BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125835
CBER Received Date	September 30, 2024
PDUFA Goal Date	May 30, 2025
Division / Office	DCTR / OVRR
Priority Review (Yes/No)	Yes
Reviewer Names	Timothy P. Brennan, MD, PhD, MS CRB3/DCTR/OVRR Brittany Shepherd, MD, MSc CRB3/DCTR/OVRR
Review Completion Date / Stamped Date	May 30, 2025
Supervisory Concurrence	Rachel Zhang, MD; Team Lead CRB3/DCTR/OVRR Anuja Rastogi, MD, MHS; Branch Chief CRB3/DCTR/OVRR
Applicant	Moderna TX, Inc.
Established Name	COVID-19 Vaccine, mRNA
Proposed Trade Name	mNexspike
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each 0.2 mL dose contains 10 micrograms mRNA encoding the linked N-terminal domain (NTD) and receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein, encapsulated in lipid particles
Dosage Form and Route of Administration	Suspension for intramuscular injection (IM)
Dosing Regimen	Single 0.2 mL dose
Indication and Intended Population	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.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
BIMO	bioresearch monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSR	clinical study report
DMG	dimyristoyl glycerol
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDCA	Federal Food, Drug, and Cosmetic Act
GCP	Good Clinical Practice
GLSM	geometric least square mean
GMC	geometric mean concentration
GMFR	geometric mean fold-rise
GMT	geometric mean titer
HR	hazard ratio
IM	intramuscular
IND	investigational new drug
LB	lower bound
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance image
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
mITT	modified intent-to-treat
nAb	neutralizing antibody
NTD	N-terminal domain
PCR	polymerase chain reaction
PDUFA	Prescription Drug User Fee Act
PEG	polyethylene glycol
PMR	postmarketing requirement
PPIS	Per-Protocol Immunogenicity Subset
PPSE	Per-Protocol Set for efficacy
PREA	Pediatric Research Equity Act
PsVNA	pseudotyped virus neutralization assay
PT	Preferred Term
QD	daily

RBD	receptor-binding domain
RT-PCR	reverse transcription-polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRR	seroresponse rate
STN	Submission Tracking Number
U.S.	United States
USPI	U.S. Prescribing Information
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. Executive Summary

On September 30, 2024, ModernaTX, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the United States (U.S.) Food and Drug Administration (FDA) to support licensure of a COVID-19 mRNA vaccine, mRNA-1283 (trade name mNexspike), with a proposed indication of 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. mRNA-1283 is a nucleoside modified mRNA vaccine encoding for the linked N-terminal domain (NTD) and receptor-blinding domain (RBD) of the SARS-CoV-2 spike (S) glycoprotein, encapsulated in lipid particles.

Data from 4 clinical studies were submitted in support of the BLA. The primary data to support the safety and effectiveness of mRNA-1283 was from Study mRNA-1283-P301 (hereafter referred to as Study P301), a Phase 3, randomized, observer-blind, active-controlled study conducted in the U.S., United Kingdom, and Canada, which evaluated the safety, noninferior efficacy, and noninferior immunogenicity of mRNA-1283.222 (bivalent formula encoding the linked NTD-RBD of the S protein from SARS-CoV-2 Wuhan-Hu 1 strain [Original] and SARS-CoV-2 Omicron variant lineages BA.4 and BA.5) compared with Moderna COVID-19 Vaccine, Bivalent[1] in 11,417 participants 12 years of age and older. Study mRNA-1282-P301-Japan (hereafter referred to as Study P301-Japan) provided supportive safety and immunogenicity data for a monovalent formula of mRNA-1283, and was a Phase 3, randomized, observer-blind, active-controlled study conducted in Japan which evaluated mRNA-1283.815 (monovalent formula encoding the linked NTD-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 689 participants 12 years of age and older. Studies mRNA-1283-P201 (hereafter referred to as Study P201) and mRNA-1283-P101 (hereafter referred to as Study P101) were early phase dose- and formula-finding studies and provided data to support the dose selection for Phase 3, as well as additional supportive safety data.

Effectiveness

In Study P301, participants 12 years of age and older who had received a previous COVID-19 vaccine were randomized 1:1 to receive a single dose of mRNA-1283.222 (n=5,706) or Moderna COVID-19 Vaccine, Bivalent (n=5,711). The primary efficacy objective was to demonstrate the noninferior relative vaccine efficacy (rVE) of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent to prevent symptomatic COVID-19 starting 14 days after vaccination. The study met the pre-specified success criterion for demonstration of rVE, with a rVE point estimate of 9.3% (99.4% confidence interval [CI]: −6.6, 22.8), based on a median follow-up duration for efficacy of 8 months after vaccination. The primary immunogenicity objectives were to demonstrate the noninferior neutralizing antibody responses of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent as measured by (1) geometric mean concentration (GMC) ratio and seroresponse[2] rate (SRR) difference against Omicron BA.4/BA.5 at 28 days after vaccination (Day 29), and (2) GMC ratio and SRR difference against the Original SARS-CoV-2 strain (D614G) at Day 29. The study met the pre-specified success criteria for demonstration of noninferior immunogenicity of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent. Although not powered for subgroup analyses by age, there was a trend observed of increasing rVE and relative immunogenicity with increasing age,

1 Authorized under Emergency Use Authorization (EUA) at the time of this study.

[2] 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.

with the highest rVE and neutralizing antibody GMC ratios observed in the ≥65 years age cohort.

In Study P301-Japan, participants 12 years of age and older who have received a previous COVID-19 vaccine were randomized 1:1 to receive a single dose of mRNA-1283.815 (n=343) or Spikevax (n=346). The study met the primary objective of demonstration of non-inferior immunogenicity of mRNA-1283.815 compared with Spikevax as measured by neutralizing antibody GMC ratio against XBB.1.5 at Day 29. Descriptive analyses of the secondary endpoint of seroresponse against XBB.1.5 showed similar percentages of participants achieving seroresponse across the two groups and would have met the conventional noninferiority criterion of the lower limit of the 95% CI for SRR difference >-10%.

Safety
Safety data from Study P301 included 11,417 vaccinated participants, which included 5,706 mRNA-1283.222 recipients with a median follow-up of 8.8 months. Overall, mRNA-1283.222 recipients reported lower rates of solicited local adverse reactions and similar rates of solicited systemic adverse reactions compared with Moderna COVID-19 Vaccine, Bivalent recipients. The rates of unsolicited adverse events (AEs) through 28 days were similar across the two groups. Serious adverse events (SAEs) were balanced across groups (2.7% in the mRNA-1283.222 group and 2.6% in the Moderna COVID-19 Vaccine, Bivalent group), with no SAEs assessed as related to mRNA-1283.222 by FDA. Safety data from Study P301-Japan was limited to 689 participants (343 mRNA-1283.815 and 346 Spikevax) with a median follow-up of 35 days postvaccination. No SAEs were reported in the study. Review of the safety data from the early phase studies P201 and P101 did not reveal any safety concerns. Although no vaccine-related cases of myocarditis or pericarditis were reported in the clinical studies of mRNA-1283, the safety database was not large enough to rule out rare events (i.e., <1/10,000). The Applicant will be required to conduct additional postmarketing required studies to further evaluate the risk of myocarditis after mRNA-1283 vaccination.

Conclusion
Substantial evidence of mRNA-1283 vaccine effectiveness was supported by the demonstration of noninferior relative vaccine efficacy and noninferior immunogenicity of a bivalent formula of mRNA-1283 (mRNA-1283.222) compared to an authorized COVID-19 vaccine in Study P301 and the demonstration of noninferior immunogenicity of a monovalent formula of mRNA-1283 (mRNA-1283.815) compared with Spikevax in Study P301-Japan. Safety data from both studies suggest that mRNA-1283 has a similar safety profile compared with Spikevax, with no safety concerns identified. Therefore, the available data submitted to this application support FDA assessment of a favorable benefit-risk of mRNA-1283 in individuals 12 years of age and older for the proposed indication.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Effectiveness
In Study P301, subgroup analyses of the efficacy and immunogenicity endpoints by demographics and baseline characteristics are described in Section 6.1.11.2 and Section 6.1.11.7, respectively. These analyses were limited by small numbers of participants in some subgroups.

Safety
In Study P301, there was slightly higher rate of solicited adverse reactions reported among participants in the younger age cohorts (12 through 17 years of age and 18 through 64 years of

age) compared with the older adult cohort (≥65 years of age). No clinically meaningful differences in the occurrence of unsolicited AEs or SAEs were observed across the subgroups by demographic and baseline characteristics.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. 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 (WHO, 2025). Disease symptoms vary; many individuals present with asymptomatic or mild disease, while individuals 65 years of age and older and individuals with certain co-morbid conditions may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome leading to multiorgan failure and death (CDC, 2025a). Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2025b).

In the U.S., more than 1.2 million deaths from COVID-19 have been reported to the CDC (CDC, 2025c), 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 (CDC, 2025c). Individuals 65 years of age and older accounted for 76% of deaths (CDC, 2025d), while those ≥75 years accounted for 46% of COVID-19 hospitalizations; the in-hospital death rate was 27/100,000 in those 65-74 years and 62/100,000 in persons ≥75 years. Importantly, only 8% of persons 65-74 years and 16% of those ≥75 years with a COVID-19 associated hospitalization had received the 2023-2024 vaccine dose (Havers, 2024). Since the start of the pandemic, surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses.

The SARS-CoV-2 Omicron variant has evolved into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome, leading to successive waves across the globe. In June 2023, XBB sublineages dominated, both in the U.S. and globally and accounted for >95% of the circulating virus variants in the U.S. In June 2024, an increase in the prevalence of KP.2 sublineage led the FDA to advise the manufacturers of the licensed and authorized COVID-19 to manufacture monovalent KP.2-based COVID-19 vaccines (2024-2025 Formula) for use in the U.S. beginning Fall 2024. On May 22, 2025, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States. The committee recommended a monovalent JN.1-lineage be used in 2025-2026 COVID-19 vaccine formulations. Based on the totality of the evidence, FDA advised the manufacturers of the approved COVID-19 vaccines that to more closely match currently circulating SARS-CoV-2 viruses, the COVID-19 vaccines for use in the U.S. beginning in fall 2025 should be monovalent JN.1-lineage-based COVID-19 vaccines (2025-2026 Formula), preferentially using the LP.8.1 strain.

Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, SARS-CoV-2 evolution is complex and remains unpredictable. Intrinsic viral factors, e.g., 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. Thus far, the impressive plasticity, especially in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

2.2.1 FDA-Approved Therapies for COVID-19

Oral antivirals:

Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), who are either hospitalized, or not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Immune modulators

Olumiant (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra (tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

2.2.2 Emergency Use Authorized Pharmacological Products for Pre-Exposure Prophylaxis of COVID-19, Post-Exposure Prophylaxis and/or Treatment of COVID-19

Oral antivirals

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults and authorized for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 through 17 years of age and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults 18 years of age and older with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies:
On March 22, 2024, FDA authorized a new monoclonal antibody, Pemgarda (pemivibart) for preexposure prophylaxis for individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2; and who have moderate-to-severe immune compromise due to a medical condition or due to taking immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination.

Immune modulators

Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation, or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 years to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Tocilizumab is authorized for the treatment of COVID-19 in hospitalized pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

2.3 Safety and Efficacy of Pharmacologically Related Products

Spikevax and Moderna COVID-19 Vaccine (2024-2025 formula)

Spikevax (COVID-19 Vaccine, mRNA) manufactured by Moderna is approved 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. Spikevax contains nucleoside-modified messenger RNA (mRNA), encoding pre-fusion stabilized full-length Spike (S) protein of the SARS-CoV-2 Omicron variant KP.2, encapsulated in lipid particles. Moderna COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the (b) (4) as Spikevax, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 through 11 years of age, two-dose regimen in those individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, and a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with Moderna COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Moderna COVID-19 Vaccine (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine (2024-2025 Formula) are documented in the decision memorandum.

Comirnaty and Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula)

Comirnaty (COVID-19 Vaccine, mRNA) manufactured by Pfizer for BioNTech, is approved 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. Comirnaty contains a mRNA encoding the viral Spike (S) glycoprotein of the SARS-CoV-2 Omicron variant KP.2 that is formulated in lipid particles. Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Comirnaty, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 through 11 years of age, three-dose regimen in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two-dose regimen if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer BioNTech COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) Fact Sheet. Safety and effectiveness data supporting approval of Comirnaty and authorization of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are documented in the decision memorandum.

Nuvaxovid and Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)

Nuvaxovid (COVID-19 Vaccine, Adjuvanted) manufactured by Novavax, Inc. is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults 65 years and older, and for individuals 12 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Nuvaxovid contains recombinant S protein of the SARS-CoV-2 Omicron variant JN.1 and Matrix-M adjuvant. Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Nuvaxovid, is authorized under EUA for administration of a single-dose regimen at least 2 months after receipt of the last previous dose of COVID-19 vaccine to individuals 12 years of age and older previously vaccinated with any COVID-19 Vaccine. In individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, Novavax COVID-19 Vaccine (2024-2025 Formula), Adjuvanted is authorized under EUA for administration as a two-dose regimen. Individuals with certain kinds of immunocompromise 12 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)
Fact Sheet. Safety and effectiveness data supporting approval of Nuvaxovid and authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) are documented in the decision memorandum.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Currently, mRNA-1283 is not licensed in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following timeline includes a list of major regulatory activities associated with the submission of this BLA (under IND 27196):

- June 13, 2023: Center for Biologics Evaluation and Research (CBER) responded to the Applicant's questions pertaining to an Accelerated Approval pathway for licensure of mRNA-1283. CBER stated that the available data from the Applicant's Phase 1 and 2

clinical development program did not demonstrate that mRNA-1283 provided a clinically meaningful (i.e., safety or effectiveness) therapeutic benefit over available COVID-19 vaccines, including Spikevax. Absent evidence that all qualify criteria for Accelerated Approval (under 21 CFR 601.40) are met, including that the investigational product provides a meaningful therapeutic benefit to patients over existing therapies, an Accelerated Approval pathway for mRNA-1283 would not be considered acceptable.

- July 10, 2024: A Pre-BLA meeting was held with the Applicant. At the meeting, CBER communicated that a data package to support a BLA submission for mRNA-1283 is expected to include 1) data demonstrating noninferior rVE and noninferior immunogenicity of a bivalent formulation of mRNA-1283 compared with a bivalent formulation of Spikevax in COVID-19 vaccine-experienced individuals, 2) data demonstrating noninferior immunogenicity of a monovalent formulation of mRNA-1283 compared with a monovalent formulation of Spikevax in COVID-19 vaccine-experienced individuals, and 3) data demonstrating noninferior immunogenicity of mRNA-1283 as compared with Spikevax in COVID-19 vaccine-naïve individuals. The Applicant asked whether the indication for mRNA-1283 could be limited to previously vaccinated individuals if data are not available to address point (3) above. CBER confirmed that this would be acceptable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. Please see review memorandum by Data Standards reviewer for additional details regarding the quality of the study datasets.

3.2 Compliance With Good Clinical Practices And Submission Integrity

All clinical trials submitted to the BLA were conducted in accordance with the International Council on Harmonization's Good Clinical Practice (GCP) guidelines [E6(R2)]. The informed, written consent was obtained from all participants as per GCP guidelines and contained all the essential elements of informed consent as stated in 21 CFR 50.25.

Bioresearch Monitoring (BIMO) inspections were issued for 5 clinical sites, including 3 study sites in the U.S. (from Study P301) and 2 study sites in Japan (from study P301-Japan). No deficiencies have been identified that would impact the integrity of the clinical trial data submitted to this BLA. Please see review memorandum by the BIMO reviewer.

3.3 Financial Disclosures

Studies P301 and P301-Japan
Was a list of clinical investigators provided? ☑ Yes ☐ No
Total number of investigators identified: 236
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The CBER Chemistry, Manufacturing, and Controls (CMC) reviewer identified no issues that would impact the conclusions of the clinical review. The CMC reviewer also reviewed the CMC data on the 2024-2025 Formula of mRNA-1283.

4.2 Assay Validation

The submitted data for the assays used in the clinical studies, including the pseudovirus neutralization assay (PsVNA) used to assess neutralizing antibody concentrations for the different SARS-CoV-2 strains, the (b) (4) reverse-transcription polymerase chain reaction (RT-PCR) assay used for detection of current SARS-CoV-2 infection, and the Roche Elecsys anti-SARS-CoV-2 nucleocapsid antibody assay used to identify individuals with recent or prior SARS-CoV-2 infection, have been adequately validated and found to be suitable for their intended purposes. These assays were previously used and reviewed to support the licensure of Spikevax and continue to demonstrate acceptable performance across the qualified laboratories. See clinical memorandum from CBER assay reviewer for additional details regarding the assays used in the clinical studies.

4.3 Nonclinical pharmacology/Toxicology

Please refer to the Toxicology Reviewer Memorandum. No significant toxicology signal was identified.

4.4 Statistical

CBER statistical reviewers verified the key statistical analyses for safety, immunogenicity, and efficacy, and did not identify any major statistical concerns that would affect the interpretation of the data or overall conclusions.

4.5 Pharmacovigilance

Clinical studies for mRNA-1283 have not uncovered any important identified risks to date; however, myocarditis and pericarditis are considered potential risks given the product's similarity to other approved mRNA COVID-19 vaccines, including Spikevax, which carry a known risk of these events. The Applicant proposed enhanced pharmacovigilance measures for myocarditis and pericarditis, including expedited reporting to the Vaccine Adverse Event Reporting System (VAERS), use of a standardized questionnaire, and interval and cumulative analyses in periodic safety reports. The risk of my myocarditis and pericarditis will be further evaluated through two postmarketing required safety studies. The Applicant has also committed to conduct additional studies to address missing information on pregnancy and long-term safety after mRNA-1283. Please see Section 11.6 and CBER Pharmacovigilance review memorandum for further details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This BLA submission contains data from 4 clinical studies. Study P301 serves as the primary source of data to support the safety and effectiveness of mRNA-1283. Study P301-Japan contributes supportive safety and immunogenicity data for the monovalent formulation of mRNA-1283. Studies P201 and P101 were small, dose- and formulation-finding studies that had

limited contribution to the overall safety and effectiveness assessment; therefore, their results will not be discussed in detail in this BLA clinical review.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed by the clinical review team in support of this application:

Table 1. Amendments Reviewed for BLA 125835

Amendment Number	Date Submitted	Module(s)
0	September 30, 2024	Modules 1, 2, and 5
3	November 20, 2024	Module 1
4	November 22, 2024	Modules 1 and 5
7	December 4, 2024	Module 1
8	December 12, 2024	Modules 1 and 5
9	December 16, 2024	Module 1
14	January 24, 2025	Module 1
26	March 7, 2025	Module 1
28	March 7, 2025	Module 1
36	March 27, 2025	Module 1
43	April 18, 2025	Module 1
44	April 18, 2025	Module 1
48	April 28, 2025	Module 1
54	May 7, 2025	Modules 1 and 5
55	May 8, 2025	Module 1
60	May 20, 2025	Module 1

Source: FDA-generated table.

The amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

5.3 Overview of Clinical Studies

The application includes data from 4 clinical studies summarized in Table 2 below. Study P301 is a Phase 3, multi-center, randomized, observer-blinded, active-controlled study evaluating the safety, immunogenicity, and efficacy of a bivalent formulation of mRNA-1283 compared with Moderna COVID-19 Vaccine, Bivalent and is the primary focus of this review. Study P301-Japan is a randomized, observer-blinded, active-controlled study assessing the safety and immunogenicity of a monovalent formulation of mRNA-1283 compared with Spikevax. Study P201 was a Phase 2 dose-ranging study to assess the safety and immunogenicity of different dose levels of mRNA-1283 in participants previously vaccinated with mRNA-1273. Study P101 was a Phase 1 dose- and regimen-finding study which evaluated the safety and immunogenicity of 2-dose and single-dose regimens of mRNA-1283 in COVID-19 vaccine-naïve and SARS-CoV-2 infection-naïve individuals.

