, 209, and 394
- Vaccine seroconversion (≥LLOQ if baseline <LLOQ, or ≥4-fold rise from baseline)

Study Results

Immunogenicity Analyses (Descriptive)

Descriptive immunogenicity analyses through Day 57 showed that all dose levels of mRNA-1283 (10 µg, 30 µg, and 100 µg) induced neutralizing antibody responses against SARS-CoV-2 variants, including D614G, Beta, and Omicron BA.1. The 10-ug dose of mRNA-1283 elicited GMTs and SRR that were comparable to or numerically higher than those observed with Spikevax at 100 ug. Responses were detectable through Day 394. Binding antibody responses and T-cell analyses were consistent with neutralizing antibody results.

b. Bioresearch Monitoring (BiMo)

BiMo inspections were issued for the sponsor and five clinical investigator study sites that participated in the conduct of Study mRNA-1283-P301. The inspections did not

reveal significant issues impacting the data submitted in this original Biologics License Application (BLA).

Pediatrics

To address requirements of the Pediatric Research Equity Act, the Applicant submitted a request for deferral of the following studies in pediatric individuals <12 years of age. The deferred studies are:

- Deferred pediatric study mRNA-1283-P302 to evaluate the safety and effectiveness of mRNA-1283 in children 6 months to <12 years of age
- Deferred pediatric study mRNA-1283-P3XX to evaluate the safety and effectiveness of mRNA-1283 in infants <6 months of age

The deferral request and pediatric plans were presented to the FDA Pediatric Review Committee (PeRC) on March 18, 2025. The Applicant provided safety, immunogenicity and efficacy data to support the use of this vaccine in individuals 12 years of age and older. The Phase 3 efficacy study included adolescents 12 years of age and older along with adults, and the data showed that this vaccine's effectiveness was non-inferior to SPIKEVAX with a comparable safety profile. PeRC agreed with the division's decision to issue two PREA PMRs as discussed for the birth to less than 12-year age group. At the meeting, PeRC also provided feedback that the interval of 12-15 months between study completion and report submission for the two proposed pediatric studies is unreasonable and they recommended that the study reports be submitted earlier. An IR was sent to the Applicant and the Applicant has agreed to revise the final report submission dates to be ~6 months after study completion. The review team agrees with the revised timelines.

c. Other Special Populations

Geriatric Use

Of the 15,184 study participants in P301 who were originally randomized to mRNA-1283 vaccine and included in the Safety Set, 28.6% (n=1634) were ≥65 years of age and 5.6% (n=322) were ≥75 years of age. Vaccine efficacy in geriatric participants was consistent with that seen in younger adult participants, and no safety concerns specific to the geriatric age group were identified.

7. Safety and Pharmacovigilance

Clinical Trials

Study P301

In Study P301, there were 11,417 participants included in the Safety Set, 5,706 participants in the mRNA-1283.222 group and 5,711 participants in the Moderna COVID-19 Vaccine, Bivalent group. As of the 23 Feb 2024 data cutoff, the median duration of safety follow-up was 8.8 months. Most common AEs: Solicited local adverse reaction (ARs) were nominally lower in the mRNA-1283.222 group at 70.3% (CI: 69.1 – 71.5) versus the mRNA-1273.222 group at 78.4% (CI: 77.3 – 79.5). However, solicited systemic ARs were similar in both groups. In both groups the most frequently reported local AR was injection site pain and the most frequently reported systemic ARs were fatigue and headache. Most of the adverse reactions were Grade 1 and 2 in severity.

The incidence of unsolicited AEs was similar in both groups through Day 28 after vaccination as well as through data cutoff. The most common unsolicited AEs in both groups were in the infections and infestations SOC. Specifically, upper respiratory tract infections were the most frequently reported Preferred Term (PT), and the only PT reported in more than 1% of participants in either group.

The incidence of SAEs was similar in both groups through 28 days after vaccination (0.2% mRNA-1283.222 versus 0.3% Moderna COVID-19 Vaccine, Bivalent) and through data cutoff (2.7% mRNA-1283.222 versus 2.6% Moderna COVID-19 Vaccine, Bivalent). The PTs for SAEs were reviewed, and there were no trends or imbalances noted, overall or by age group (adolescents 12 to <18 years, adults 18 to <65 years, ≥65 years). There were no SAEs assessed as related to mRNA-1283.222 by FDA. There were 15 deaths reported, of which five occurred in participants exposed to mRNA-1283.222. These were assessed as not related to study vaccination by the Investigator and Sponsor. The deaths among participants who were exposed to mRNA-1283.222 were reviewed individually. All the participants had a long period of latency, had significant risk factors contributing to death, or had circumstances of death clearly unrelated to vaccine exposure.