Table 2. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of mRNA-1283

Study Number	Study Description	Total randomized (N) Total mRNA-1283 (n)	Dose Level of mRNA-1283 Assessed	Study Status
P301	Phase 3, randomized, observer-blind, active-controlled study to evaluate efficacy, immunogenicity, and safety of mRNA-1283 (*mRNA-1283.222 bivalent formulation*) in COVID-19 vaccine-experienced individuals 12 years of age and older	N=11,454 n=5706	10 µg	Ongoing
P301-Japan	Phase 3, randomized, observer-blind, active-controlled study in Japan to evaluate immunogenicity and safety of mRNA-1283 (*mRNA-1283.815 monovalent formulation*) in COVID-19 vaccine-experienced individuals 12 years of age and older	N=692 n=343	10 µg	Ongoing
P201	Phase 2 observer-blind, active-controlled, dose-ranging study to evaluate safety and immunogenicity of mRNA-1283 (*mRNA-1283 monovalent formulation and mRNA-1283.211 bivalent formulation*) in COVID-19 vaccine-experienced individuals 18 years of age and older	N=540 n=483	2.5 µg, 5 µg, 10 µg	Completed
P101	Phase 1 randomized, observer-blind, active-controlled, dose-ranging study to evaluate safety and immunogenicity of mRNA-1283 (*mRNA-1283 monovalent formulation*) in COVID-19 vaccine-naïve and SARS-CoV-2 infection-naïve individuals 18 through 55 years of age	N=105 n=82	2-dose regimen: 10 µg, 30 µg, 100 µg Single dose regimen: 100 µg	Completed

Source: Reviewer-generated table; Abbreviations: N=total number of participants randomized in study.; n=total number of participants who received mRNA-1283.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Study mRNA-1283-P301

NCT05815498

Title: "A randomized, 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 Overview: Study mRNA-1283-P301 (hereafter referred to as P301) is a multi-country study designed to evaluate the safety, immunogenicity, and relative vaccine efficacy (rVE) of mRNA-1283.222 compared with a previously authorized COVID-19 vaccine (Moderna COVID-19 Vaccine, Bivalent) for the prevention of COVID-19 in healthy adolescents and adults ≥12 years of age. Both the investigational and the comparator vaccines used were aligned with 2022-2023 formula for COVID-19 vaccines recommended by the FDA and WHO (bivalent (Original + Omicron BA.4/BA.5)). The study was conducted in 196 sites in the U.S., United Kingdom, and Canada, and was initiated on March 28, 2023. The clinical study report (CSR)

submitted in support of this BLA includes data with >97% of participants in the study having at least 6 months of follow-up postvaccination.

6.1.1 Objectives

Primary Objectives

Primary Efficacy Objective

To demonstrate noninferior rVE of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent to prevent COVID-19.

Endpoint

rVE of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent to prevent the first event of COVID-19 (see Table 3 below for case definitions) starting 14 days after study injection.

Statistical Criterion for Success:

Noninferiority is demonstrated if the lower bound (LB) of the 2-sided alpha-adjusted CI for the rVE to prevent CDC-defined COVID-19 is > -10%, with rVE defined as 100 x (1 – hazard ratio (HR) [mRNA-1283.222 versus Moderna COVID-19 Vaccine, Bivalent])%

Primary Immunogenicity Objectives

1. To demonstrate a noninferior neutralizing antibody response of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent against SARS-CoV-2 Omicron BA.4/BA.5 based on geometric mean concentration (GMC) ratio and seroresponse rate[3] (SRR) percentage difference at Day 29.

Endpoints:

a. GMC ratio, defined as GMCs against Omicron BA.4/BA.5 elicited by mRNA-1283.222 divided by the GMCs against Omicron BA.4/BA.5 elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29.

Statistical Criterion for Success:

Noninferiority is demonstrated if the LB for the 2-sided 95% CI for the GMC ratio is > 0.667

b. 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.

Statistical Criterion for Success:

[3] 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.

Noninferiority is demonstrated if the LB for the 2-sided 95% CI for the SRR percentage difference is > −10%

2. 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.

   Endpoints:

   a. GMC ratio, defined as GMCs against D614G elicited by mRNA-1283.222 divided by GMCs against D614G elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29.

      Statistical Criterion for Success:
      Noninferiority is demonstrated if the LB for the 2-sided 95% CI for the GMC ratio is > 0.667.

   b. Difference in seroresponse rates against D614G, 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.

      Statistical Criterion for Success:
      Noninferiority is demonstrated if the LB for the 2-sided 95% CI for the SRR percentage difference is > −10%

Primary Safety Objective

1. To evaluate the safety and reactogenicity of mRNA-1283.222.

   Endpoints:

   a. Solicited local and systemic reactogenicity adverse reactions (ARs) during a 7-day follow-up period.
   b. Unsolicited adverse events (AEs) during the 28-day follow-up period.
   c. Serious adverse events (SAEs), medically attended adverse events (MAAEs), AEs leading to withdrawal, and adverse events of special interest (AESIs) from Day 1 to end of study.

Secondary Objectives

Only study objectives with data submitted to this BLA and integral to the assessment of safety and effectiveness will be reviewed in this clinical memo.

1. To assess SARS-CoV-2 infection regardless of symptoms (mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent).

   Endpoints:

   a. SARS-CoV-2 infection (symptomatic or asymptomatic).
   b. Asymptomatic SARS-CoV-2 infection, 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[4].

Exploratory Objectives

1. To characterize the antibody response against emerging variants.
   Endpoint: GMCs against emerging (future) SARS-CoV-2 variants at Day 29 or other timepoints after study injection.

2. To evaluate the immune response markers as correlates of risk and correlate of protection against COVID-19
   Endpoint: Immune response markers.

***Clinical Reviewer Comment**: Please see the CBER statistical review memorandum for review of the Applicant's Correlate of Risk/Correlate of Protection report.*

6.1.2. Design Overview

Study P301 is an ongoing randomized, stratified, observer-blind study evaluating the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283.222 (bivalent Original and Omicron BA.4/BA.5) compared with Moderna COVID-19 Vaccine, Bivalent, in individuals ≥12 years of age who have previously received a COVID-19 vaccine primary series according to the locally authorized or approved regimen. 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 was12 months. For the primary efficacy analyses, the data cutoff was January 31, 2024 and reflected a median follow-up for efficacy of 8.0 months. Safety analyses had a data cutoff of February 23, 2024 and reflected a median duration of follow-up for safety of 8.8 months.

6.1.3 Population

Key Inclusion Criteria

- Healthy individuals ≥12 years of age who were medically stable
- Female participants of childbearing potential were required to have a negative pregnancy test at Screening and at Day 1 and to practice adequate contraception ≥28 days before vaccine administration and through 90 days thereafter.
- Fully vaccinated for COVID-19 with primary series according to the locally authorized or approved regimen, with last COVID-19 vaccine dose administered ≥90 days prior to Day 1. Participants ≥18 years of age also needed to have received at least 1 booster dose (no booster dose requirement for adolescents).

Key Exclusion Criteria

- Recent (within 90 days from screening) COVID-19 vaccination or SARS-CoV-2 infection.

4 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.

- Participants with an episode of myocarditis, pericarditis, or myopericarditis that had not resolved over the last 3 months.
- History of congenital or acquired immunodeficiency or immunocompromising/ immunosuppressive conditions or use of systemic immunosuppressants.

6.1.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1283.222

- Dose and route of administration: 0.2 mL intramuscular (IM)
- Formulation: 10 µg of mRNA consisting of equal amounts of mRNA encoding the linked NTD-RBD of the S protein of the Wuhan-Hu 1 strain of SARS-CoV-2 and SARS-CoV-2 Omicron variant lineages BA.4 and BA.5, formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for injection
- Lots: 8525600101, 8525600102, 8525600104, 8525000101, 8525000102, 8525000103

mRNA-1273.222 (Moderna COVID-19 Vaccine, Bivalent)[5]

- Dose and route of administration: 0.5 mL IM
- Formulation: 50 µg of mRNA consisting of equal amounts of mRNA encoding the entire S glycoproteins of the Wuhan-Hu 1 strain of SARS-CoV-2 and SARS-CoV-2 Omicron variant lineages BA.4 and BA.5, formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for injection
- Lots: 8524100103, 8525700101, 8525700102, 8525700103

  Clinical Reviewer Comment: *Because there were differences in volume for the study interventions, separate site personnel were responsible for dose preparation and administration to maintain study blind. Once vaccine administration was completed, only the blinded study staff interacted with the participants and performed further study assessments.*

6.1.5 Directions for Use

A single IM injection of either mRNA-1283.222 or Moderna COVID-19 Vaccine, Bivalent administered in the deltoid muscle or thigh.

6.1.6 Sites and Centers

Study P301 enrolled participants at 196 clinical sites, including 150 sites in the United States, 38 sites in the United Kingdom, and 8 sites in Canada.

5 Authorized under EUA at the time of this study.

6.1.7 Surveillance/Monitoring

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents.

An unblinded independent Data Safety Monitoring Board (DSMB) composed of external independent participant matter experts and a statistician, conducted closed sessions of unblinded reviews of safety data on a routine basis, and could convene ad hoc as needed. The DSMB also reviewed the rVE interim data based on prespecified decision rules regarding Part 2 enrollment (see Section 6.1.9).

An independent Cardiac Event Adjudication Committee (CEAC) consisting of cardiologists reviewed Investigator-reported suspected cases of myocarditis, pericarditis, or myopericarditis to determine if they met CDC criteria (see Appendix B) of "probable" or "confirmed" event, and to assess severity. The CEAC operated under the rules of an approved charter that was written and reviewed at the organizational meeting of the CEAC.

Following the screening visit, all participants were to complete up to 5 scheduled clinic visits and 3 scheduled telephone visits, with the following major study activities:

- Visit 1: Day 1 (Clinic)
  Single IM injection of Moderna COVID-19 Vaccine, Bivalent or mRNA-1283.222, nasal swab for polymerase chain reaction (PCR) testing, blood collection for SARS-CoV-2 surveillance, blood collection for humoral immunogenicity, eDiary activation for recording of solicited adverse reactions and unsolicited, including AEs, medically attended adverse events (MAAEs), AESIs, SAEs, and AEs leading to study withdrawal.
- Visits 2 and 3: Days 8 and 22, respectively (Telephone)
  Review of eDiary for solicited ARs, recording of unsolicited AEs, MAAEs, AESIs, SAEs, and AEs leading to study withdrawal.
- Visit 4: Day 29 (Clinic)
  Nasal swab for PCR testing, blood collection for SARS-CoV-2 surveillance, blood collection for humoral immunogenicity, eDiary prompts for COVID-19 symptoms and major changes in health every 2 weeks starting at Day 29 through Day 365/EoS (±1 day), recording of unsolicited AEs, MAAEs, AESIs, SAEs, and AEs leading to study withdrawal.
- Visits 5 and 6: Days 91 and 181, respectively (Clinic)
  Nasal swab for PCR testing, blood collection for SARS-CoV-2 surveillance, blood collection for humoral immunogenicity, eDiary prompts for COVID-19 symptoms and major changes in health every 2 weeks starting at Day 29 through Day 365/EoS (±1 day), recording of MAAEs, AESIs, SAEs, and AEs leading to study withdrawal.
- Visit 7: Day 271 (Telephone)
  eDiary prompts for COVID-19 symptoms and major changes in health every 2 weeks starting at Day 29 through Day 365/EoS (±1 day), recording of unsolicited AEs, MAAEs, AESIs, SAEs, and AEs leading to study withdrawal.
- Visit 8: Day 365/EoS (Clinic)
  Nasal swab for PCR testing, blood collection for SARS-CoV-2 surveillance, blood collection for humoral immunogenicity, eDiary prompts for COVID-19 symptoms and major changes in health every 2 weeks starting at Day 29 through Day 365/EoS (±1 day), recording of MAAEs, AESIs, SAEs, and AEs leading to study withdrawal.

Safety Monitoring

All solicited ARs were to be monitored and recorded daily using electronic diaries (eDiaries) during the 7 days following vaccination (i.e., the day of vaccination and 6 subsequent days).

Solicited local ARs monitored were:

- injection site pain[6]
- injection site erythema[7]
- injection site swelling/induration[10]
- axillary swelling or tenderness ipsilateral to the side of injection[9]

Solicited systemic ARs monitored were:

- headache[8]
- fatigue[11]
- myalgia[11]
- arthralgia[11]
- nausea/vomiting[9]
- fever[10]
- chills[11]

Unsolicited AEs occurring during the 28 days following vaccination (i.e., the day of vaccination and 27 subsequent days) were recorded. AEs leading to discontinuation from study participation, MAAEs, AESIs and SAEs were monitored and recorded from Day 1 through end of study (EOS) or withdrawal from study. The Applicant had pre-specified a list of AESI in the study protocol (see Appendix A)

Efficacy Monitoring

Surveillance for COVID-19 symptoms was conducted biweekly via electronic diary (eDiary) prompts from enrollment through the end of the study. Participants with a qualifying symptom (see Table 3 below) were requested to present as soon as possible, but within 72 hours, for an unscheduled visit for clinical evaluation and collection of respiratory samples for SARS-CoV-2 PCR testing using a validated PCR assay. Additionally, similar SARS-CoV-2 PCR testing was performed during the routine scheduled clinic visits (Days 29, 91, 181, and 365) in the presence of qualifying symptoms. Participants who had a lateral flow/rapid SARS-CoV-2 antigen test in response to symptoms were required to present to the clinic for PCR testing, regardless of result, as only PCR results were used to support the primary rVE objective. If participants have

6 Grading scale for injection site pain and axillary swelling or tenderness: Grade 1 (Mild): no interference with activity; Grade 2 (Moderate): some interference with activity; Grade 3 (Severe): prevents daily activity; Grade 4 (Life-threatening): requires emergency room visit or hospitalization

7 Grading scale for injection site erythema and swelling/induration: Grade 1 (Mild): 25-50 mm / 2.5-5 cm; Grade 2 (Moderate): 51-100 mm / 5.1-10 cm; Grade 3 (Severe): >100 mm / >10 cm; Grade 4 (Life-threatening): necrosis or exfoliative dermatitis

8 Grading scale for headache, fatigue, myalgia, and arthralgia: Grade 1 (Mild): no interference with activity; Grade 2 (Moderate): some interference with activity; Grade 3 (Severe): prevents daily activity; Grade 4 (Life-threatening): requires emergency room visit or hospitalization

9 Grading scale for nausea/vomiting: Grade 1 (Mild): no interference with activity or 1-2 episodes/24 hours; Grade 2 (Moderate): some interference with activity or >2 episodes/24 hours; Grade 3 (Severe): Prevents daily activity, requires outpatient intravenous hydration; Grade 4 (Life-threatening): Requires emergency room visit or hospitalization for hypotensive shock

10 Grading scale for fever: Grade 1 (Mild): 38.0-38.4°C (100.4-101.1°F); Grade 2 (Moderate): 38.5-38.9°C (101.2-102.0°F); Grade 3 (Severe): 39.0-40.0°C (102.1-104.0°F); Grade 4 (Life-threatening): >40.0°C (>104.0°F)

11 Grading scale for chills: Grade 1 (Mild): no interference with activity; Grade 2 (Moderate): some interference with activity not requiring medical intervention; Grade 3 (Severe): prevents daily activity and requires medical intervention; Grade 4 (Life-threatening): requires emergency room visit or hospitalization

an approved/authorized SARS-CoV-2 PCR test outside the study site, then they were required to report the results of the PCR test to the study clinic and provide a copy of the results. Finally, participants were also directed to undergo PCR testing if they came into close contact with someone who had known COVID-19 or SARS-CoV-2 infection. For the analyses of rVE, the date of the COVID-19 event is the date of the positive RT-PCR test or the date of the eligible symptom for primary definition of COVID-19, whichever is later. The positive RT-PCR and the first eligible symptom must be within 14 days of each other.

Immunogenicity Monitoring

Blood samples were collected at baseline, Day 29, Day 91, Day 181, and Day 365, and neutralizing antibody responses were evaluated using validated PsVNA for SARS-CoV-2 D614G and Omicron BA.4/BA.5 [D614G: PsVNA (VAC62) (b) (4); Omicron BA.4/BA.5: PsVNA (VAC137) (b) (4)]. (b) (4) reverse-transcription polymerase chain reaction (RT-PCR) was used for detection of current SARS-CoV-2 infection. The Roche Elecsys anti-SARS-CoV-2 nucleocapsid antibody assay was used to identify individuals with recent or prior SARS-CoV-2 infection. Timepoints collected after Day 29 were used to support secondary immunogenicity analyses without hypothesis testing.

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1 above and Section 6.1.9 below.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

While the study had three primary objectives (rVE, immunogenicity, and safety), sample size for the study was driven by the estimated sample size required for the primary rVE objective. Study P301 was initially planned to be conducted over multiple seasons in 2 Parts. Target enrollment for Part 1 of Study P301 was 11,500 participants to be randomized 1:1 to receive either mRNA-1283.222 or Moderna COVID-19 Vaccine, Bivalent. Based on the proportional hazard assumption and with a 1:1 randomization ratio, a total of 2087 events per ~20,122 participants (Part 1 and Part 2 total sample size) would provide approximately 80% power to demonstrate noninferiority with a 10% margin at 1-sided alpha of 0.025. Amendment 3 to study P301 introduced an adaptive study design element with a sample size re-estimation based on an early rVE interim analysis, where O'Brien-Fleming alpha spending function was used to control the type I error (1-sided alpha of 0.025). According to the adaptive design introduced in amendment 3, the DSMB would review interim rVE information in a closed session, and based on predefined conditional power rules, make a recommendation to the Applicant of whether to increase the sample size by enrolling Part 2 of the Study. This DSMB review was defined to be triggered when at least 700 COVID-19 events had been accrued. At that time, the DSMB would calculate 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 interim DSMB review and the originally estimated total number of COVID-19 events needed (i.e., 2087 events), assuming the same data trend.

The primary immunogenicity analyses were assessed in a subset of participants (Per Protocol Immunogenicity Subset [PPIS]) irrespective of baseline SARS-CoV-2 status. With approximately 882 evaluable participants (441 for both mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent) in the PPIS, there was approximately 90% power to demonstrate noninferior antibody responses of mRNA-1283.222 versus Moderna COVID-19 Vaccine, Bivalent for each co-primary immunogenicity endpoint at a 2-sided alpha of 0.05. With a 10% estimate of participants

excluded from the PPIS, an immunogenicity subset sample size of 980 (490 in each group) was needed.

With respect to safety, there was at least a 90% probability to observe at least one participant reporting an AE if the true rate of AEs was 0.1%, with ~10,061 (total N = ~20,122) to ~16,787 (total N = ~33,574) participants receiving mRNA-1283.222.

Methods

Immunogenicity

The primary immunogenicity objectives were to demonstrate noninferior neutralizing antibody responses of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent against Omicron BA.4/BA.5 and D614G based on GMC ratio and SRR difference at Day 29. The study would meet the primary immunogenicity objective if noninferiority is demonstrated for all 4 co-primary immunogenicity endpoints. The primary endpoint analyses were based on the PPIS and the following null hypotheses were tested:

1. $\mathbf{H^1_0}$: Antibody GMC after vaccination with mRNA-1283.222 is inferior to that after vaccination with Moderna COVID-19 Vaccine, Bivalent against Omicron BA.4/BA.5, based on the GMC ratio defined as the ratio of GMC elicited by mRNA-1283.222 at Day 29 divided by the GMC elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29. The prespecified noninferiority margin is 1.5 or 0.667.
2. $\mathbf{H^2_0}$: Antibody SRR[12] after vaccination with mRNA-1283.222 is inferior to that after vaccination with Moderna COVID-19 Vaccine, Bivalent against Omicron BA.4/BA.5, based on the SRR percentage difference defined as the SRR percentage of mRNA-1283.222 against Omicron BA.4/BA.5 at Day 29 minus the SRR percentage of Moderna COVID-19 Vaccine, Bivalent against Omicron BA.4/BA.5 at Day 29. The prespecified noninferiority margin is 10%.
3. $\mathbf{H^3_0}$: Antibody GMC after vaccination with mRNA-1283.222 is inferior to that after vaccination with Moderna COVID-19 Vaccine, Bivalent against ancestral SARS-CoV-2 D614G, based on the GMC ratio defined as the ratio of GMC elicited by mRNA-1283.222 at Day 29 over the GMC elicited by Moderna COVID-19 Vaccine, Bivalent at Day 29. The prespecified noninferiority margin is 1.5 or 0.667.
4. $\mathbf{H^4_0}$: Antibody SRR after vaccination with mRNA-1283.222 is inferior to that after vaccination with Moderna COVID-19 Vaccine, Bivalent against ancestral SARS-CoV-2 D614G, based on the SRR percentage difference defined as the SRR percentage of mRNA-1283.222 against D614G at Day 29 minus the SRR percentage of Moderna COVID-19 Vaccine, Bivalent against D614G at Day 29. The prespecified noninferiority margin is 10%.

Efficacy

Analysis of rVE

The hypothesis for the rVE endpoint was only to be tested if all 4 co-primary immunogenicity endpoints were met. The primary rVE objective was to demonstrate a noninferior rVE of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent in preventing the first event of

12 Seroresponse (primary definition) is defined as an antibody value change from baseline below the lower limit of quantification (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-study vaccination.

COVID-19 (based on the primary COVID-19 case definition) starting 14 days after study vaccination. Relative vaccine efficacy (rVE) was defined as 1−Hazard Ratio (HR), estimated by a Cox proportional hazards model using Efron's method to handle ties and with treatment group as a fixed effect, stratified by the stratification factor of age group at randomization: (12 to <18 years, 18 to <65 years, or ≥65 years). For the primary efficacy analysis, the following null hypothesis was tested:

H_0: rVE ≤-10% (this is equivalent to hazard ratio ≥1.1, where rVE = 1-HR)

The primary efficacy objectives were considered met if the lower bound of the alpha-adjusted 99.4% CI >10%

Clinical Reviewer Comment: *Statistical testing of immunogenicity endpoints preceded testing of the clinical efficacy endpoint. However, the analyses of the clinical efficacy endpoints were considered critical to CBER's evaluation of substantial evidence of vaccine effectiveness.*

Case Definitions

The case definitions for the efficacy endpoints for Study P301 are shown below in Table 3.

Table 3. COVID-19 Case Definitions, Study P301

Term	Case Definition
CDC-Defined COVID-19 (Primary)	The presence of ≥1 CDC-listed symptom: • Fever or chills • Cough • Shortness of breath or difficulty breathing • Sore throat • Congestion or runny nose • New loss of taste or smell • Fatigue • Muscle or body aches • Headache • Nausea or vomiting • Diarrhea AND • A positive RT-PCR test on a respiratory sample.
Protocol-Defined COVID-19 (Secondary)	Experienced ≥2 systemic symptoms: Fever (≥38°C/100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR Experienced ≥1 respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND ≥1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report
Abbreviations: CDC = Center's for Disease Control and Prevention, RT-PCR = reverse transcriptase – polymerase chain reaction, NP = nasopharyngeal, COVID-19 = Coronavirus disease 2019

Clinical Reviewer Comment: *Compared with the CDC-Defined COVID-19 case definition, the Protocol-Defined COVID-19 case definition is more stringent and specific and was used*

in the 2020 Phase 3 pivotal field efficacy study to establish the efficacy of Spikevax. The CDC definition was used as a secondary endpoint for the Spikevax study and in other COVID-19 vaccine studies, providing a standardized approach for the evaluation of COVID-19 cases across different investigational COVID-19 vaccine clinical development programs.

Analysis Timing

The final analysis of all endpoints were performed after participants had completed all planned study procedures. The protocol pre-specified an interim analysis for rVE to occur when at least 700 COVID-19 events have accrued in Part 1 of the study. An adaptive design implemented in amendment 3 for Study P301 introduced DSMB rules for the interim analysis. If the observed rVE met success criteria for efficacy based on the O'Brien-Fleming boundary, the DSMB would inform the Applicant regarding early success due to overwhelming efficacy, which would trigger no enrollment for study Part 2. If the early success criterion was not met, then the DSMB would provide recommendations for changes to enrollment goals or whether the study should proceed based on the conditional power.

> ***Clinical Reviewer Comment****: The interim analysis met the rVE success criteria, which triggered the DSMB to inform the Applicant of early success and to not initiate study Part 2. Therefore, the interim analysis is now considered the primary analysis for this BLA.*

Sensitivity and Subgroup Analyses

rVE

- The analysis of the primary efficacy endpoint based on the protocol-defined COVID-19 definition (secondary definition)
- The analysis of the primary efficacy endpoint without excluding participants who received off-study COVID-19 vaccination.
- The analysis of the primary efficacy endpoint using either a positive antigen test or positive RT-PCR, or positive multiplex SARS-CoV-2 test instead of the protocol required RT-PCR test.
- rVE to prevent first COVID-19 event starting after study vaccine injection.
- Earlier date of either positive RT-PCR test or eligible symptom for primary COVID-19 definition as the date of the COVID-19 event

Immunogenicity

- Analysis of SRR using the secondary seroresponse definition

Subgroup Analyses

Safety, efficacy and immunogenicity endpoints may be analyzed in the following subgroups:

- Sex
- Age (12 to <18 Years, 18 to <65 Years, ≥65 Years)
- Race
- Ethnicity
- Baseline SARS-CoV-2 Status
- Number of prior COVID-19 booster doses
- Number of prior COVID-19 vaccine doses
- Country
- Geographic region (North America including United States and Canada versus Europe including United Kingdom)

- Type of last prior COVID-19 vaccines
- Dosing interval
- Previous COVID-19 vaccination status (Yes/No)

Protocol Amendments and Changes to Planned Analyses

The original protocol was dated 27 Feb 2023.

Protocol Amendment 1 (dated 02 May 2023) included the following substantial changes:

- Changed the noninferior rVE from a key secondary endpoint to a primary endpoint.
- Revision of the rVE noninferiority margin from 20% to 15%.
- The number of participants was increased to at least 6000 and up to 10,748.

Protocol Amendment 2 (dated 08 Aug 2023) included the following substantial changes:

- Addition of 1000 adolescent participants 12 to <18 years of age.

Protocol Amendment 3 (dated 20 Dec 2023) included the following substantial changes:

- Revision of the rVE noninferiority margin from 15% to 10%.
- Addition of Part 2 to enroll up to an additional 22,074 participants, based on results of the interim analysis
- Specified the minimum number of COVID-19 events needed for a Part 1 rVE interim analysis and specified the requirements for an interim rVE analysis.
- Specified that the DSMB would also review interim rVE data and provide recommendations to the Applicant based on prespecified decision rules.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Populations used in the study analyses are defined in Table 4. The Per-Protocol Set for Efficacy was the primary population used for the analyses of efficacy, while the Per-Protocol Immunogenicity Subset was used for the analyses of immunogenicity endpoints.

Table 4. Analysis Populations

Population	Description
Full Analysis Set (FAS)	All randomized participants who received study vaccine.
Immunogenicity Subset	A random sample of adult participants in the FAS and the first 210 dosed adolescent participants.
Per-Protocol Immunogenicity Subset (PPIS)	All participants in the immunogenicity subset who received the planned dose of study vaccination, have pre-vaccination and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data, and had no major protocol deviations that impact key or critical data.
Per-Protocol Set for Efficacy (PPSE)	All participants in the FAS who received the planned dose of study vaccine and have no major protocol deviations that impact vaccine efficacy data.
Safety Set	All randomized participants who received study vaccine.
Solicited Safety Set	All randomized participants who received study vaccine and contributed any solicited AR data. The Solicited Safety Set was used for the analyses of solicited ARs.

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report

6.1.10.2 Demographics

The demographics of participants in the Safety Set are shown in Table 5. In general, the demographics of the Safety Set were balanced across the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups. The median age of the population was 56 years; 8.7% of participants were 12 years through 17 years, 62.6% were 18 years through 64 years, and 28.7% were 65 years and older. Overall, most participants were White (82.2%), non-Hispanic or Latino (85.2%), and from study sites in the U.S. (75.6%). Most participants had evidence of prior SARS-CoV-2 infection at baseline (74.3%), had 3 (39.4%) or 4 (39.1%) prior COVID-19 vaccine doses, and received a mRNA bivalent vaccine as the last prior COVID-19 vaccine (50.6%). The median interval from last prior dose of COVID-19 vaccine to study vaccination was 9.8 months. The demographics and baseline characteristics for the Per-Protocol Immunogenicity Subset (PPIS) and the Per-Protocol Set for Efficacy (PPSE), which were used for the primary immunogenicity and efficacy analyses, respectively, were similar to the demographics and characteristics described for the Safety Set.

Table 5. Demographic and Baseline Characteristics, Safety Set, Study mRNA-1283-P301

Characteristic	mRNA-1283.222 N=5706	Moderna COVID-19 Vaccine, Bivalent N=5711
Sex, n (%)	--	--
Male	2586 (45.3)	2631 (46.1)
Female	3120 (54.7)	3080 (53.9)
Age, years	--	--
Median age (min, max)	56.0 (12, 96)	55.0 (12, 90)
12 to <18 years, n (%)	497 (8.7)	495 (8.7)
18 to <65 years, n (%)	3575 (62.7)	3576 (62.6)
≥ 65 years, n (%)	1634 (28.6)	1640 (28.7)
≥75 years, n (%)	322 (5.6)	269 (4.7)
Race, n (%)	--	--
African American/Black	640 (11.2)	635 (11.1)
American Indian or Alaska Native	20 (0.4)	26 (0.5)
Asian	225 (3.9)	183 (3.2)
Native Hawaiian or other Pacific Islander	9 (0.2)	6 (0.1)
White	4670 (81.8)	4711 (82.5)
Multiracial	81 (1.4)	94 (1.6)
Other	20 (0.4)	20 (0.4)
Unknown	5 (0.09)	10 (0.2)
Not reported	36 (0.6)	26 (0.5)
Ethnicity, n (%)	--	--
Hispanic/Latino	769 (13.5)	741 (13.0)
Not Hispanic/Latino	4860 (85.2)	4864 (85.2)
Unknown	18 (0.3)	19 (0.3)
Not reported	59 (1.0)	87 (1.5)
Country, n (%)	--	--
United States	4323 (75.8)	4312 (75.5)
Canada	101 (1.8)	112 (2.0)
United Kingdom	1282 (22.5)	1287 (22.5)
Body Mass Index, n (%)	--	--
Median (min, max)	28.30 (14.4, 81.9)	28.30 (14.6, 76.7)
<30 kg/m^2	3338 (58.5)	3372 (59.0)

Characteristic	mRNA-1283.222 N=5706	Moderna COVID-19 Vaccine, Bivalent N=5711
≥30 kg/m^2	2306 (40.4)	2273 (39.8)
≥40 kg/m^2	451 (7.9)	489 (8.6)
Missing	62 (1.1)	66 (1.2)
Baseline SARS-CoV-2 Status [a], n (%)	--	--
Negative	1402 (24.6)	1372 (24.0)
Positive	4211 (73.8)	4270 (74.8)
Missing	93 (1.6)	69 (1.2)
Number of Prior COVID-19 Vaccine Doses, n (%)	--	--
0[b]	1 (0.02)	0
1	7 (0.1)	1 (0.02)
2	335 (5.9)	324 (5.7)
3	2243 (39.3)	2253 (39.5)
4	2210 (38.7)	2250 (39.4)
5	903 (15.8)	882 (15.4)
≥6	6 (0.1)	1 (0.02)
Missing	1 (0.02)	0
Type of Last Prior COVID-19 Vaccine, n (%)	--	--
mRNA, Original monovalent	2605 (45.7)	2618 (45.8)
mRNA, bivalent[c] (Original + Omicron BA.4/BA.5)	2882 (50.5)	2900 (50.8)
Non-mRNA	204 (3.6)	181 (3.2)
No Prior COVID-19 Vaccine[b]	1 (0.02)	0
Unknown	13 (0.2)	12 (0.2)
Missing	1 (0.02)	0
Dosing Interval from Last Prior Dose COVID-19 Vaccine to Study Vaccine Day (months)[d]	--	--
Median (min, max)	9.8 (0.1, 37.9)	9.8 (0.1, 32.5)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.1.3.1. Data cutoff 23 Feb 2024.
Abbreviations: COVID-19=coronavirus disease 2019; max=maximum; min=minimum; N=total number of participants in the specified group; n=number of participants with the specified characteristic; RT-PCR=reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; Original= Wuahn-Hu-1 strain
a. Baseline SARS-CoV-2 Status: positive 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 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.
b. One participant with no prior COVID-19 vaccine was enrolled into the study by error, this was a protocol deviation.
c. Participants with last mRNA Covid-19 vaccine dose date as 1 September 2022 or later.
d. Dosing interval from last prior dose covid-19 vaccine to investigational vaccine Day (months)=Date of vaccine – date of last prior dose covid vaccine +1) / 30.4375. The median (months) used to calculate the proportion participants is based on the median from the overall median per Analysis Set: 9.82 months.

Notable differences in demographic and baseline characteristics across the age subgroups in the Safety Set are summarized below.

- *Dosing Interval from Last Prior Dose COVID-19 Vaccine:*
  The median interval from the last COVID-19 dose to receiving the study vaccine was longer for participants 12 through 17 years of age (16 months) compared with participants 18 through 64 years of age (10 months) and participants ≥65 years of age (9 months).
- *Evidence of Prior COVID-19 Infection:*
  Most (90.1%) participants 12 through 17 years of age had evidence of prior SARS-CoV-2 infection at baseline, compared with 76.4% of participants 18 through 64 years of age and 64.9% of participants ≥65 years of age.

- *Number of Prior COVID-19 Doses:*
  Among participants 12 through 17 years of age, the majority had received 2 (38.2%) or 3 (40.2%) prior doses of COVID-19 vaccine. Among participants 18 through 64 years of age, the majority had received 3 (46.6%) or 4 (39.1%) prior doses of COVID-19 vaccine. Among participants ≥65 years of age, the majority had received 4 (44.6%) or 5 (30.7%) prior doses of COVID-19 vaccine.
- *Type of Last Prior COVID-19 Vaccine (Original Monovalent versus Bivalent Omicron BA.4/BA.5):*
  The majority (65.6%) of participants 12 through 17 years of age received an mRNA original monovalent COVID-19 vaccine as the last prior COVID-19 vaccine, while the majority (66.0%) of participants ≥65 years of age received an mRNA bivalent vaccine (Original + Omicron BA.4/BA.5) as the last prior COVID-19 vaccine. Among participants 18 through 64 years of age, a comparable percentage received an mRNA original monovalent vaccine (49.2%) or an mRNA bivalent vaccine (46.7%).

6.1.10.3 Participant Disposition

Study disposition tables are presented below in Table 6 (efficacy and immunogenicity populations) and Table 7 (Safety Set).

The proportion of participants who were excluded from the Per-Protocol Set for Efficacy was comparable across the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups (0.5% and 0.4%, respectively). Most participants were excluded from the Per-Protocol Set for Efficacy due to protocol deviation. The proportion of participants who were excluded from the Per-Protocol Immunogenicity Subset was also comparable across the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups (8.4% and 8.7%, respectively). Most participants were excluded from the Per-Protocol Immunogenicity Subset due to missing baseline or Day 29 immunogenicity data.

Table 6. Participant Disposition, Immunogenicity and Efficacy Populations, Study mRNA-1283-P301

Population	mRNA-1283.222 n (%)	Moderna COVID-19 Vaccine, Bivalent n (%)
Randomization Set	N=5728	N=5726
Full Analysis Set (FAS)[a]	5706 (99.6)	5711 (99.7)
Per-Protocol Set for Efficacy (PPSE)[a]	5679 (99.1)	5687 (99.3)
Excluded from PPSE	27 (0.5)	24 (0.4)
Reason for exclusion from PPSE	--	--
Major Protocol Deviations that Impact Key or Critical Data	27 (0.5)	24 (0.4)
Immunogenicity Subset[a]	678 (11.8)	622 (10.9)
Per-Protocol Immunogenicity Subset (PPIS)[b]	621 (91.6)	568 (91.3)
Excluded from PPIS	57 (8.4)	54 (8.7)
Reason for exclusion from PPIS	--	--
Major Protocol Deviations that Impact Key or Critical Data	3 (0.4)	3 (0.5)
Did not have baseline or Day 29 (occurring between 21 and 42 days) Immunogenicity Data	54 (8.0)	51 (8.2)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.1.2.1, 14.1.2.3; 14.1.2.2. Data cutoff 23 Feb 2024.
Abbreviations: N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic;
a. Numbers are based on planned treatment group and percentages are based on the number of participants in Randomization Set.
b. Percentages are based on the number of participants in Immunogenicity Subset.

Of the 11,417 participants who received a study vaccine, 261 (4.6%) from the mRNA-1283.222 group and 214 (3.8%) from the Moderna COVID-19 Vaccine, Bivalent group discontinued from the study. Of those 475 participants that discontinued, the most common reasons included withdrawal of consent (55%) and lost to follow-up (34%). Five participants discontinued from the study due to an AE (3 participants in the mRNA-1283.222 group and 2 participants in the Moderna COVID-19 Vaccine, Bivalent group). There were 15 discontinuations due to deaths recorded in the study, with 5 deaths occurring in the mRNA-1283.222 group and 10 deaths occurring in the Moderna COVID-19 Vaccine, Bivalent group. These discontinuations due to AEs and deaths will be discussed in detail in the safety section below. The median duration of follow-up for safety for study participants was 8.8 months.

Table 7. Participant Disposition, Safety Populations, Study mRNA-1283-P301

Population	mRNA-1283.222 n (%)	Moderna COVID-19 Vaccine, Bivalent n (%)
Randomization Set	N=5728	N=5726
Safety Set[a]	5706 (99.6)	5711 (99.7)
Solicited Safety Set[b]	5702 (99.9)	5706 (99.9)
Discontinued from the Study[c]	261 (4.6)	214 (3.8)
Reason for Discontinuation[c]		
Adverse Event	3 (0.1)	2 (<0.1)
Death	5 (0.1)	10 (0.2)
Lost to Follow-Up	92 (1.6)	70 (1.2)
Physician Decision	11 (0.2)	10 (0.2)
Pregnancy	1 (<0.1)	0
Protocol Violation	2 (<0.1)	1 (<0.1)
Withdrawal of Consent by Participant	144 (2.5)	119 (2.1)
Other	3 (0.1)	2 (<0.1)
Median follow-up (months) (min, max)	8.8 (0.1, 10.7)	8.8 (0.2, 11.0)
≥6 months since vaccination	5540 (97.1)	5574 (97.6)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.1.1.1, 14.1.2.1, 14.1.1.5. Data cutoff 23 Feb 2024.
Abbreviations: N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic;
a. Numbers are based on actual treatment group and percentages are based on the number of participants in Randomization Set.
b. Numbers are based on actual treatment group and percentages are based on the number of subjects in Safety Set.
c. Numbers are based on randomization treatment group and percentages are based on the number of participants received vaccine.

> ***Clinical Reviewer Comment****: The rates and reasons for discontinuation were generally balanced across the study groups. The median follow-up duration for the adolescent cohort (6.5 months) was shorter compared with the 18 to <64 years and ≥65 years age cohorts (8.8 months).*

6.1.11 Analyses of Vaccine Effectiveness

6.1.11.1 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 January 31, 2024. In this analysis, the median duration of follow-up for efficacy was 8 months. 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 CDC-defined COVID-19 starting 14 days after study vaccination, with a noninferiority margin of 10%.