Adverse events of special interest (AESIs): There were no myocarditis or pericarditis events in either group within 28 days post-injection or up to the data cutoff. There were three pregnancies in the mRNA-1283.222 group that were pending outcomes at the time of the data lock point. In a response to an IR submitted to STN125835/0.27, the Sponsor stated that the three pregnancies in the mRNA-1283 group resulted in full-term births without complications.

Study P301 – Japan

The Study P301-Japan Safety Set included 343 mRNA-1283.185 recipients and 346 SPIKEVAX recipients. The median duration of follow-up through a data cutoff date of May 2, 2024, was 35 days for all participants in both vaccine groups. As of data cut-off, all participants had at least 1 month of follow-up post-vaccination.

The safety profile of mRNA-1283.815 was overall comparable to that of Spikevax. Solicited local and systemic adverse reactions, including Grade 3 ARs, were reported by a slightly lower percentage of mRNA-1283.815 recipients compared with Spikevax recipients. There were no notable imbalances in the overall percentages and types of unsolicited adverse events across the two groups. As of the data cutoff, with a median follow-up duration of 35 days, there were no deaths, SAEs, or AESIs reported for either group. Overall, the data from study P301-Japan support the safety and effectiveness of a monovalent formulation of mRNA-1283 (mRNA-1283.815) compared with Spikevax in participants 12 years of age or older.

Study P201 (Parts A and B)

In Study P201 Part A, the safety and reactogenicity of a single dose of mRNA-1283 (2.5 µg, 5 µg, 10 µg) and mRNA-1283.211 (5 µg, 10 µg) was evaluated and compared with Spikevax (50 µg). Solicited adverse reactions (ARs) were similar or lower for mRNA-1283 compared with Spikevax. Most solicited ARs were mild to moderate in severity, with no Grade 4 reactions reported. Through the entire study period of 12 months after vaccination, there were no SAEs assessed as related to the vaccine by the investigator. No deaths were reported in the study and there were no events of myocarditis, pericarditis, or anaphylaxis.

In Study P201 Part B, safety and reactogenicity of mRNA-1283.529 booster vaccine candidate (5 µg, 10 µg) was assessed. Through the entire study period of 12 months after vaccination, there were no SAEs assessed as related to study vaccine by the investigator. Two deaths were reported during the study, both occurred more than 90 days after vaccination in participants with underlying chronic medical conditions, and both were assessed as not related to study vaccine by FDA, in agreement with the investigator. No cases of myocarditis, pericarditis, or anaphylaxis were observed.

Study P101

In Study P101 the safety and reactogenicity of a 2-dose series of mRNA-1283 (10 µg, 30 µg, 100 µg), a 2-dose series of Spikevax (100 µg), and a single dose of mRNA-1283 (100 µg) was assessed. The overall safety profile of mRNA-1283 was favorable and consistent with SPIKEVAX. Most solicited adverse reactions (ARs) were mild to moderate, with fewer Grade 3 events in the mRNA-1283 10-µg group (14.3%) compared with SPIKEVAX 100 µg (18.2%). Injection site pain, fatigue, and headache were the most reported ARs. The 10µg-dose had the lowest reactogenicity among all mRNA-1283 dose levels. Unsolicited adverse events occurred less frequently in the mRNA-1283 10-µg group (38.1%) than in the SPIKEVAX group (54.5%), with most considered unrelated to the vaccine. One death occurred due to a self-inflicted gunshot wound in the SPIKEVAX group and was deemed unrelated. No vaccine-related serious adverse events myocarditis, anaphylaxis, or other major safety concerns were reported.

Safety in Specific Subgroups

Currently, clinical safety data for mRNA-1283 are lacking for certain groups, including children under 11 years of age, pregnant or breastfeeding women, and those with specific types of immunocompromise. Although no studies have directly assessed safety in pregnant or lactating women, available data from use in nonpregnant, nonlactating women do not suggest any specific safety concerns that would preclude future use in these populations.

Myocarditis/Pericarditis

There were no participants in any of the pivotal and non-pivotal studies who received mRNA-1283 and experienced myocarditis or pericarditis. However, because the vaccine contains portions of mRNA for the spike protein of SARS-CoV-2 and Moderna's mRNA-1273 vaccine has a known risk of myocarditis/pericarditis, myocarditis and pericarditis are listed as important potential risks.

Rare Adverse Events and the Need for Extended Follow-Up

It remains unclear whether the incidence of myocarditis and/or pericarditis following mRNA-1283 administration is comparable to, higher, or lower than observed with Spikevax in individuals aged 12 years and older. The current limitations—such as the relatively short duration of safety monitoring and the size of the safety dataset—reduce the ability to identify infrequent adverse events, which may become apparent with wider

use and longer-term follow-up. Continued safety monitoring through both active and passive surveillance systems is planned post-authorization to identify any emerging safety signals.