The primary efficacy analysis demonstrated a rVE of 9.3% (99.4% CI: −6.6, 22.8), which met the prespecified noninferiority success criterion of the lower bound (LB) of the 99.4% CI > −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.

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

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]
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 versus 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 versus Moderna COVID-19 Vaccine, Bivalent]).

> ***Clinical Reviewer Comment:*** *The primary analyses demonstrating noninferior relative vaccine efficacy of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent through a median follow-up of 8 months support the clinical benefit of mRNA-1283 in individuals ≥12 years of age, with a median time interval of 9.8 months since the*

last prior dose COVID-19 vaccine and in the background of approximately 74% of participants with evidence of prior SARS-CoV-2 infection.

6.1.11.2 Supportive Analyses of the Primary Efficacy Endpoint

The Applicant also conducted several descriptive sensitivity analyses of the primary efficacy endpoint to evaluate the consistency of the results obtained in the primary rVE analysis.

Analysis of rVE with February 23, 2024 Data Cutoff Date

A descriptive analysis of rVE was conducted with all COVID-19 events (primary definition) that were accrued through cutoff date of February 23, 2024. The median follow-up time for this later cutoff was approximately 8.8 months. From the primary cutoff date of January 31, 2024 through this later cutoff date of February 23, 2024 an additional 97 COVID-19 events were accrued. There were 613 cases (10.8%) in the mRNA-1283.222 group compared with 661 cases (11.6%) in the Moderna COVID-19 Vaccine, Bivalent group, with a hazard ratio-based rVE of 7.3% (95% CI: −3.4, 17.0).

***Clinical Reviewer Comment**: Results of the descriptive analysis of rVE based on an 8.8 months of duration of follow-up were consistent with the results of the primary analysis that had 8 months duration of follow-up.*

Analysis of rVE using a secondary COVID-19 case definition

The Applicant conducted a descriptive analysis of rVE, based on data cutoff date of January 31, 2024, using the prespecified secondary COVID-19 case definition (see Table 3 above). There were 498 (8.8%) cases in the mRNA-1283.222 group and 556 (9.8%) cases in the Moderna COVID-19 Vaccine, Bivalent group, with a hazard ratio-based rVE of 10.5% (95% CI: −1.0, 20.7).

***Clinical Reviewer Comment**: Because the secondary case definition is more specific compared with the primary case definition, a smaller number of COVID-19 cases contributed to this analysis. The use of a more specific case definition did not substantially change the rVE results.*

rVE Analysis Based on PCR or SARS-CoV-2 Antigen Testing

The Applicant also conducted a descriptive analysis of rVE based including COVID-19 cases confirmed using SARS-CoV-2 antigen test, in addition to the cases which were confirmed using RT-PCR as specified by the study protocol, based on January 31, 2024 cutoff date. There were 634 (11.2%) cases in the mRNA-1283.222 group and 693 (12.2%) cases in the Moderna COVID-19 Vaccine, Bivalent group, with a hazard ratio-based rVE of 8.6% (95% CI: −1.8, 17.9), which was consistent with the results of the primary efficacy analysis.

6.1.11.3 Subpopulation Analyses

Subgroup Analyses by Age

Although Study P301 was not powered to evaluate rVE by age subgroups, the protocol had prespecified three age subgroups for study stratification and for descriptive analyses: 12 to <18 years, 18 to <65 years, and ≥65 years. In the PPSE, 8.7% of participants were 12 to <18 years of age, 62.6% were 18 to <65 years of age, and 28.7% were ≥65 years of age.

Descriptive analyses of rVE by age subgroup, based on the January 31, 2024 data cutoff date, are shown in Table 9. Similar results were observed when the age subgroup analyses were conducted based on the secondary COVID-19 case definition or based on a later cutoff date of February 23, 2024.

Table 9. Descriptive Analyses of Relative Vaccine Efficacy (rVE) to Prevent COVID-19 Starting 14 Days Postvaccination, Subgroup Analysis Based on Age, PPSE, Data Cutoff January 31, 2024, Study mRNA-1283-P301

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]	Descriptive rVE % (95% CI)
12 to <18 Years	29/491 (5.9) 1.0	23/490 (4.7) 0.8	-29.2 (−123.3, 25.3)
18 to <65 Years	382/3558 (10.7) 1.4	422/3562 (11.8) 1.6	9.7 (−3.8, 21.3)
≥65 Years	149/1630 (9.1) 1.3	172/1635 (10.5) 1.5	13.5 (−7.7, 30.6)

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=total number of participants in the specified group; 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 versus Moderna COVID-19 Vaccine, Bivalent), hazard ratio and CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect.

***Clinical Reviewer Comment**:*

1. *Study P301 was not powered to demonstrate relative VE in a specific age subgroup.*
2. *The adolescent subgroup sample size was small (only 8.7% of participants in the PPSE were 12 to <18 years of age) and had fewer COVID-19 cases (52 cases) compared with the two older age cohorts (804 cases 18-64 years; 321 cases ≥65 years). Adolescent participants also had a shorter median duration of follow-up for efficacy (5.7 months) compared with the younger and older adult cohorts (8.1 months). The incidence rate for COVID-19 in the adolescent age subgroup was 0.8%-1.0% compared with 1.3-1.6% for the adult subgroups. The negative rVE point estimate with associated wide confidence intervals therefore preclude an assessment of rVE in the adolescent age subgroup. However, as shown in Section 6.1.11.7 below, the immune response measured by neutralizing antibody concentrations were higher in the adolescent subgroup relative to the 18 through 64 years and ≥ 65 years of age subgroups, which provides support for the effectiveness of mRNA-1283.222 in the adolescent age group. Therefore, these data suggest that efficacy potentially could have been demonstrated for the adolescent subpopulation if the study was designed accordingly with larger adolescent populations enrolled and with longer follow-up.*
3. *The two adult subgroups (18 through 64 years and ≥65 years) had larger sample sizes (7120 and 3265 participants, respectively) and had 804 and 321 COVID-19 cases, respectively, of the 1177 cases reported to support the primary analyses. The descriptive rVE in each of these two groups was 9.7 (−3.8, 21.3) for adults 18 to <64*

years and 13.5 (−7.7, 30.6) for adults ≥65 years of age. If applying the conventional noninferiority criterion for rVE (LB of the 95% CI for rVE >-10%), the 18 to <65 years subgroup and the ≥65 years subgroup would have achieved study success.

4. *Additional clinical considerations that impacted the descriptive analyses of rVE by age included differences in baseline characteristics between the 12 to <18 years subgroup and the adult subgroups. Relative to the adult subgroups, adolescent participants had a longer median time interval from last COVID-19 vaccination with fewer prior doses of COVID-19 vaccine and were also more likely to have had prior SARS-CoV-2 infection.*

Subgroup Analyses by Baseline SARS-CoV-2 Status

Descriptive analyses of rVE were conducted (using January 31, 2024 data cutoff) based on evidence of prior SARS-CoV-2 infection at baseline (baseline SARS-CoV-2 status) pre-study vaccination (Table 10). Relative vaccine efficacy was higher among participants who had no evidence of prior SARS-CoV-2 infection at baseline compared with participants with evidence of prior infection, and was observed across all age subgroups.

Table 10. Descriptive Analyses of Relative Vaccine Efficacy (rVE) to Prevent COVID-19 Starting 14 Days Postvaccination, Based on Baseline SARS-CoV-2 Status, PPSE, Data Cutoff January 31, 2024, Study mRNA-1283-P301

Age Group and Baseline SARS-CoV-2 Status*	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]	Descriptive rVE[c] % (95% CI)
All participants	--	--	--
Positive	350/4186 (8.4) 1.2	380/4254 (8.9) 1.2	6.5 (−8.1, 19.2)
Negative	195/1401 (13.9) 2.0	232/1366 (17.0) 2.4	18.9 (1.9, 33.0)
Participants 12 to <18 years	--	--	--
Positive	24/434 (5.5) 0.9	19/449 (4.2) 0.7	-32.3 (−141.5, 27.5)
Negative	4/50 (8.0) 1.6	4/40 (10.0) 1.8	10.0 (−260.1, 77.5)
Participants 18 to <65 years	--	--	--
Positive	245/2677 (9.2) 1.2	277/2760 (10.0) 1.3	8.7 (−8.5, 23.1)
Negative	123/817 (15.1) 2.1	142/761 (18.7) 2.7	21.6 (0.2, 38.4)
Participants ≥65 years	--	--	--
Positive	81/1075 (7.5) 1.1	84/1045 (8.0) 1.1	8.1 (−24.8, 32.2)
Negative	68/534 (12.7) 1.8	86/565 (15.2) 2.2	14.5 (−17.5, 37.8)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Amendment 4
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; N=number of participants at risk; PPSE=per-protocol set for efficacy;
*Baseline SARS-CoV-2 Status: positive 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 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.

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 versus 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. For age subgroup analysis, actual age group is used. Age stratification was removed from Cox proportional hazard model for age subgroup analysis.

> ***Clinical Reviewer Comment****: Among vaccinated participants, an increased incidence of COVID-19 was observed in participants with no evidence of prior SARS-CoV-2 infection at baseline pre-vaccination. This finding could reflect the benefit of hybrid immunity in participants with prior SARS-CoV-2 infection and then subsequently received COVID-19 vaccine. The increased COVID-19 incidence was not observed equally across study groups, with the Moderna COVID-19 Vaccine, Bivalent group reporting a higher incidence of COVID-19 cases compared with mRNA-1283.222 in all age subgroups among participants who were baseline SARS-CoV-2 negative, likely contributing to the higher rVE in these subgroups. However, interpretation of these results is limited by the wide and overlapping 95% CIs in these analyses.*

Additional Subgroup Analyses

In addition to the analyses described above, the Applicant also conducted subgroup analyses for rVE based on sex, race, ethnicity, country, number of prior COVID-19 vaccine doses, type of last prior COVID-19 vaccination, and dosing interval since last prior COVID-19 vaccination. Although rVE results were generally similar across the various subgroups, the smaller numbers of cases and wide CIs limits interpretation of the analysis results in some subgroups.

6.1.11.4 Analyses of Secondary Efficacy Endpoints

Descriptive secondary efficacy objectives evaluated the incidence of SARS-CoV-2 infection, regardless of symptoms and the incidence of asymptomatic SARS-CoV-2 infection. Asymptomatic SARS-CoV-2 infection was defined as the absence of clinical symptoms and either a positive RT-PCR test on a respiratory sample or a positive serologic test for anti-nucleocapsid antibody for those participants with a negative SARS-CoV-2 status at baseline.

Table 11. Descriptive Analyses of Relative Vaccine Efficacy to Prevent All SARS-CoV-2 Infection and Asymptomatic SARS-CoV-2 Infection, PPSE, Data Cutoff January 31, 2024, Study mRNA-1283-P301

Category	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]	Descriptive rVE[c] % (95% CI)
All SARS-CoV-2 Infection, Regardless of Symptoms	894/5679 (15.7) 2.268	942/5687 (16.6) 2.388	5.1 (−4.0, 13.4)
Asymptomatic SARS-CoV-2 Infection	333/5679 (5.9) 0.8	321/5687 (5.6) 0.8	-3.8 (−21.0, 11.0)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.2.5.2
Abbreviations: CI =confidence interval; COVID-19=coronavirus disease 2019; N=total number of participants in the specified group; PPSE=per-protocol set for efficacy.
a. Cases are defined as the absence of clinical symptoms and either a positive RT-PCR test on a respiratory sample or a positive serologic test for anti-nucleocapsid antibody for those participants with a negative SARS-CoV-2 status at baseline.
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. For age subgroup analysis, actual age group is used. Age stratification was removed from Cox proportional hazard model for age subgroup analysis.

Clinical Reviewer Comment*: The majority of cases included in the analysis for "All SARS-CoV-2 infection" were symptomatic COVID-19 cases which contributed to the primary efficacy analysis. Therefore, the results for rVE for prevention of all SARS-CoV-2 was consistent with that of the primary efficacy endpoint of rVE for prevention of CDC-defined COVID-19. Although analyzed descriptively, the results for the rVE endpoint for prevention of asymptomatic SARS-CoV-2 infection would not have met the conventional noninferiority success criterion of a LB >-10%. This secondary objective for evaluation of asymptomatic SARS-CoV-2 infection relies on SARS-CoV-2 testing at scheduled clinic visits. This testing design will likely underestimate the number of asymptomatic SARS-CoV-2 cases in the study due to the limited number of pre-specified timepoints for testing. Furthermore, the comparator vaccine (Moderna COVID-19 Vaccine, Bivalent, or Spikevax) is not specifically indicated for the prevention of "all SARS-CoV-2 infection" or asymptomatic SARS-CoV-2 infection, which limits the interpretation of this comparative analysis.*

6.1.11.5 Post hoc Analyses of Efficacy

Study P301 did not include an endpoint assessing for severe COVID-19. In response to request by CBER during the review of the P301 study protocol, the Applicant revised the protocol for Part 2 of Study P301 to include a secondary objective assessing the incidence of severe COVID-19; however, Part 2 of the study was never initiated due to the positive results from the interim analysis in Part 1. Because data on efficacy against severe COVID-19 are relevant to the assessment of the overall benefit-risk profile of mRNA-1283, the Applicant was requested to provide a post hoc descriptive analysis of rVE against severe COVID-19 from Part 1 of study P301, based on the case definition for severe COVID-19 specified for Part 2 of the study and also used in the pivotal Phase 3 efficacy study for Spikevax. The severe COVID-19 definition was as follows:

Virologically confirmed SARS-CoV-2 with ANY of the following starting 14 days after study injection:

- 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 PaO2/FiO2 <300 mmHg; 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.

In a descriptive, post hoc analysis, there were 21 (0.4%) severe COVID-19 events in the mRNA-1283.222 group and 34 (0.6%) in the Moderna COVID-19 Vaccine, Bivalent group, with an estimated rVE of 38.6% (95% CI: -6.7, 64.1)

> ***Clinical Reviewer Comment:*** *Although the case split and the rVE estimate suggest mRNA-1283.222 may have improved protection against severe COVID-19 compared with Moderna COVID-19 Vaccine, Bivalent, this post hoc, descriptive analysis has many limitations. Since the severe COVID-19 case definition was not specified in the study protocol and prospectively assessed, this analysis relies on the review of previously collected clinical data to determine whether reported cases of COVID-19 could have met the case definition of severe COVID-19, and is not able to discriminate between participants who may have met the definition for severe illness for reasons other than COVID-19 and those that met the severity definition as a direct result of their COVID-19 illness. Approximately 93% of the severe COVID-19 cases identified met the case definition based only on the vital sign or oxygen saturation criterion. Of the 55 severe COVID-19 cases identified in this analysis, only 3 cases were associated with hospitalizations (2 in the mRNA-1283.222 group and 1 in the Moderna COVID-19, Bivalent group). These 3 associated hospitalizations were identified based on their temporal relationship with virologically confirmed SARS-CoV-2, but it is not clear that any of these hospitalizations were directly related to COVID-19.*

6.1.11.6 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 nAb 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 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 12 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 criterion 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 12. 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 N=621 GMC (95% CI)[a]	Moderna COVID-19 Vaccine, Bivalent N=568 GMC (95% CI)[a]	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 (1.2, 1.5)

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 versus 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 versus 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 13 below. Seroresponse was defined as the change from pre-vaccination 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 of the SRR percentage difference >-10% would also have been met for both Omicron BA.4/BA.5 and D614G.

Table 13. 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 N1=621 SRR % [95% CI][c]	Moderna COVID-19 Vaccine, Bivalent N1=568 SRR % [95% CI][c]	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.

***Clinical Reviewer Comment**: Noninferiority of Ab responses based on GMC ratio and difference in SRR percentages was 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.*

The primary immunogenicity analyses included 5 participants (3 in the mRNA-1283.222 group and 2 in the Moderna COVID-19 Vaccine, Bivalent group) in the PPIS who had SARS-CoV-2 infection within 28 days postvaccination, but this small number of participants is not expected to impact the overall immunogenicity results.

6.1.11.7 Subpopulation Immunogenicity Analyses

Descriptive subgroup analyses to evaluate the consistency of neutralizing antibody responses against D614D and BA.4/BA.5 across age groups for both mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent are presented in Table 14 and Table 15 below. In all age cohorts, neutralizing antibody responses observed after vaccination with mRNA-1283.222 were similar to, or higher than, those observed after vaccination with Moderna COVID-19 Vaccine, Bivalent. For each age subgroup, the lower bound of the 95% CI of the GMC ratios would have met noninferiority criteria (>0.667). Similarly, SRR percentage differences in all age cohorts would have met the noninferiority criterion of the lower bound of the 95% CI of the SRR percentage difference >-10%.

Table 14. Descriptive Analyses of Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Age Subgroup, PPIS, Study mRNA-1283-P301

Age Group and Strain	mRNA-1283.222 GMC (95% CI)[a]	Moderna COVID-19 Vaccine, Bivalent GMC (95% CI)[a]	GMC Ratio (mRNA-1283.222/Moderna COVID-19 Vaccine, Bivalent) (95% CI)[a]
12 to <18 years of age	N1=91	N1=93	--
D614G	13617.7 (12006.3, 15445.3)	12404.3 (10966.5, 14030.6)	1.1 (0.9, 1.3)
Omicron BA.4/BA.5	3561.4 (3037.5, 4175.7)	3398.9 (2908.9, 3971.4)	1.0 (0.8, 1.3)
18 to <65 years of age	N1=378	N1=316	--
D614G	9734.8 (8938.8, 10601.7)	8251.3 (7517.2, 9057.1)	1.2 (1.0, 1.3)
Omicron BA.4/BA.5	2120.6 (1917.3, 2345.6)	1661.0 (1487.8, 1854.4)	1.3 (1.1, 1.5)
≥65 years of age	N1=152	N1=159	--
D614G	11451.1 (9936.3, 13196.9)	7463.3 (6499.4, 8570.1)	1.5 (1.3, 1.9)
Omicron BA.4/BA.5	2339.5 (1984.3, 2758.3)	1326.8 (1130.0, 1557.7)	1.8 (1.4, 2.2)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.1.1.4.2. Data cutoff 23 Feb 2024.
Abbreviations: N1=total number of participants in the specified group with non-missing data; ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=coronavirus disease 2019; GLSM=geometric least square mean; GMC=angeometric mean concentration; LLOQ=lower limit of quantification; LS=least squares; PPIS=pe-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 versus 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 versus 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.

Table 15. Descriptive Analyses of Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against the D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Age Subgroup, PPIS, Study mRNA-1283-P301

Age Group and Strain	mRNA-1283.222 SRR % [95% CI][c]	Moderna COVID-19 Vaccine, Bivalent SRR % [95% CI][c]	Difference in SRR (mRNA-1283.222 - Moderna COVID-19 Vaccine, Bivalent) % (95% CI)[d]
12 to <18 years of age	N1=91	N1=93	--
D614G	85.7 [76.8, 92.2]	74.2 [64.1, 82.7]	11.5 (−0.1, 23.1)
Omicron BA.4/BA.5	87.9 [79.4, 93.8]	80.6 [71.1, 88.1]	7.3 (−3.4, 18.0)
18 to <65 years of age	N1=378	N1=316	--
D614G	83.1 [78.9, 86.7]	75.9 [70.8, 80.6]	7.1 (1.1, 13.2)
Omicron BA.4/BA.5	79.6 [75.2, 83.6]	63.6 [58.0, 68.9]	16.0 (9.3, 22.7)
≥65 years of age	N1=152	N1=159	--
D614G	83.6 [76.7, 89.1]	66.0 [58.1, 73.4]	17.5 (8.0, 26.9)
Omicron BA.4/BA.5	75.7 [68.0, 82.2]	60.4 [52.3, 68.0]	15.3 (4.9, 25.3)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.2.1.1.4.3, Table 14.2.1.1.4.4. 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.
PPIS consisted of participants in Immunogenicity Subset who have pre-booster and Day 29 (occurring between 21 and 42 days after vaccination) neutralizing antibody data, received treatment as planned and have no major protocol deviations that impact vaccine immunogenicity data
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)
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 pre-booster.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) method.

***Clinical Reviewer Comment**: Although not powered for these subgroup analyses, the overall trend in the immunogenicity results across age groups (i.e., increasing GMC ratio/SRR difference with increasing age) is similar to the trend observed in the subgroup analyses for rVE (i.e., increasing rVE with increasing age). However, it is notable that the absolute neutralizing antibody concentrations, and the geometric mean fold rise of the nAb*

concentrations, were higher in the adolescent group relative to the 18 through 64 year old and ≥ 65 year old groups, which provides support for the effectiveness of mRNA-1283.222 in the adolescent age group.

Additional Subgroup Analyses

Analyses By Baseline SARS-CoV-2 Status

Table 16 and Table 17 below show the results of the descriptive subgroup analyses of GMC and seroresponse rate by evidence of prior SARS-CoV-2 infection (baseline SARS-CoV-2 status). mRNA-1283.222 elicited higher neutralizing antibody GMCs and seroresponse rates relative to Moderna COVID-19 Vaccine, Bivalent, irrespective of baseline SARS-CoV-2 status, with the exception of SRR against D614G in participants who are baseline SARS-CoV-2 negative, which was similar across the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups.

Table 16. Descriptive Analyses of Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Baseline SARS-CoV-2 Status, PPIS, Study mRNA-1283-P301.

Baseline SARS-CoV-2 Status[a] and Strain	mRNA-1283.222 GMC (95% CI)[b]	Moderna COVID-19 Vaccine, Bivalent GMC (95% CI)[b]	GMC Ratio (mRNA-1283.222 / Moderna COVID-19 Vaccine, Bivalent) (95% CI)[c]
Positive	N1=487	N1=434	
D614G	11211.8 (10466.0, 12010.8)	9576.1 (8903.3, 10299.7)	1.2 (1.1, 1.3)
Omicron BA.4/BA.5	2737.8 (2526.0, 2963.1)	2202.8 (2024.4, 2397.0)	1.2 (1.1, 1.4)
Negative	N1=132	N1=134	
D614G	8765.6 (7285.2, 10546.8)	6001.3 (5124.3, 7028.5)	1.5 (1.1, 1.8)
Omicron BA.4/BA.5	1321.8 (1066.2, 1616.6)	838.1 (682.3, 1029.6)	1.6 (1.2, 2.1)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.2.1.1.4.2. Data cutoff 23 Feb 2024.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMC=geometric mean concentration; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ULOQ=upper limit of quantification.; N1= Number of participants with non-missing data at baseline and the corresponding timepoint 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. Baseline SARS-CoV-2 Status: positive is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1; negative 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.
b. 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.
c. The log-transformed antibody levels are analyzed using an analysis of covariance (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 COVID-19 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. If the factor is within its own subgroup, this factor is excluded from model. Actual age group is used for subgroup analysis.

Table 17. Descriptive Analyses of Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against the D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Baseline SARS-CoV-2 Status, PPIS, Study mRNA-1283-P301

Baseline SARS-CoV-2 Status[a] and Strain	mRNA-1283.222 SRR % [95% CI][b]	Moderna COVID-19 Vaccine, Bivalent SRR % [95% CI][b]	Difference in SRR (mRNA-1283.222 - Moderna COVID-19 Vaccine, Bivalent) % (95% CI)[c]
Positive	N1=487	N1=434	
D614G	83.0 (79.3, 86.2)	69.4 (64.8, 73.7)	13.6 (8.1, 19.1)
Omicron BA.4/BA.5	80.7 (76.9, 84.1)	67.5 (62.9, 71.9)	13.2 (7.6, 18.8)
Negative	N1=132	N1=134	
D614G	85.6 (54.8, 71.8)	84.3 (53.9, 70.9)	1.3 (−7.5, 10.0)
Omicron BA.4/BA.5	76.5 (68.4, 83.5)	59.0 (50.1, 67.4)	17.6 (6.4, 28.4)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.2.1.1.4.3. Data cutoff 23 Feb 2024.
Abbreviations: CI=confidence interval; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; N1= Number of participants with non-missing data at baseline and the corresponding timepoint
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. Percentages are based on N1.
a. Baseline SARS-CoV-2 Status: positive is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1; negative 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.
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Analyses By Number of Prior COVID-19 Booster Doses Received

Table 18 and Table 19 below show the results of the descriptive subgroup analyses of GMC and seroresponse rate by number of prior COVID-19 booster doses received. A booster dose is defined as any additional dose after the COVID-19 vaccine primary series based on locally authorized/approved regimen. mRNA-1283.222 elicited higher neutralizing antibody GMCs and seroresponse rates relative to Moderna COVID-19 Vaccine, Bivalent, irrespective of the number of prior COVID-19 booster doses received.

Table 18. Descriptive Analyses of Geometric Mean Concentrations (GMCs) as Measured by Pseudovirus nAb Assay Against D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Number of Prior COVID-19 Booster Doses, PPIS, Study mRNA-1283-P301.

Number of Prior COVID-19 Boosters and Strain	mRNA-1283.222 GMC (95% CI)[a]	Moderna COVID-19 Vaccine, Bivalent GMC (95% CI)[a]	GMC Ratio (mRNA-1283.222/Moderna COVID-19 Vaccine, Bivalent) (95% CI)[b]
1	N1=263	N1=236	--
D614G	11984.4 (10796.6, 13302.8)	10800.7 (9675.9, 12056.2)	1.1 (1.0, 1.3)
Omicron BA.4/BA.5	2721.0 (2403.3, 3080.8)	2159.9 (1895.0, 2461.8)	1.3 (1.1, 1.5)

Number of Prior COVID-19 Boosters and Strain	mRNA-1283.222 GMC (95% CI)[a]	Moderna COVID-19 Vaccine, Bivalent GMC (95% CI)[a]	GMC Ratio (mRNA-1283.222/Moderna COVID-19 Vaccine, Bivalent) (95% CI)[b]
2	N1=186	N1=178	--
D614G	9749.5 (8621.7, 11024.8)	7518.8 (6630.9, 8525.6)	1.3 (1.1, 1.5)
Omicron BA.4/BA.5	2091.7 (1824.7, 2397.7)	1539.7 (1339.1, 1770.3)	1.4 (1.1, 1.7)
≥3	N1=141	N1=124	--
D614G	8840.3 (7794.6, 10026.3)	6287.7 (5500.5, 7187.7)	1.4 (1.2, 1.7)
Omicron BA.4/BA.5	1796.0 (1526.9, 2112.6)	1198.3 (1008.4, 1423.9)	1.5 (1.2, 1.9)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.2.1.1.4.2. Data cutoff 23 Feb 2024.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMC=geometric mean concentration; 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; N1= Number of participants with non-missing data at baseline and the corresponding timepoint
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. Moderna COVID-19 Vaccine, Bivalent) as fixed effect, adjusted by SARS-CoV-2 status at pre-booster, randomization age group, number of prior COVID-19 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. If the factor is within its own subgroup, this factor is excluded from model. Actual age group is used for subgroup analysis.

Table 19. Descriptive Analyses of Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay Against the D614G and Omicron BA.4/BA.5 at 28 Days Postvaccination, By Number of Prior COVID-19 Booster Doses, PPIS, Study mRNA-1283-P301

Number of Prior COVID-19 Boosters and Strain	mRNA-1283.222 SRR % [95% CI][a]	Moderna COVID-19 Vaccine, Bivalent SRR % [95% CI][a]	Difference in SRR (mRNA-1283.222 - Moderna COVID-19 Vaccine, Bivalent) % (95% CI)[b]
1	N1=263	N1=236	--
D614G	87.5 (82.8, 91.2)	80.9 (75.3, 85.7)	6.5 (0.1, 13.1)
Omicron BA.4/BA.5	85.2 (80.3, 89.2)	71.6 (65.4, 77.3)	13.6 (6.4, 20.8)
2	N1=186	N1=178	--
D614G	81.7 (75.4, 87.0)	64.6 (57.1, 71.6)	17.1 (8.1, 26.0)
Omicron BA.4/BA.5	75.3 (68.4, 81.3)	57.9 (50.3, 65.2)	17.4 (7.8, 26.8)

Number of Prior COVID-19 Boosters and Strain	mRNA-1283.222 SRR % [95% CI][a]	Moderna COVID-19 Vaccine, Bivalent SRR % [95% CI][a]	Difference in SRR (mRNA-1283.222 - Moderna COVID-19 Vaccine, Bivalent) % (95% CI)[b]
≥3	N1=141	N1=124	--
D614G	76.6 (68.7, 83.3)	62.9 (53.8, 71.4)	13.7 (2.6, 24.6)
Omicron BA.4/BA.5	72.3 (64.2, 79.5)	57.3 (48.1, 66.1)	15.1 (3.6, 26.3)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Tables 14.2.1.1.4.3. Data cutoff 23 Feb 2024.
Abbreviations:; CI=confidence interval; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ULOQ=upper limit of quantification. N1= Number of participants with non-missing data at baseline and the corresponding timepoint
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. Percentages are based on N1.
a. 95% CI is calculated using the Clopper-Pearson method.
b. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Clinical Reviewer Comment: *Although descriptive, the subgroup analyses of GMC ratio and SRR percentage difference by baseline SARS-CoV-2 status and number of prior COVID-19 booster doses would have all met the conventional success criteria for noninferiority (>0.67 for GMC ratio and >-10% for SRR percentage difference), irrespective of the baseline characteristic. There appeared to be decreasing GMCs and SRRs with increasing number of prior booster doses. It is possible that this finding may be attributable to the population included in the subgroups, since the ≥3 booster doses subgroup is likely to be composed of mainly participants in the older age cohort.*

6.1.11.9 Exploratory Immunogenicity Endpoints

The Applicant conducted exploratory analyses to assess the cross-neutralization of mRNA-1283.222 against SARS-CoV-2 variants not contained in the vaccine. Specifically, the Applicant assessed the ability of mRNA-1283.222, relative to Moderna COVID-19 Vaccine, Bivalent, to generate a neutralizing antibody response against the Omicron XBB.1.5 variant, which was the variant lineage included in the monovalent formulation of Spikevax licensed for use in the U.S. in September 2023 (Study mRNA-1283-P301 began enrollment in March 2023). Results of this exploratory analysis are presented below in Table 20.

Table 20. Descriptive Analysis of Geometric Mean Concentrations and Seroresponse Rates as Measured by Pseudovirus nAb Assay Against XBB.1.5 at 28 Days Postvaccination, PPIS (Random Sample from Immunogenicity Subset), Study mRNA-1283-P301

Analysis	mRNA-1283.222 N=126	Moderna COVID-19 Vaccine, Bivalent N=120
Baseline GMC (95% CI)[a]	80.8 (65.5, 99.6)	95.3 (73.3, 123.8)
Day 29 GMC (95% CI)[a]	520.9 (421.0, 644.4)	512.5 (411.0, 639.0)
GMFR (95% CI)[a]	6.6 (5.3, 8.1)	5.4 (4.4, 6.6)

Analysis	mRNA-1283.222 N=126	Moderna COVID-19 Vaccine, Bivalent N=120
Seroresponse rate[b] % (95% CI)	71.2 (62.4, 78.9)	60.0 (50.7, 68.8)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.2.1.2.3.1.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GLSM=geometric least square mean; GMC=geometric mean concentration; GMFR=geometric mean fold rise; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ULOQ=upper limit of quantification. N=random sample from the Immunogenicity Subset.
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 or the difference in the log-transformed values for GM and GMFR, respectively, then back transformed to the original scale for presentation
b. 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.

Clinical Reviewer Comment*: mRNA-1283.222 elicited similar neutralizing antibody GMCs, and slightly higher GMFR and SRR, against Omicron XBB.1.5 compared with Moderna COVID-19 Vaccine, Bivalent, suggesting that mRNA-1283 may be as effective at neutralizing emerging variants as Spikevax.*

6.1.12 Safety Analyses

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 February 23, 2024 data cutoff, the median duration of safety follow-up was 8.8 months.

6.1.12.1 Methods

Please see Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Table 21 provides an overview of the rates of solicited adverse reactions and unsolicited AEs in the mRNA-1283.222 group compared with the Moderna COVID-19 Vaccine, Bivalent group during the study. Overall, the rates of solicited adverse reactions through 7 days, unsolicited AEs through 28 days, SAEs, and AESIs were similar across the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups.

Table 21. Number and Percentage of Participants Reporting at Least One Safety Event, Safety Set and Solicited Safety Set, Study mRNA-1283-P301

Event Type	mRNA-1283.222 N=5706 % (n/N1)	Moderna COVID-19 Vaccine, Bivalent N=5711 % (n/N1)
Solicited adverse reactions within 7 days[a]	--	--
Any solicited adverse reaction	80.2 (4571/5702)	83.8 (4781/5706)
Any solicited local AR[b]	70.3 (4007/5701)	78.4 (4473/5705)
Grade 3 or above solicited local AR	1.6 (92/5701)	2.1 (122/5705)
Any solicited systemic AR[c]	64.4 (3672/5702)	64.2 (3664/5706)
Grade 3 or above solicited systemic AR	7.2 (408/5702)	5.8 (330/5706)
Unsolicited adverse events[d]	--	--
Unsolicited adverse event through 28 days after vaccination	12.3 (701/5706)	11.9 (680/5711)

Event Type	mRNA-1283.222 N=5706 % (n/N1)	Moderna COVID-19 Vaccine, Bivalent N=5711 % (n/N1)
Non-serious unsolicited adverse event[e]	12.1 (688/5706)	11.6 (662/5711)
Severe non-serious unsolicited AE[e]	0.1 (5/5706)	0.1 (6/5711)
Medically attended adverse events through data cutoff	33.9 (1932/5706)	33.0 (1883/5711)
Related MAAE[f]	0.2 (12/5706)	0.2 (13/5711)
SAE through data cutoff	2.7 (156/5706)	2.6 (151/5711)
Related SAE[f]	<0.1 (2/5706)	<0.1 (1/5711)
AESI through data cutoff	1.1 (60/5706)	1.1 (60/5711)
Related AESI[f]	<0.1 (1/5706)	0
Deaths through data cutoff	0.1 (5/5706)	0.2 (10/5711)
Related deaths[f]	0	0
AE leading to study discontinuation through data cutoff	0.1 (8/5706)	0.2 (12/5711)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1, Table 14.3.1.2.1.1, Table 14.3.1.2.1.2. Data cutoff 23 Feb 2024.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BD=booster dose; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants who received a study intervention. n=number of participants with the specified event; N1=number of participants in the specified group.
Note: Participants were allocated to the vaccine groups as received.
a. Percentages under this section are based on the number of exposed participants who submitted any data for the event.
b. Solicited local reactions included pain, erythema (redness), swelling (hardness), axillary swelling or tenderness.
c. Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.
d. Percentages under this section are based on the number of participants in the Safety Set.
e. Participants without any SAE and with any non-serious AE.
f. Relatedness to study vaccine as determined by principal investigator.

6.1.12.3 Solicited Adverse Reactions

Solicited local and systemic reactions (ARs) occurring within 7 days postvaccination were assessed using the Solicited Safety Set, which included all randomized participants who received any study vaccine and contributed any solicited AR data. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling/induration, and axillary swelling/tenderness) and systemic reactions (headache, fatigue, myalgia, arthralgia, nausea/vomiting, fever, and chills (as described above in section 6.1.7).

Solicited Local Adverse Reactions

Table 22 below includes the percentages of mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent recipients who reported any solicited local AR, by maximum severity. Within 7 days postvaccination, the percentage of participants reporting any local AR was lower in the mRNA-1283.222 group (70.3%) compared with the Moderna COVID-19 Vaccine, Bivalent group (78.4%). The most frequently reported local reaction in both groups was pain at the injection site, reported by 68.5% of participants in the mRNA-1283.222 group and 77.5% of participants in the Moderna COVID-19 Vaccine, Bivalent group. Most solicited local ARs were Grade 1 in severity. Severe (Grade 3) solicited local reactions were reported by 1.6% and 2.1% of participants in the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups, respectively. There were no reported Grade 4 local ARs in either group.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days of Vaccination, Solicited Safety Set, Study mRNA-1283-P301

Event	mRNA-1283.222 N1=5701 %	Moderna COVID-19 Vaccine, Bivalent N1=5705 %
Local adverse reaction	--	--
Any	70.3	78.4
Grade 1	49.4	49.6
Grade 2	19.3	26.7
Grade 3	1.6	2.1
Pain[a]	--	--
Any	68.5	77.5
Grade 1	49.9	50.9
Grade 2	17.5	25.3
Grade 3	1.1	1.3
Erythema (redness)[b]	--	--
Any ≥25 mm	2.2	3.9
Grade 1	1.3	2.2
Grade 2	0.6	1.4
Grade 3	0.2	0.4
Swelling (hardness)[b]	--	--
Any ≥25 mm	3.6	6.3
Grade 1	2.2	3.9
Grade 2	1.1	1.8
Grade 3	0.3	0.6
Axillary swelling or tenderness[c]	--	--
Any	19.7	18.4
Grade 1	14.5	13.7
Grade 2	4.9	4.3
Grade 3	0.3	0.3

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1. Data cutoff 23 Feb 2024.
Abbreviations: AR=adverse reaction; N1=number of exposed participants who submitted any data for the event.
There were no Grade 3 solicited local ARs reported.
a. Pain: Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Prevents daily activity Grade 4: Requires emergency room visit or hospitalization.
b. Erythema (redness) and swelling (hardness): Grade 1: 25-50 mm Grade 2: 51-100 mm Grade 3: >100 mm Grade 4: Necrosis or exfoliative dermatitis.
c. Axillary swelling or tenderness: Grade 1: No interference with activity Grade 2:Some interference with activity Grade 3: Prevents daily activity Grade 4: Requires emergency room visit or hospitalization.
Any=Grade 1 or higher.

The median day of onset for solicited local ARs was 2 days postvaccination in both the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups. Solicited local ARs had a median duration of 2 days in the mRNA-1283.222 group and 3 days in the Moderna COVID-19 Vaccine, Bivalent group, with a similar percentage persisting beyond 7 days (0.5% for mRNA-1283.222 and 0.4% for Moderna COVID-19 Vaccine, Bivalent).

> ***Clinical Reviewer Comment****: The slightly lower rates of solicited local ARs in the mRNA-1283.222 group compared with the Moderna COVID-19 Vaccine, Bivalent group may be partly attributable to the differences in injection volume (0.2mL versus 0.5mL, respectively).*

Solicited Systemic Adverse Reactions

Table 23 below includes the percentages of mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent recipients who reported any solicited systemic AR, by maximum severity. Within 7 days

postvaccination, the percentages of participants reporting any systemic AR was similar between the mRNA-1283.222 (64.4%) and Moderna COVID-19 Vaccine, Bivalent (64.2%) groups. The most frequently reported systemic reaction among mRNA-1283.222 recipients were fatigue (50.4%), headache (44.2%), and myalgia (38.2%). Fever was reported in 5.6% of mRNA-1283.222 recipients compared with 4.5% of Moderna COVID-19 Vaccine, Bivalent recipients. Grade 3 fever (39 – 40°C) was reported in 0.6% of mRNA-1283.222 recipients compared with 0.5% of Moderna COVID-19 Vaccine, Bivalent recipients. Fever was the only solicited AR reported in any participant at Grade 4 (defined as >40°C) and was only reported by one participant in the Moderna COVID-19 Vaccine, Bivalent group. While the majority of solicited systemic ARs were Grade 1 or 2 in severity, Grade 3 or Grade 4 systemic ARs were reported in 7.2% of mRNA-1283.222 recipients compared with 5.8% of Moderna COVID-19 Vaccine, Bivalent recipients.