Pharmacovigilance Plan

The Applicant's Pharmacovigilance Plan (PVP) includes the important potential risks of myocarditis and pericarditis. Areas of missing information include data from use in pregnancy and long-term safety information. The Applicant did not propose any identified risks.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80 for all adverse events. Enhanced pharmacovigilance for myocarditis and pericarditis, will be performed by submission of expedited (15-day) reports for spontaneous reports regardless of seriousness or relatedness, and inclusion of a summary and analysis in periodic safety reports.

For the important potential risk of myocarditis and pericarditis, the Applicant will conduct two safety studies as postmarketing requirements. One PMR study is a postmarketing retrospective cohort study using commercial and Medicare claims databases to evaluate the occurrence of myocarditis and pericarditis following administration of MNEXSPIKE in the United States (Study mRNA-1283-P901). The second PMR study is a retrospective cohort study using administrative claims and health system medical records to evaluate long-term sequelae of myocarditis following administration of MNEXSPIKE compared with myocarditis in patients who have not received a COVID-19 vaccine (Study mRNA-1283-P904); participants will have at least five years of follow-up for long-term outcomes of myocarditis.

In addition, for the missing information for use in pregnancy, the Applicant will conduct an observational cohort study using administrative claims data to assess maternal and infant outcomes following exposure to MNEXSPIKE during pregnancy (Study mRNA-1283-P902) as a postmarketing commitment.

8. Labeling

The Applicant originally requested the review of the proprietary name "(b) (4)" which was subsequently withdrawn by the applicant and acknowledged by CBER. The Applicant then submitted a new proprietary name of "MNEXSPIKE" which was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) and found to be acceptable. CBER communicated this decision to the Applicant on February 14, 2025. The APLB found the Package Insert (PI), Patient Package Insert (PPI) and carton/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, PPI, and package/container labels with ModernaTX Inc. 6 versions of the PI (the original submission and amendments 44, 55, 61, 62, and 64), 8 versions of carton/container labels (the original submission and amendments 1, 41, 52, 55, 62, 63, and 64), and 6 versions of the PPI (the original submission and amendments 44, 55, 61, 62, and 64) were submitted to STN 125835/0 by ModernaTX Inc. during labeling negotiations. The PI submitted on May 30, 2025 (amendment 64), the package/container labels submitted on May 30, 2025 (amendment 64) and the PPI submitted on May 30, 2025 (amendment 64) were considered final for approval.

9. Advisory Committee Meeting

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held for this application, as there were no issues or concerns that presented during the course of review of the application that required a discussion at the advisory committee meeting.

10. Other Relevant Regulatory Issues

Priority Review Voucher (PRV)
A priority review voucher was redeemed by the applicant for this submission.

Applicant's Plans for Distribution of MNEXSPIKE (2024-2025 Formula)
The Applicant indicated in the response document submitted under STN 125835.0 amendment 63 (SN 0064) received May 29, 2025, their intent to not distribute any doses of MNEXSPIKE (2024-2025 Formula) and intend to release their first lots of MNEXSPIKE with an anticipated 2025-2026 Formula.

Safety Labeling Changes
In alignment with a request from the CBER Office of the Center Director (OCD), labeling changes were proposed by the applicant to highlight: (1) data from the Biologics Effectiveness and Safety System on the estimated incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines and (2) results from a postapproval study in patients with COVID-19 vaccine-associated myocarditis showing persistence of abnormal cardiac magnetic resonance imaging findings that are a marker for myocardial injury at a median follow-up of approximately 5 months.

Center Director Override Memo

Section 506B Postmarketing Commitment
In response to the information requests from CBER OCD dated May 23, 2025, and May 28, 2025, the Applicant submitted the following 506B Postmarketing Commitment (PMC) agreement under amendment 62, received May 28, 2025, which was incorporated into the Approval Letter as 506B PMC #6:

> Randomized, Observer Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of mRNA-1283 variant-containing formulation in Adults 50 to 64 years of age Without High-Risk Conditions for Severe COVID-19".
>
> Study Initiation: November 30, 2025
> Interim Results: May 31, 2026
> Study Completion: July 31, 2026
> Final Report Submission: January 31, 2027
> Benefit-Risk Assessment Submission: May 31, 2027

The Applicant's 506B PMC is consistent with CBER OCD's request as detailed in the Center Director Override Memo dated May 30, 2025.