A similar percentage of participants in both groups reported any use of antipyretic or pain medication.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days of Vaccination, Solicited Safety Set, Study mRNA-1283-P301

Event	mRNA-1283.222 N1=5697-5702 %	Moderna COVID-19 Vaccine, Bivalent N1=5699-5706 %
Any systemic adverse reaction	--	--
Any	64.4	64.2
Grade 1	26.7	28.7
Grade 2	30.6	29.7
Grade 3	7.2	5.8
Grade 4	0	0.02
Fever[a]	--	--
Any	5.6	4.5
Grade 1	3.3	2.9
Grade 2	1.7	1.1
Grade 3	0.6	0.5
Grade 4	0	0.02
Headache[b]	--	--
Any	44.2	41.2
Grade 1	23.6	23.7
Grade 2	18.0	15.4
Grade 3	2.6	2.1
Grade 4	0	0
Fatigue[b]	--	--
Any	50.4	49.0
Grade 1	22.0	23.1
Grade 2	23.8	22.1
Grade 3	4.6	3.8
Grade 4	0	0
Myalgia[b]	--	--
Any	38.2	37.0
Grade 1	17.9	18.7
Grade 2	16.7	15.8
Grade 3	3.6	2.6
Grade 4	0	0

Event	mRNA-1283.222 N1=5697-5702 %	Moderna COVID-19 Vaccine, Bivalent N1=5699-5706 %
Arthralgia[b]	--	--
Any	29.7	27.6
Grade 1	15.6	15.1
Grade 2	12.1	11.0
Grade 3	2.1	1.6
Grade 4	0	0
Nausea/vomiting[c]	--	--
Any	12.1	11.0
Grade 1	8.8	8.3
Grade 2	3.2	2.5
Grade 3	0.1	0.2
Grade 4	0	0
Chills[d]	--	--
Any	22.7	19.8
Grade 1	11.9	10.8
Grade 2	10.1	8.4
Grade 3	0.7	0.5
Grade 4	0	0
Use of antipyretic or pain medication	32.6	32.1

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1, 14.1.5.1.3. Data cutoff 23 Feb 2024.
Abbreviations: AR=adverse reaction; N1=number of exposed participants who submitted any data for the event.
Any=Grade 1 or higher.
a. Fever: Grade 1: 38 – 38.4°C; Grade 2: 38.5 – 38.9°C; Grade 3: 39 – 40°C; Grade 4: >40°C
b. Headache, Fatigue, Myalgia, Arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
c. Nausea/Vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires emergency room visit or hospitalization for hypotensive shock.
d. Chills: Grade 1: No interference with activity; Grade 2: Some interference with activity not requiring medical attention; Grade 3: Prevents daily activity and requires medical attention; Grade 4: Requires emergency room visit or hospitalization.

The median day of onset for solicited systemic ARs was 2 days postvaccination in both groups. Solicited systemic ARs had a median duration of 2 days in both groups, and a similar percentage persisted beyond 7 days (1% for both groups).

Subgroup Analyses for Solicited Adverse Reactions

Age

Solicited local ARs are generally lower in mRNA-1283.222 recipients relative to Moderna COVID-19 Vaccine, Bivalent recipients across all age cohorts. In general, the percentage of solicited systemic ARs reported was similar between mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent recipients, irrespective of age cohort, with a trend of decreased reactogenicity observed among older adult participants (≥65 years) compared with younger adult participants and adolescents. Reported rates of solicited local and systemic ARs within 7 day of vaccination, by age subgroup, are shown in Table 24, Table 25, and Table 26.

Table 24. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days of Vaccination in Participants 12 Years Through 17 Years, Solicited Safety Set, Study mRNA-1283-P301

Adverse Reaction	mRNA-1283.222 N1=496-497 %	Moderna COVID-19 Vaccine, Bivalent N1=494-495 %
Local Adverse Reactions	--	--
Pain, Any	68.8	78.8
Grade 3[a]	2.0	3.8
Axillary swelling or tenderness, Any	34.6	27.1
Grade 3[a]	1.2	0.4
Swelling (hardness) ≥25 mm	3.6	5.1
Grade 3[b]	0.8	0.4
Erythema (redness) ≥25 mm	1.2	2.6
Systemic Adverse Reactions	--	--
Headache, Any	54.5	58.0
Grade 3 [a]	7.0	4.0
Fatigue, Any	47.3	50.7
Grade 3 [a]	6.8	4.4
Myalgia, Any	39.2	36.0
Grade 3 [a]	5.6	3.4
Chills, Any	31.6	31.9
Grade 3[c]	1.2	0.2
Arthralgia, Any	23.9	23.6
Grade 3 [a]	2.0	1.2
Nausea/vomiting, Any	16.1	17.6
Grade 3[d]	0	0.4
Fever, Any	9.9	9.3
Grade 3[e]	0.8	0.4
Use of antipyretic or pain medication	37.4	42.6

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1, 14.1.5.1.3. Data cutoff 23 Feb 2024.
Abbreviations: AR=adverse reaction; N1=number of exposed participants who submitted any data for the event.
Any=Grade 1 or higher.
Absence of rows for Grade 3 or Grade 4 adverse reactions indicates no events were reported.
a. Grade 3 pain, axillary swelling or tenderness, headache, fatigue, myalgia, arthralgia: Defined as prevents daily activity.
b. Grade 3 swelling: Defined as >100 mm / >10 cm.
c. Grade 3 chills: defined as prevents daily activity and requires medical attention
d. Grade 3 nausea/vomiting: defined as prevents daily activity, requires outpatient intravenous hydration.
e. Grade 3 fever: defined as 39 – 40°C.

Table 25. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days of Vaccination in Participants 18 Years Through 64 Years, Solicited Safety Set, Study mRNA-1283-P301

Adverse Reaction	mRNA-1283.222 10 µg N1=3572-3,573 %	Moderna COVID-19 Vaccine, Bivalent 50 µg N1=3570-3,574 %
Local Adverse Reactions	--	--
Pain, Any	74.8	81.7
Grade 3[a]	1.1	1.4
Axillary swelling or tenderness, Any	21.7	21.0
Grade 3[a]	0.3	0.4

Adverse Reaction	mRNA-1283.222 10 µg N1=3572-3,573 %	Moderna COVID-19 Vaccine, Bivalent 50 µg N1=3570-3,574 %
Swelling (hardness) ≥25 mm	3.9	6.9
Grade 3[b]	0.3	0.5
Erythema (redness) ≥25 mm	2.4	4.3
Grade 3 [b]	0.3	0.5
Systemic Adverse Reactions	--	--
Headache, Any	47.8	44.3
Grade 3[c]	2.5	2.1
Fatigue, Any	54.3	52.5
Grade 3[c]	4.8	4.4
Myalgia, Any	41.6	41.1
Grade 3[c]	4.0	2.9
Chills, Any	24.3	21.3
Grade 3[d]	0.7	0.6
Arthralgia, Any	32.4	30.6
Grade 3[c]	2.4	1.7
Nausea/vomiting, Any	13.8	11.9
Grade 3[e]	0.1	<0.1
Fever, Any	5.4	3.9
Grade 3[f]	0.8	0.5
Use of antipyretic or pain medication	34.8	34.3

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1, 14.1.5.1.3. Data cutoff 23 Feb 2024.
Abbreviations: AR=adverse reaction; N1=number of exposed participants who submitted any data for the event.
Solicited Safety Set consists of all randomized participants who received study vaccine and contributed any solicited AR data.
Any=Grade 1 or higher.
Absence of rows for Grade 3 or Grade 4 adverse reactions indicates no events were reported.
a. Grade 3 pain and axillary swelling/tenderness: Defined as prevents daily activity.
b. Grade 3 swelling: Defined as >100 mm / >10 cm.
c. Grade 3 headache, fatigue, myalgia, arthralgia: defined as prevents daily activity
d. Grade 3 chills: defined as prevents daily activity and requires medical attention
e. Grade 3 nausea/vomiting: defined as prevents daily activity, requires outpatient intravenous hydration.
f. Grade 3 fever: defined as 39 – 40°C.

Table 26. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days of Vaccination in Participants 65 Years and Older, Solicited Safety Set, Study mRNA-1283-P301

Adverse Reaction	mRNA-1283.222 10 µg N1=1629-1,631 %	Moderna COVID-19 Vaccine, Bivalent 50 µg N1=1635-1,637 %
Local Adverse Reactions	--	--
Pain, Any	54.6	67.7
Grade 3[a]	0.7	0.4
Axillary swelling or tenderness, Any	10.7	10.0
Grade 3[a]	0.1	0.1
Swelling (hardness) ≥25 mm	2.9	5.4
Grade 3[b]	<0.1	0.7
Erythema (redness) ≥25 mm	2.0	3.7
Grade 3 [b]	0.1	0.4
Systemic Adverse Reactions	--	--
Headache, Any	33.1	29.3

Adverse Reaction	mRNA-1283.222 10 µg N1=1629-1,631 %	Moderna COVID-19 Vaccine, Bivalent 50 µg N1=1635-1,637 %
Grade 3[c]	1.3	1.3
Fatigue, Any	43.0	41.0
Grade 3[c]	3.6	2.5
Myalgia, Any	30.5	28.5
Grade 3[c]	2.0	1.6
Chills, Any	16.5	12.8
Grade 3[d]	0.6	0.5
Arthralgia, Any	25.6	22.4
Grade 3[c]	1.5	1.3
Nausea/vomiting, Any	7.3	7.0
Grade 3[e]	0.1	0.3
Fever, Any	4.6	4.3
Grade 3[f]	0.1	0.6
Grade 4[g]	0	<0.1
Use of antipyretic or pain medication	26.3	24.0

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Table 14.3.1.1.1.1, 14.1.5.1.3. Data cutoff 23 Feb 2024.
Abbreviations: AR=adverse reaction; n=number of participants with the specified event; N1=number of exposed participants who submitted any data for the event.
Solicited Safety Set consists of all randomized participants who received study vaccine and contributed any solicited AR data.
Any=Grade 1 or higher.
Absence of rows for Grade 3 or Grade 4 adverse reactions indicates no events were reported.
a. Grade 3 pain and axillary swelling/tenderness: Defined as prevents daily activity.
b. Grade 3 swelling: Defined as >100 mm / >10 cm.
c. Grade 3 headache, fatigue, myalgia, arthralgia: defined as prevents daily activity
d. Grade 3 chills: defined as prevents daily activity and requires medical attention
e. Grade 3 nausea/vomiting: defined as prevents daily activity, requires outpatient intravenous hydration.
f. Grade 3 fever: defined as 39 – 40°C.
g. Grade 4 fever: defined as >40°C.

Baseline SARS-CoV-2 Status

Across both groups, the reported rates of solicited ARs were similar between participants who had evidence of prior SARS-CoV-2 infection and participants without evidence of prior infection.

Number of Prior COVID-19 Vaccinations

The reported rates of solicited ARs did not differ substantially based on the number or type of prior COVID-19 vaccination.

6.1.12.4 Unsolicited Adverse Events

Unsolicited Adverse Events Through 28 days After Vaccination

Overall, the percentages of unsolicited AEs within 28 days postvaccination were similar among mRNA-1283.222 recipients (12.3%) and Moderna COVID-19 Vaccine, Bivalent recipients (11.9%). Unsolicited AEs were most commonly reported under the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) *Infections and infestations* (4.2% mRNA-1283.222 and 4.0% Moderna COVID-19 Vaccine, Bivalent). By MedDRA preferred term (PT), the most frequently reported AE in both the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups were upper respiratory tract infection (1.4% and 1.5%, respectively) and oropharyngeal pain (0.4% in each group).

Unsolicited AEs within 28 days that were assessed as related by the investigator were reported for 0.8% (n=45) of mRNA-1283.222 recipients and 0.9% (n=51) of Moderna COVID-19 Vaccine, Bivalent recipients. These AEs primarily represented events that were specified in the protocol as solicited adverse reactions.

> ***Clinical Reviewer Comment****: There were no notable imbalances in unsolicited AEs within 28 days postvaccination across the two groups.*

Subgroup Analyses for Unsolicited Adverse Events

Rates of unsolicited AEs were generally similar across subgroups based on sex, race, ethnicity, and baseline SARS-CoV-2 status, though these analyses were limited by the low number of participants in several subgroups.

Medically Attended Adverse Events

Through the February 23, 2024 cutoff date, the percentages of medically-attended adverse events (MAAEs) were similar across the mRNA-1283.222 group (33.9%) and the Moderna COVID-19 Vaccine, Bivalent group (33.0%). The percentage of MAAEs assessed as related by the Investigator to study vaccination was also similar across the two groups (0.2% in each group).

Standard MedDRA Queries

Standardized MedDRA queries (SMQs) using FDA-developed software were conducted to evaluate the Safety Set for constellations of unsolicited AEs with onset following vaccination through the February 23, 2024 data cutoff. The SMQs were conducted on AE PTs that could represent various conditions, including but not limited to embolic & thrombotic events, convulsions, central nervous system (CNS) vascular disorders, hypersensitivity, peripheral neuropathy, demyelination, cardiac arrhythmias, and cardiomyopathy. There were no notable imbalances observed between the mRNA-1283.222 group and Moderna COVID-19 Vaccine, Bivalent group based on analyses conducted using the SMQs.

6.1.12.5 Deaths

Overall, through the February 23, 2024 data cutoff, there were 5 deaths (0.09%) in the mRNA-1283.222 group and 10 deaths (0.2%) in the Moderna COVID-19 Vaccine, Bivalent group (Table 27). None of the reported deaths in the mRNA-1283.222 group were considered related to vaccination by the investigator, and all occurred at least 81 days after vaccination. Of the 10 reported deaths in Moderna COVID-19 Vaccine, Bivalent recipients, one death was assessed as related to study vaccine by the investigator and is described in more detail below.

Table 27. Deaths Through the Data Cutoff Date (February, 23 2024), Safety Set, Study mRNA-1283-P301

Preferred Term / Verbatim Term	Sex / Age	Study Day
mRNA-1283.222	--	--
Myocardial rupture / ruptured myocardium	Male / 67 years	Day 149
Respiratory failure / respiratory failure	Male / 91 years	Day 82
Cardiac arrest / cardiac arrest	Male / 60 years	Day 251
Death / death by homicide	Male / 16 years	Day 248
Cardiac arrest / cardiac arrest	Male/ 76 years	Day 160
Moderna COVID-19 Vaccine, Bivalent	--	--
Esophageal carcinoma / esophageal cancer	Male / 71 years	Day 124
Cardiac arrest / cardiac arrest	Male / 82 years	Day 47
Pulmonary embolism / pulmonary embolism	Female / 64 years	Day 234

Preferred Term / Verbatim Term	Sex / Age	Study Day
Death / death – cause unknown	Female / 77 years	Day 7
Gastrointestinal hemorrhage / gastrointestinal hemorrhage	Female / 89 years	Day 259
Hepatic cancer / liver cancer	Female / 74 years	Day 274
Myocardial infarction / heart attack	Female / 51 years	Day 256
Toxicity to various agents / drug intoxication	Male / 52 years	Day 43
Death / death by homicide	Female / 14 years	Day 248
Completed suicide / suicide	Male / 41 years	Day 236

Source: Adapted from STN 125835/0, mRNA-1283-P301 Clinical Study Report, Listing 16.2.7.7. Data cutoff 23 Feb 2024.

> ***Clinical Reviewer Comment****: In general, the causes of death among study participants are representative of common causes of death among adults and adolescents in the general U.S. population (i.e., heart disease, cancer, homicide).*

Death Reported as Related by Investigator (Moderna COVID-19 Vaccine, Bivalent Recipient): A 77-year-old female participant with history of atrial fibrillation, status post ablation, hypertension, hypothyroidism, major depressive disorder, chronic pain syndrome, asthma, was reported to have died in her sleep on Day 7. There were no reactogenicity symptoms or unsolicited adverse events reported in her eDiary through Day 4 and no additional information available regarding the events leading up to the death. A family member reported that the participant was found unresponsive at home in the morning and was unable to be resuscitated by emergency medical services. No autopsy was performed. The participant was taking several prescription medications, including antiarrhythmics, some of which had been initiated 2 months prior to the fatal event. The investigator assessed the death as possibly related due to the temporal relationship with study vaccination. The Applicant assessed the death as unrelated to study vaccination.

> ***Reviewer Comment****: This reviewer agrees with the Applicant that the death is unlikely to be related to study vaccination. Based on the available information for this 77-year-old participant, alternative causes of death are plausible, including the participant's extensive medical history and medications, which are all more likely implicated in sudden cardiac death. The lack of reported systemic reactogenicity through 4 days postvaccination also suggest alternative etiologies other than those associated with postvaccination inflammatory processes.*

6.1.12.6 Serious Adverse Events (SAEs)

SAEs within 28 days of vaccination were reported in 0.2% (n=13) and 0.3% (n=18) of participants in the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups, respectively. Of the SAEs reported within 28 days, one event in the mRNA-1283.222 group (anaphylactic reaction, described below) and one event in the Moderna COVID-19 Vaccine, Bivalent group (death in 77-year old participant, described in Section 6.1.12.5) were assessed as related by the investigators. Through the cutoff date of February 23, 2024, SAEs were reported in 2.7% of participants in the mRNA-1283.222 group and 2.6% of participants in the Moderna COVID-19 Vaccine, Bivalent group. There were two additional SAEs (acute aseptic arthritis and oligoarthritis, both in same participant and described below) assessed as related by the investigator in the mRNA-1283.222 group and no additional related SAEs in the Moderna COVID-19 Vaccine, Bivalent group.

SAEs assessed as related to mRNA-1283.222 by the Investigator

1. **Anaphylactic Reaction:** A 41-year-old female with hypothyroidism and baseline low blood pressures had a reported SAE of anaphylactic reaction approximately 18 hours after vaccination. The participant reported fevers (101.8° F), chills, headache, fatigue and syncopal episode about 18 hours following vaccination. Blood pressure measured at home was 60/50 mmHg. The participant also reported a brief episode of anterior chest pain, nausea, and dizziness, and subsequent diarrhea 3.5 hours later. She denied any urticaria/erythema or respiratory symptoms. The participant took antipyretics and all symptoms resolved within hours except for the diarrhea, which resolved 2 days later. She did not seek medical care for these symptoms, but was evaluated in clinic on Day 7, where vital signs were notable for a blood pressure of 80/54 mmHg, and a normal electrocardiogram (ECG). The investigator considered this a case of possible delayed anaphylaxis given its seriousness and symptoms involving two organ systems and assessed it as being possibly related to the study vaccine. The Applicant disagreed with the diagnosis of delayed anaphylaxis.

***Reviewer Comment**: The reviewer agrees with the Applicant that this case is unlikely to be representative of anaphylaxis, based on the 2022 revised Brighton Collaboration definition of anaphylaxis (the participant had only 2 documented organ system involvement [hypotension and diarrhea] with slow progression [3.5 hours] between symptoms), resolution of symptoms despite lack of treatment, the participant's history of baseline low blood pressures, and persistent diarrhea for 2 days possibly suggesting an alternative etiology for the participant's gastrointestinal symptoms.*

2. **Acute Aseptic Arthritis and Oligoarthritis**

   Two SAEs of acute aseptic arthritis and oligoarthritis were reported on Days 56 and 108, respectively, for the same participant. A 37-year-old male, who was born in India and had been living in the United Kingdom for 6 years and had a reported history of tuberculosis (TB) exposure from his mother and sister approximately 10 to 14 years prior, presented with sudden left knee swelling upon wakening on Day 56 postvaccination. He was hospitalized for further evaluation, and a joint aspiration ruled out septic arthritis, gout and pseudogout, and culture for TB was negative. Magnetic resonance image (MRI) was negative for evidence of osteomyelitis. The acute arthritis resolved but the participant subsequently developed left toe and ankle swelling.

   Approximately 2 months later, the participant reported a fever of 38.2ºC along with profuse night sweats and worsening pain in his knee and was hospitalized on Day 108 for evaluation of oligoarthritis. A QuantiFERON-TB test was positive with presumptive diagnosis of TB arthritis and was started on treatment, with no improvement in symptoms. Rheumatology subsequently diagnosed with participant with oligoarticular arthritis that was likely to be a seronegative inflammatory arthritis. The participant later was found to be HLA-B27 positive and was started on a Disease-Modifying Antirheumatic Drug (DMARD). The participant's oligoarthritis was still ongoing at the time of the data cutoff.