Revised Indications and Usage, and Associated Labeling

In response to the information requests from CBER OCD dated May 23, 2025, and May 28, 2025, the Applicant submitted the following in amendment 62, received May 30, 2025:

- Revised USPI, to include a change in indications and usage from:

  "MNEXSPIKE is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older who have been previously vaccinated with any COVID-19 vaccine."

  to:

  "MNEXSPIKE is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

  MNEXSPIKE is approved for use in individuals who have been previously vaccinated with any COVID-19 vaccine and are:

  - 65 years of age and older, or
  - 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19."

- Revised PPI, to include a change under section "**What is MNEXSPIKE?**" from:

  "MNEXSPIKE is a vaccine to protect you against COVID-19. MNEXSPIKE is for people 12 years of age and older who have received a COVID-19 vaccine before."

  to:

  "MNEXSPIKE is a vaccine to protect against COVID-19. MNEXSPIKE is for people who have received a COVID-19 vaccine before and are:
  - 65 years of age and older, or
  - 12 years through 64 years of age at high risk for severe COVID-19."

- Revised carton labels, to include changes in the age for use from:

  "For 12 years and older"

  to:

  "For 65 years of age and older
  For 12 years through 64 years at high risk for severe COVID-19"

- Revised container label, to remove the age for use.

The Revised Indications and Usage and Associated Labeling submitted by the Applicant are consistent with CBER OCD's request as detailed in the Center Director Override Memo dated May 30, 2025

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the BLA, including clinical, nonclinical, and product-related data, and the labeling submitted in the BLA, the Review Committee recommends approval of

MNEXSPIKE for the proposed indication and usage ““MNEXSPIKE is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older who have been previously vaccinated with any COVID-19 vaccine.”

b. Benefit/Risk Assessment

COVID-19 remains a significant global and national health concern. Despite increasing population-level infection-acquired, vaccine-induced, and hybrid immunity, the virus continues to evolve with antigenically distinct variants (e.g., JN.1, KP.2, and LP.8.1) leading to recurrent waves of infection. Hospitalization rates remain a concern, and COVID-19 continues to rank among the leading causes of death in the U.S. Considering the data submitted to support the safety and effectiveness of MNEXSPIKE that have been presented and discussed in this document, as well as the quantitative benefit-risk assessment conducted by FDA, the Review Committee agrees that the benefit-risk assessment for MNEXSPIKE is favorable and may serve as a variant-updated vaccine option for individuals 12 years of age and older. Ongoing monitoring will assess long-term safety, effectiveness, and durability of protection.

c. Recommendation for Postmarketing Activities

ModernaTX Inc., has committed to conduct the following postmarketing activities, which will be included in the approval letter:

POSTMARKETING REQUIREMENTS UNDER SECTION 505B(a)

1. Deferred pediatric study under PREA (mRNA-1283-P302) to evaluate the safety and effectiveness of MNEXSPIKE in infants and children 6 months to <12 years of age for the prevention of COVID-19.

   Final Protocol Submission: January 31, 2026
   Study Completion Date: December 31, 2029
   Final Report Submission: June 30, 2030

2. Deferred pediatric study under PREA (mRNA-1283-PXXX) to evaluate the safety and effectiveness of MNEXSPIKE in neonates and infants < 6 months of age for the prevention of COVID-19.

   Final Protocol Submission: March 31, 2030
   Study Completion Date: December 31, 2034
   Final Report Submission: June 30, 2035

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

3. A postmarketing retrospective cohort study utilizing commercial and Medicare claims databases to evaluate the occurrence of myocarditis and pericarditis following administration of MNEXSPIKE in the United States (Study mRNA-1283-P901).

   Final Protocol Submission: June 30, 2025
   Study Completion Date: March 30, 2029
   Final Report Submission: September 30, 2029

4. A postmarketing retrospective cohort study using administrative claims and health system medical records to evaluate long-term sequelae of myocarditis following administration of MNEXSPIKE compared to myocarditis in patients who have not received a COVID-19 vaccine (Study mRNA-1283-P904). Participants will have at least five years of follow-up for long-term outcomes of myocarditis.

   Final Protocol Submission: November 30, 2025
   Study Completion Date: March 31, 2033
   Final Report Submission: March 31, 2034

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

5. An observational cohort study using administrative claims data to assess maternal and infant outcomes following exposure to MNEXSPIKE during pregnancy (Study mRNA-1283-P902).

   Final protocol submission: August 31, 2025
   Study/Clinical trial completion: December 15, 2031
   Final Report Submission: December 15, 2032

12. References

1. World Health Organization. (2025) Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Accessed May 12, 2025.
2. CDC (2025) Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. (website), Updated February 6, 2025 https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
3. CDC (2025) COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services. https://covid.cdc.gov/covid-data-tracker
4. CDC (2025) COVID Data Tracker: Demographic Trends of COVID-19 cases in the US Reported to the NVSS https://covid.cdc.gov/covid-data-tracker/#datatracker-home