   The investigator assessed the acute aseptic arthritis and oligoarthritis as related to study vaccine, given the lack of another medical explanation at the time. The Applicant assessed these two SAEs as unrelated.

***Reviewer Comment**: The reviewer agrees with the Applicant that these two SAEs are unlikely to be related to the study intervention given the latency of onset after vaccination,*

especially for the event of oligoarthritis, and the clinical course described which is more consistent with an underlying rheumatologic condition.

6.1.12.7 Adverse Events of Special Interest (AESIs)

Protocol-defined AESIs can be found in Appendix B.

AESIs Through 28 Days Postvaccination

Through 28 days postvaccination, AESIs were reported in 0.05% (n=3) of participants and 0.1% (n=6) of participants in the mRNA-1283.222 and the Moderna COVID-19 Vaccine, Bivalent groups, respectively. There were no reported cases of myocarditis or pericarditis. In the mRNA-1283.222 group, the AESIs reported were appendicitis, anaphylaxis, and acute myocardial infarction. Only one event (anaphylactic reaction), also reported as an SAE, was assessed as related by the investigator and was discussed previously in Section 6.1.12.6.

In the Moderna COVID-19 Vaccine, Bivalent group, the AESIs reported were anosmia (2 cases), atrial fibrillation (2 cases), myocardial infarction (2 cases), and chilbains, or cold-induced erythrocyanotic skin lesions (1 case). One participant reported concurrent atrial fibrillation and myocardial infarction. No AESIs in the Moderna COVID-19 Vaccine, Bivalent group were assessed by the investigator as related.

AESIs Through Data Cutoff Date (February 23, 2024)

Through the data cutoff date, 1.1% (n=60) participants reported AESIs in each of the mRNA-1283.222 and Moderna COVID-19 Vaccine, Bivalent groups. There were no reported cases of myocarditis or pericarditis in the mRNA-1283.222 group. There was one event of pericarditis in the Moderna COVID-19 Vaccine, Bivalent group, in a 50-year-old female participant with onset 136 days after vaccination, which was assessed as unrelated to vaccination by the investigator. Besides the one event of anaphylactic reaction discussed previously, there were no additional AESIs in either group assessed as related by the investigator.

***Clinical Reviewer Comment**: The frequencies of reported AESIs through the data cutoff were balanced across the two groups. Based on an independent review of the case narratives, the clinical reviewer agrees with the investigator that the AESIs reported were unlikely to be related to study vaccine.*

6.1.12.8 Pregnancies

There were 10 pregnancies reported in study mRNA-1283-P301 through the data cutoff, 3 in the mRNA-1283.222 and 7 in the Moderna COVID-19 Vaccine, Bivalent groups. Of the 3 pregnancies in the mRNA-1283.222 group, all resulted in full-term births with no complications. Of the 7 pregnancies in the Moderna COVID-19 Vaccine, Bivalent group, one had an induced abortion on Day 37, 3 were term births with no complications, and the outcomes for the remaining 3 pregnancies were pending.

6.1.12.9 Dropouts and/or Discontinuations

Up to the February 23, 2024 data cutoff, AEs leading to study discontinuation were reported in 0.1% (n=8) of participants in the mRNA-1283.222 group and 0.2% (n=12) of participants in the Moderna COVID-19 Vaccine, Bivalent group. Discontinuation due to death accounted for 5 of the 8 participants in the mRNA-1283.222 group and 10 of the 12 participants in the Moderna COVID-19 Vaccine, Bivalent group. The 3 remaining nonfatal AEs leading to study discontinuation in the mRNA-1283.222 group were metastatic gastric cancer, polycythemia vera, and suicide attempt, all occurring beyond 28 days postvaccination. The 2 remaining non-

fatal AEs leading to study discontinuation in the Moderna COVID-19 Vaccine, Bivalent group were esophageal carcinoma and stage IV pancreatic carcinoma. None of the AEs leading to study discontinuation were assessed as related to the study intervention by the Investigator.

> ***Clinical Reviewer Comment****: The clinical reviewer agrees with the Applicant that the discontinuations above not likely to be related to the study vaccination.*

6.1.13 Study Summary and Conclusions

Study P301 was the primary study submitted to support the safety, efficacy, and immunogenicity of mRNA-1283 in individuals 12 years of age and older. The primary objectives for the demonstration of noninferior relative vaccine efficacy (rVE) and neutralizing antibody responses after mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent were met.

Safety data from Study P301 are available from 11,417 participants (5,706 participants in the mRNA-1283.222 group and 5,711 participants in the Moderna COVID-19 Vaccine, Bivalent group), with a median follow-up of approximately 8.8 months post-vaccination. Lower rates of solicited local ARs and similar rates of systemic adverse reactions were observed in mRNA-1283.222 recipients as compared with participants who received the Moderna COVID-19 Vaccine, Bivalent. There were no notable imbalances in the overall percentages and types of unsolicited adverse events, including serious adverse events, across the study groups. There were no SAEs or deaths assessed as related to mRNA-1283.222 based on FDA review. There were no cases of vaccine-related myocarditis or pericarditis reported in the study.

Overall, the data from Study P301 support the safety and noninferior effectiveness of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent in individuals 12 years of age and older.

6.2 Study mRNA-1283-P301-Japan

Title: “A randomized, observer-blind, active-controlled Phase 3 study to investigate the safety and immunogenicity of mRNA-1283 compared with mRNA-1273 in participants aged 12 years and older for the prevention of COVID-19”

Study Overview:

Study mRNA-1283-P301-Japan Addendum (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 linked NTD-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). Only study objectives and results available at the time of the BLA submission are described below.

> ***Reviewer Comment****: Data from Study P301-Japan support the review of the overall safety and effectiveness of mRNA-1283 because a monovalent XBB.1.5 formulation (mRNA-1283.815) was assessed.* (b) (4)

6.2.1 Objectives

Primary 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.

Endpoints: 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.

Statistical Criterion for Success: The lower bound (LB) of the 95% CI of the GMC ratio is >0.667.

Safety (Descriptive):

To evaluate the safety and reactogenicity of mRNA-1283.815

Endpoints:

- Solicited local and systemic ARs during the 7-day follow-up period after study injection
- Unsolicited AEs during the 28-day follow-up period after the study injection
- SAEs, MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study

Secondary Objective (Descriptive):

To characterize the neutralizing antibody response against Omicron XBB.1.5 and ancestral SARS-CoV-2 D614G (hereafter referred to as D614G) at all study timepoints.

Endpoints:

- Omicron XBB.1.5 and D614G GMCs at all planned timepoints
- Seroresponse[13] rate (SRR) against Omicron XBB.1.5 and D614G at all planned timepoints

***Reviewer Comment*:** *The Japan-specific study protocol was not under the purview of CBER review. However, during pre-BLA meeting communications with the Applicant, CBER recommended that the Applicant include the SRR endpoint as a co-primary endpoint, to align with the primary immunogenicity endpoints evaluated for the main P301 study. The SRR endpoint was included as a descriptive secondary endpoint because study analysis was ongoing at the time of the pre-BLA meeting.*

6.2.2 Design Overview

Study P301-Japan is an ongoing randomized, observer-blind, active-controlled, trial in Japan designed to assess the safety and immunogenicity of mRNA-1283.815 compared with Spikevax

13 Seroresponse at the participant level (primary definitions) is defined as an antibody value change from baseline below the LLOQ to ≥4xLLOQ, or at least a 4-fold rise if baseline is ≥LLOQ and <4xLLOQ, or at least a 2-fold rise if baseline is ≥4xLLOQ. A secondary definition for seroresponse was 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.

in participants 12 years of age and older, 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 were aligned with the 2023-2024 Formula for COVID-19 vaccines recommended by FDA and WHO (monovalent Omicron XBB.1.5). This study was a country-specific substudy of the main mRNA-1283-P301 study (reviewed in Section 6.1) and was conducted across 12 sites in Japan. A total of 689 participants were randomized 1:1 to receive either mRNA-1283.815 (n=343) or Spikevax (n=346) as a single dose. Randomization was stratified by age group (12 to <18 years, 18 to <65, and ≥65 years), with a target to enroll 20% of participants in the 12 to <18 years of age group and 20% of participants in the ≥65 years age group. Participants were to be followed for 12 months postvaccination.

6.2.3 Population

This P301-Japan study included the same eligibility criteria as the main mRNA-1283-P301 study (see section 6.1.3).

6.2.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1283.815

- Dose and route of administration: 0.2 mL IM
- Formulation: 10 ug of mRNA encoding the linked NTD-RBD of S protein from SARS-CoV-2 variant lineage Omicron XBB.1.5, formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot: 7068323001

Spikevax (2023-2024 Formula) (COVID-19 Vaccine, mRNA)

- Dose and route of administration: 0.5 mL IM
- Formulation: 50 µg of mRNA encoding the full-length S glycoproteins of the SARS-CoV-2 variant lineage Omicron XBB.1.5, formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot: 7068423001

6.2.5 Directions for Use

A single IM injection of either mRNA-1283.815 or Spikevax administered in the deltoid muscle or thigh.

6.2.6 Sites and Centers

Study P301-Japan enrolled participants at 12 clinical sites in Japan.

6.2.7 Surveillance/Monitoring

Safety oversight and monitoring for P301-Japan was consistent with those for the main mRNA-1283-P301 study (see section 6.1.7).

Immunogenicity

Blood samples for immunogenicity assessments will be collected from all participants at scheduled time points (Days 1, 29, 91, 181, and 365) and evaluated using validated pseudovirus neutralization assays against SARS-CoV-2 Omicron XBB.1.5 [PsVNA (VAC 150) (b) (4)] and ancestral D614G [PsVNA (VAC62) (b) (4)]. On Day 1, blood samples were collected prior to administration of study vaccine.

> ***Clinical Reviewer Comment****: The interim analysis submitted to this BLA consists of data only from the blood samples collected pre-vaccination and at Day 29 for immunogenicity assessment.*

6.2.8 Endpoints and Criteria for Study Success

See section 6.1.1 and 6.1.9.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size for Study P301-Japan was determined to support the primary immunogenicity objective of demonstrating noninferiority of mRNA-183.815 compared with Spikevax based on GMC ratio of neutralizing antibody levels against Omicron XBB.1.5 at Day 29. Assuming a true GMC ratio of 1.0, a standard deviation of 1.8 for log-transformed antibody levels, and a noninferiority margin of 1.5, approximately 622 evaluable participants (311 per group) would provide 80% power to demonstrate noninferiority at a two-sided alpha level of 0.05. To account for up to 10% of participants being excluded from the per-protocol immunogenicity analysis set (e.g., due to missing samples), the total targe enrollment was set at 692 participants, with 346 randomized to each vaccine group.

Methods

For the primary immunogenicity objective, an analysis of covariance (ANCOVA) model was used to evaluate the GMC ratio levels against Omicron XBB.1.5 on Day 29. The fixed variable in the model was the treatment group (mRNA-1283.815 versus Spikevax), with adjustments made for baseline SARS-CoV-2 status, age group at randomization, the number of prior boosters, and the type of last vaccine received before study entry. The GMCs were estimated using the geometric least square mean (GLSM) from this model. The GMC ratio of antibody levels at Day 29 (mRNA-1283.815 versus Spikevax) was calculated by comparing the GLSMs of both groups, and a two-sided 95% CI was provided to determine the difference in antibody response.

Null hypothesis H_0: Antibody GMCs against Omicron XBB.1.5 after mRNA-1283.815 is inferior to that after Spikevax, based on the GMC ratio defined as the ratio of GMCs against Omicron XBB.1.5 after mRNA-1283.815 at Day 29 versus the GMCs against Omicron XBB.1.5 after Spikevax at Day 29.

> Noninferiority is demonstrated if the lower bound of the 95% CI for the GMC ratio is greater than 0.667, with a one-sided alpha of 0.025.

The secondary immunogenicity objective was to assess the number and percentage of participants with seroresponse at Day 29, with two-sided 95% CIs calculated using the Clopper-Pearson method. Differences in seroresponse rate (SRR) between the two groups at Day 29, along with their 95% CIs, were computed using the Miettinen-Nurminen score method. This endpoint was analyzed descriptively, with no pre-specified hypothesis testing.

Seroresponse at the participant level was defined as:

- Primary definition: An antibody value change from baseline below the lower limit of quantification (LLOQ) to ≥4 x LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ and <4 x LLOQ, or a 2-fold rise if the baseline is ≥4 x LLOQ.
- Secondary definition: An antibody change from baseline below the LLOQ to ≥4 x LLOQ, or at least a 4-fold rise if baseline ≥LLOQ.

Planned Analyses

Planned analyses for Study P301-Japan include both interim and final analyses. An interim analysis of safety and immunogenicity was conducted after all participants completed at least 29 day of follow-up post-injection. This BLA submission includes data from the interim analysis of the P301-Japan study.

The final analysis of all study endpoints will occur after all participants have completed the full study schedule, with results to be summarized in the final clinical study report.

6.2.10 Study Population and Disposition

This BLA submission includes data from this study from the study start on March 15, 2024 through the interim analysis data cutoff date of May 2, 2024. There was a total of 692 participants randomized.

6.2.10.1 Populations Enrolled/Analyzed

Populations used for the study analyses are defined in Table 28.

Table 28. Analysis Populations

Population	Description
Full Analysis Set (FAS)	All participants who are randomized and receive the study vaccine. Participants will be analyzed according to their randomized study group.
Safety Set	All randomized participants who received the study vaccine. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received the study vaccine and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Japan Per-Protocol Immunogenicity Set	The PPIS included all Japan cohort participants in the FAS who received the assigned dose of study vaccination and have no major protocol deviations that impact key or critical data. The PPIS will the primary analysis set of analyses of immunogenicity unless otherwise specified.

Source: Adapted from STN 125835/0, mRNA-1083-P301-Japan Clinical Study Report, Table 4

6.2.10.2 Demographics

The demographics of participants in the Safety Set are shown in Table 29. Overall, the demographic characteristics were similar across the two groups. The median age was 52 years. There was a slightly greater percentage of participants who were male (65.7%). Most

participants had evidence of prior SARS-CoV-2 infection at baseline (70.0%). Most participants had 3 (35.6%) or 4 (41.8%) prior COVID-19 doses. The median interval from last COVID-19 vaccination to receipt of study vaccine was 16.7 months.

The demographic characteristics of the Per-Protocol Immunogenicity set were similar to those of the Safety Set.

Table 29. Demographic and Baseline Characteristics, Safety Set, Study mRNA-1283-P301-Japan

Characteristic	mRNA-1283.815 N=343	Spikevax N=346
Sex, n (%)	--	--
Male	225 (65.6)	228 (65.9)
Female	118 (34.4)	118 (34.1)
Age, years	--	--
Median age (min, max)	52.0 (12, 83)	52.0 (12, 82)
12 to <18 years, n (%)	70 (20.4)	70 (20.2)
18 to <65 years, n (%)	203 (59.2)	202 (58.4)
≥65 years, n (%)	70 (20.4)	74 (21.4)
≥75 years, n (%)	8 (2.3)	8 (2.3)
Race, n (%)	--	--
Asian	343 (100)	346 (100)
Body Mass Index, n (%)	--	--
<30 kg/m^2	317 (92.4)	321 (92.8)
≥30 kg/m^2	26 (7.6)	24 (6.9)
≥40 kg/m^2	1 (0.3)	0
Missing	0	1 (0.3)
Baseline SARS-CoV-2 Status, n (%)[a]	--	--
Negative	111 (32.4)	96 (27.7)
Positive	232 (67.6)	250 (72.3)
Number of Prior COVID-19 Vaccine Doses, n (%)	--	--
<2	0	0
2	18 (5.2)	23 (6.6)
3	133 (38.8)	112 (32.4)
4	137 (39.9)	151 (43.6)
5	55 (16.0)	60 (17.3)
≥6	0	0
Type of Last Prior COVID-19 Vaccine, n (%)[b]	--	--
mRNA, Original monovalent	117 (34.1)	110 (31.8)
mRNA, bivalent (Original + Omicron BA.4/BA.5)	216 (63.0)	225 (65.0)
mRNA, Omicron XBB.1.5 monovalent	0	2 (0.6)
non-mRNA	3 (0.9)	2 (0.6)
Unknown	7 (2.0)	7 (2.0)
Dosing Interval from Last Prior Dose COVID-19 Vaccine to Study Vaccine Day (months)[c]	--	--
Median (min, max)	16.9 (7.3, 31.9)	16.6 (3.9, 30.3)

Source: Adapted from STN 125835/0, mRNA-1283-P301 Japan substudy Clinical Study Report, Table 14.1.3.1. Data cutoff 02 May 2024.
Abbreviations: COVID-19=coronavirus disease 2019; max=maximum; min=minimum; N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic; RT-PCR=reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; Original= Wuahn-Hu-1 strain
a. Baseline SARS-CoV-2 Status: positive is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1;

b. Type of formulation received is presumed based on date of receipt reported by participant and date of approval of the formulation. Participants with last mRNA COVID-19 vaccine dose date prior to September 1, 2022 were presumed to have received the Original monovalent. Participants with last mRNA COVID-19 vaccine dose date on or after September 1, 2022, but before September 20, 2023 were presumed to have received the Omicron bivalent. Two participants received the last mRNA COVID-19 vaccine dose date on or after September 20, 2023 (i.e., after approval of Omicron XBB.1.5 formulations), however, they had received a non-XBB.1.5 formulation and are not shown in the table.
c. Dosing interval from last prior dose COVID-19 vaccine to investigational vaccine Day (months)=Date of vaccine – date of last prior dose COVID vaccine +1) / 30.4375.

***Reviewer Comment**: The study was conducted entirely in individuals of Japanese ethnicity; however, the baseline characteristics of the participants in P301-Japan, including evidence of prior SARS-CoV-2 infection and prior COVID-19 vaccination history, appear generally similar to those of participants in the larger P301 study (see section 6.1.10) which included a large proportion of U.S. participants. Therefore, the results of this study are considered generalizable to broader populations beyond the Japanese cohort.*

6.2.10.3 Participant Disposition

Study disposition tables for the study are presented below in Table 30 (immunogenicity populations) and Table 31 (safety populations).

The percentage of participants who were excluded from the Per-Protocol Immunogenicity Set was comparable between the mRNA-1283.815 and Spikevax vaccine groups (2.9% and 4.0%, respectively). Most participants were excluded from the Per-Protocol Immunogenicity Set because they did not have pre-vaccination or Day 29 immunogenicity data.

Table 30. Participant Disposition, Immunogenicity Populations, Study mRNA-1283-P301-Japan

Population	mRNA-1283.815 n (%)	Spikevax n (%)
Randomization Set[a]	344 (100)	348 (100)
Full Analysis Set (FAS)[a]	343 (99.7)	346 (99.4)
Per-Protocol Immunogenicity Subset (PPIS)[a]	334 (97.1)	334 (96.0)
Excluded from PPIS[b]	9 (2.6)	12 (3.5)
Reason for exclusion from PPIS[b,c]	--	--
Major protocol deviation that impact key or critical data	0	1 (0.3)
Did not have pre-study vaccine or Day 29 (occurring between days 21 and 42) Immunogenicity Data	9 (2.6)	11 (3.2)

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Tables 14.1.2.1, 14.1.2.2. Data cutoff: 02 May 2024.
Abbreviations: n=number of participants with the specified characteristic;
a. Numbers are based on planned treatment group and percentages are based on the number of participants in Randomization Set.
b. Percentages are based on the number of participants in the FAS.
c. A participant who has multiple reasons for exclusion is listed under the reason appears earliest according to the table order.

Among participants in the Safety Set, one participant in the Spikevax group withdrew consent and discontinued from the study after vaccination. There were no study discontinuations due to AEs. All participants in both treatment groups were followed up for at least 28 days after vaccination at the time of the data cutoff.

Table 31. Participant Disposition, Safety Populations, Study mRNA-1283-P301-Japan

Population	mRNA-1283.815 n (%)	Spikevax n (%)
Randomization Set[a]	344 (100)	348 (100)

Population	mRNA-1283.815 n (%)	Spikevax n (%)
Safety Set[b]	343 (99.7)	346 (99.4)
Solicited Safety Set[c]	343 (100)	346 (100)
Discontinued from the Study[c]	0	1 (0.3)
Reason for Discontinuation	--	--
Withdrawal of Consent by Participant	0	1 (0.3)
Completed ≥28 Days of follow-up post-vaccination[c]	343 (100)	346 (100)
Median follow-up (days) (min, max)	36.0 (29, 49)	35.0 (29, 49)

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.1.1.1, Table 14.1.2.1, 14.1.1.5. Data cutoff 02 May 2024
Abbreviations: max=maximum; min=minimum; n=number of participants with the specified characteristic;
a. Numbers are based on planned treatment group and percentages are based on the number of participants in Randomization Set.
b. Numbers are based on actual treatment group and percentages are based on the number of participants in Randomization Set.
c. Numbers are based on actual treatment group and percentages are based on the number of participants in the Safety Set.

***Reviewer Comment**: Across both study groups, all participants who received study vaccine contributed to the safety analyses (including solicited safety) and almost all participants contributed to the analyses of immunogenicity.*

6.2.11 Analyses of Vaccine Effectiveness

6.2.11.1 Analysis of Primary Objective

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 32 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 lower bound CI >0.667.

Table 32. Analysis of Primary Immunogenicity Endpoint of Geometric Mean Concentrations (GMCs) as Measured by PsVNA Against Omicron XBB.1.5 at 28 Days Postvaccination, PPIS, Study mRNA-1283-P301-Japan

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]	1.2 [1.0, 1.4]

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.2.1.1.1.2. Data cutoff 02 May 2024.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=coronavirus disease 2019; 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; PsVNA = pseudovirus neutralization assay
PsVNA used: VAC150 (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 versus 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 versus 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.

6.2.11.2 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 the following composite criteria based on baseline antibody levels (pre-dose measurement):

- If baseline antibody level below the LLOQ, then a post-vaccination level ≥4xLLOQ, or
- If baseline level ≥LLOQ but <4xLLOQ, then a ≥4 fold rise, or
- If baseline level ≥4xLLOQ, then a ≥2-fold rise.

The secondary seroresponse definition was aligned with the more conventionally used seroresponse definition:

- If baseline level below the LLOQ, then ≥4xLLOQ, or
- If baseline level ≥LLOQ, then a ≥4-fold rise

Using either definition, a higher percentage of participants in the mRNA-1283.815 group achieved seroresponse compared with the Spikevax group. Descriptive analyses of the difference in SRR percentage between mRNA-1283.815 recipients and Spikevax recipients using these two seroresponse definitions are shown in Table 33.

Table 33. Descriptive Analyses of Secondary Immunogenicity Endpoint of Seroresponse Rates as Measured by PsVNA Against Omicron XBB.1.5 at 28 Days Postvaccination, PPIS, Study mRNA-1283-P301-Japan

Seroresponse Definition	mRNA-1283.815 N1=334 SRR % [95% CI][c]	Spikevax N1=334 SRR % [95% CI][c]	Difference in SRR % (mRNA-1283.815 - Spikevax) % [95% CI][d]
Seroresponse Primary Definition[a]	92.2 [88.8, 94.9]	86.8 [82.7, 90.3]	5.4 [0.8, 10.2]
Seroresponse Secondary Definition[b]	83.2 [78.8, 87.1]	75.7 [70.8, 80.2]	7.5 [1.4, 13.6]

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.2.1.1.1.3, Table 14.2.1.1.1.4. Data cutoff 02 May 2024.
Abbreviations: CI=confidence interval; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SRR=seroresponse rate. N1=number of participants with non-missing data at baseline and corresponding timepoint; PsVNA = pseudovirus neutralization assay; SRR=seroresponse rate
PsVNA used: VAC150 (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.
Percentages are based on number of participants with non-missing data at Baseline and the corresponding timepoint.
a. Seroresponse (primary definition) is defined as an antibody value change from baseline level below the 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 predose.
b. 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 level is ≥LLOQ, where baseline level refers to predose.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

> ***Reviewer Comment****: Although the analyses evaluating the secondary endpoint of 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.*
>
> *While both the primary and secondary seroresponse definitions include composite criteria based on baseline antibody levels, the primary definition only required ≥4x-fold rise in antibody titers if baseline titers are less than 4xLLOQ, and ≥ 2x-fold rise if baseline titers were greater than 4xLLOQ. In contrast, the secondary seroresponse definition required ≥4x-fold rise in all participants, including those with baseline titers greater than LLOQ. As shown in the table above, the percentage of participants achieving seroresponse with the more stringent secondary definition was generally high (83.2% versus 75.7%) for mRNA-1283 recipients and Spikevax recipients, respectively. This analysis provides assurance that individuals with high baseline antibody titers (ie, ≥4xLLOQ) associated with prior COVID-19 vaccination and/or prior SARS-CoV-2 infection generate robust (≥4x fold-rise) neutralizing antibody responses following vaccination. Inclusion of both definitions not only assist with the interpretability of the SRR analyses, but also support the benefit of mRNA-1283 vaccination in current U,S. populations ≥12 years of age with hybrid immunity based on prior SARS-CoV-2 infections and/or COVID-19 vaccinations.*

Additional secondary immunogenicity endpoints include descriptive analyses of GMC and SRR against the ancestral SARS-CoV-2 D614G at 28 days after mRNA-1283.815 or Spikevax. The neutralizing antibody GMC and SRR against D614G were similar across the mRNA-1283.815 and Spikevax groups (results not shown).

6.2.11.3 Subpopulation Analyses

Subgroup analyses of the primary immunogenicity endpoint of GMC against Omicron XBB.1.5 were performed by age (Table 34). The GMC ratios were generally similar across all age groups, although the small sample size in some of the age subgroups limit the interpretation of these results.

Table 34. Descriptive Analyses of GMCs as Measured by PsVNA Against Omicron XBB.1.5 at 28 Days Postvaccination, by Age Subgroup, PPIS, Study mRNA-1283-P301-Japan

Age Subgroup	mRNA-1283.815 GMC [95% CI][a]	Spikevax GMC [95% CI][a]	GMC Ratio (mRNA-1283.815/ Spikevax) [95% CI][a]
12 to <18 years	N1=70 3302.2 [2729.9, 3994.4]	N1=68 2753.3 [2269.8, 3339.9]	1.2 [0.9, 1.6]
18 to <65 years	N1=195 1513.0 [1313.2, 1743.2]	N1=197 1281.3 [1113.8, 1474.0]	1.2 [1.0, 1.4]
≥65 years	N1=69 1435.9 [1099.3, 1875.8]	N1=69 1123.4 [858.3, 1470.3]	1.3 [0.9, 1.9]

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.2.1.1.4.2. Data cutoff 02 May 2024.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=Coronavirus Disease-19; 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. N1=Number of participants in the subgroup with non-missing data at the specified timepoint; PPIS=per-protocol immunogenicity subset; PsVNA = pseudovirus neutralization assay
PsVNA used: VAC150 (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.The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (mRNA-1283.815 versus Spikevax) as fixed effect, adjusted by SARS-CoV-2 status at Baseline, number of prior boosters (0, 1, 2, ≥3), and type of last prior COVID-19 vaccine (mRNA Omicron bivalent versus 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.

Subgroup analyses of the secondary immunogenicity endpoint of SRR against XBB.1.5, based on the primary seroresponse definition, were performed by age (Table 35). Across both study groups, decreasing SRR point estimates was observed with increasing age. The SRRs were numerically higher in the mRNA-1283.815 group compared with the Spikevax group across all age groups, most notably for the ≥65 years cohort, but all had overlapping CIs.

Table 35. Descriptive Analyses of SRR as Measured by PsVNA Against Omicron XBB.1.5 at 28 Days Post-Vaccination, by Age Subgroup, PPIS, Study mRNA-1283-P301-Japan

Age Subgroup	mRNA-1283.815 SRR % [95% CI][c]	Spikevax SRR % [95% CI][c]	Difference in SRR % (mRNA-1283.815 - Spikevax) % [95% CI][d]
12 to <18 years	N1=70 98.6 [92.3, 100.0]	N1=68 94.1 [85.6, 98.4]	4.5 [−2.5, 13.0]
18 to <65 years	N1=195 91.8 [87.0, 95.2]	N1=197 86.8 [81.3, 91.2]	5.0 [−1.2, 11.3]

Age Subgroup	mRNA-1283.815 SRR % [95% CI][c]	Spikevax SRR % [95% CI][c]	Difference in SRR % (mRNA-1283.815 - Spikevax) % [95% CI][d]
≥65 years	N1=69 87.0 [76.7, 93.9]	N1=69 79.7 [68.3, 88.4]	7.2 [−5.4, 20.0]

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.2.1.1.4.3. Data cutoff 02 May 2024.
Abbreviations: CI=confidence interval; LLOQ=lower limit of quantification; PPIS=per-protocol immunogenicity subset; SRR=seroresponse rate. N1=number of participants with non-missing data at baseline and corresponding timepoint;
PsVNA = pseudovirus neutralization assay; SRR=seroresponse rate
PsVNA used: VAC150 (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.
Percentages are based on number of participants with non-missing data at Baseline and the corresponding timepoint.
a. Seroresponse (primary definition) is defined as an antibody value change from baseline level below the 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 predose.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

> ***Reviewer Comment****: The descriptive subgroup analyses support vaccine effectiveness across age subgroups (*12 to <18 years, 18 to <65 years, and ≥65 years)*. Although GMCs and SRRs were numerically higher in the mRNA-1283.815 group compared with Spikevax group across all age groups, the highest differential immune responses were observed in the ≥65 years age cohort, similar to the results observed in the main P301 study. Although not hypothesis tested, the GMC ratio and SRR percentage difference for each of the age subgroups would have met the conventional noninferiority criteria of LB >0.67 and LB >-10%, respectively.*

Subgroup analyses were conducted based on SARS-CoV-2 infection status pre-vaccination. Across both study groups, Day 29 GMCs and SRRs were higher in participants with evidence of prior SARS-CoV-2 infection compared with those without prior infection. Descriptive analyses of GMC ratio against XBB.1.5 (mRNA-1283.815/Spikevax) was 1.3 (95% CI: 1.1, 1.5) in participants with evidence of prior infection, and 1.0 (95% CI: 0.7, 1.5) in participants without evidence of prior infection.

Subgroup analyses based on the number of prior COVID-19 vaccine doses received showed that mRNA-1283 elicited similar neutralizing antibody GMCs compared with Spikevax, irrespective of the number of prior doses received.

6.2.12 Safety Analyses

The Study P301-Japan Safety Set included 343 mRNA-1283.185 recipients and 346 Spikevax recipients. The median duration of follow-up through the 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 28 days of follow-up post-vaccination.

6.2.12.1 Methods

Please see Section 6.1.7.

6.2.12.2 Overview of Adverse Events

Overview of Adverse Events

Table 36 provides an overview of the number and percentage of participants reporting at least one solicited adverse reaction and/or unsolicited AE in the mRNA-1283.815 group compared with the Spikevax group. Solicited adverse reactions within 7 days, including severe (grade 3) solicited adverse reactions, were reported by a lower percentage of mRNA-1283.815 recipients compared to Spikevax recipients. Unsolicited AEs within 28 days were reported by a similar percentage of participants in both groups. Through the data cutoff, MAAEs were reported in 7.0% mRNA-1283.815 recipients and 5.2% of Spikevax recipients. There were no SAEs, AEs leading to study discontinuation, AESIs, or deaths reported through the data cutoff date.

Table 36. Number and Percentage of Participants Reporting at Least One Safety Event, Safety Set and Solicited Safety Set, Study mRNA-1283-P301-Japan

Event Type	mRNA-1283.815 N=343 % (n)	Spikevax N=346 % (n)
Solicited adverse reactions within 7 days[a]	--	--
Any solicited adverse reaction within 7 days	89.5 (307)	95.7 (331)
Solicited local adverse reaction[b]	86.3 (296)	95.1 (329)
Grade 3 or above solicited local adverse reaction	2.9 (10)	6.6 (23)
Solicited systemic adverse reaction[c]	59.8 (205)	76.9 (266)
Grade 3 or above solicited systemic adverse reaction	5.2 (18)	8.7 (30)
Unsolicited adverse events[d]	--	--
Unsolicited adverse event through 28 days after vaccination	7.0 (24)	6.9 (24)
Non-serious unsolicited adverse event[e]	7.0 (24)	6.9 (24)
Severe non-serious unsolicited AE[e]	0	0
Medically attended adverse events through data cutoff	7.0 (24)	5.2 (18)
Related MAAE[c]	0.3 (1)	0
SAE through data cutoff	0	0
AESI through data cutoff	0	0
Deaths through data cutoff	0	0
AE leading to study discontinuation through data cutoff	0	0

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan Clinical Study Report, Table 14.3.1.1.1.1, Table 14.3.1.2.1.1, Table 14.3.1.2.1.2. Data cutoff: 02 May 2024.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants who received a study intervention.; n=number of participants who experienced the event;
Note: Participants were allocated to the vaccine groups as received.
a. Percentages under this section are based on the number of exposed participants who submitted any data for the event.
b. Solicited local reactions included pain, erythema (redness), swelling (hardness), axillary swelling or tenderness.
c. Solicited systemic reactions included Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.
d. Percentages under this section are based on the number of participants in the Safety Set.
e. Participants without any SAE and with any non-serious AE.
f. Relatedness to study vaccine as determined by principal investigator.Solicited Local Reactions and Systemic Adverse Events

***Reviewer Comment**: Solicited local and systemic reactions were reported at slightly lower percentages in the mRNA-1283.815 group compared with the Spikevax group. The overall safety profile of mRNA-1283.815 was generally comparable to Spikevax.*

6.2.12.3 Solicited Adverse Reactions

Solicited local and systemic reactions (ARs) occurring within 7 days postvaccination were assessed using the Solicited Safety Set, which included all randomized participants who received any study vaccine and contributed any solicited AR data. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling/induration, and axillary swelling/tenderness) and systemic reactions (headache, fatigue, myalgia, arthralgia, nausea/vomiting, fever, and chills).

Solicited Local Reactions

Table 37 summarizes the frequency of solicited local adverse reactions with 7 days of vaccination, by severity, for the Solicited Safety Set. Overall, 86.3% of mRNA-1283.815 recipients and 95.1% of Spikevax recipients experienced a local adverse reaction. Pain was the most common solicited local AR reported for both groups. Most solicited local ARs were Grade 1 in severity and no participant in either group reported a Grade 4 reaction. Grade 3 solicited local ARs were lower in the mRNA-1283.815 group (2.9%) compared with the Spikevax group (6.6%).

Table 37. Frequency of Solicited Local Adverse Reactions Within 7 Days of Vaccination, By Maximum Severity, Solicited Safety Set, Study mRNA-1283-P301-Japan

Event	mRNA-1283.815 N1=343 %	Spikevax N1=346 %
Any local adverse reaction	--	--
Any grade	86.3	95.1
Grade 1	63.0	54.9
Grade 2	20.4	33.5
Grade 3	2.9	6.6
Pain[a]	--	--
Any grade	84.8	94.5
Grade 1	63.3	59.5
Grade 2	20.4	31.2
Grade 3	1.2	3.8
Erythema (redness)[b]	--	--
Any ≥25 mm	3.8	11.0
Grade 1:	3.2	5.8
Grade 2:	0.3	3.8
Grade 3:	0.3	1.4
Swelling (hardness)[b]	--	--
Any ≥25 mm	9.3	14.7
Grade 1	6.7	8.7
Grade 2	1.2	4.0
Grade 3	1.5	2.0
Axillary swelling or tenderness[c]	--	--
Any grade	24.5	26.0
Grade 1	20.4	21.4
Grade 2	3.8	4.3

Event	mRNA-1283.815 N1=343 %	Spikevax N1=346 %
Grade 3	0.3	0.3

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan substudy Clinical Study Report, Tables 14.3.1.1.1.1. Data cutoff 02 May 2024.
Abbreviations: N1=number of exposed participants who submitted any data for the event
No grade 4 solicited adverse reactions were reported.
a. Pain: Grade 1: no interference with activity; Grade 2: some interference with activity; Grade 3: prevents daily activity; Grade 4: requires emergency room visit or hospitalization.
b. Erythema (redness) and swelling (hardness): Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm; Grade 4: necrosis or exfoliative dermatitis.
c. Axillary swelling or tenderness: Grade 1: no interference with activity; Grade 2: some interference with activity; Grade 3: prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

The median day of onset for solicited local ARs was Day 2. The median duration of solicited local adverse reactions was 3 days in mRNA-1283.815 group and Spikevax group. Solicited local adverse reactions that persisted beyond 7 days were reported by a similar percentage of participants in both groups (2.0% mRNA-1283.815 and 3.2% Spikevax).

> ***Reviewer Comment****: Solicited local adverse reactions, including grade 3 ARs, were reported less frequently in the mRNA-1283.815 group compared with the Spikevax group. This may be partly attributable to the difference in injection volume between the two study vaccines (0.2mL versus 0.5mL, respectively).*

Solicited Systemic Reactions

Table 38 presents percentages and severities of reported solicited systemic adverse reactions within 7 days following vaccination. Overall, a lower percentage of mRNA-1283.815 recipients reported any systemic AR compared with Spikevax recipients. Fatigue, headache, myalgias and arthralgias were the most reported systemic ARs in both cohorts. Most solicited systemic ARs were Grade 1 or 2 in severity and there were no Grade 4 solicited systemic ARs reported. A slightly lower percentage of mRNA-1283.815 recipients reported any Grade 3 solicited systemic AR compared with Spikevax recipients. Use of antipyretic or analgesic medications were reported by a lower percentage of mRNA-1283.815 recipients (19.5%) compared with the Spikevax recipients (27.2%).

Table 38. Frequency of Solicited Systemic Adverse Reactions Within 7 Days of Vaccination, By Maximum Severity, Solicited Safety Set, Study mRNA-1283-P301-Japan

Event	mRNA-1283.815 N1=343 %	Spikevax N1=346 %
Any systemic adverse reaction	--	--
Any	59.8	76.9
Grade 1	33.5	41.0
Grade 2	21.0	27.2
Grade 3	5.2	8.7
Fever[a]	--	--
Any grade	7.0	12.7
Grade 1	5.0	9.0
Grade 2	1.5	2.0
Grade 3	0.6	1.7
Headache[b]	--	--
Any grade	42.6	56.1
Grade 1	27.4	36.7

Event	mRNA-1283.815 N1=343 %	Spikevax N1=346 %
Grade 2	13.4	15.3
Grade 3	1.7	4.0
Fatigue[c]	--	--
Any grade	51.0	63.6
Grade 1	31.8	38.2
Grade 2	15.7	22.3
Grade 3	3.5	3.2
Myalgia[d]	--	--
Any grade	35.0	39.9
Grade 1	22.2	27.5
Grade 2	11.1	10.4
Grade 3	1.7	2.0
Arthralgia[e]	--	--
Any grade	31.8	36.1
Grade 1	21.9	26.0
Grade 2	8.5	7.8
Grade 3	1.5	2.3
Nausea/vomiting[f]	--	--
Any grade	7.9	9.0
Grade 1	6.1	6.6
Grade 2	1.7	2.3
Grade 3	0	0
Chills[g]	--	--
Any grade	21.0	31.5
Grade 1	13.1	20.2
Grade 2	6.7	9.8
Grade 3	1.2	1.4
Use of antipyretic or pain medication	19.5	27.2

Source: Adapted from STN 125835/0, mRNA-1283-P301-Japan substudy Clinical Study Report, Tables 14.3.1.1.1.1, Table 14.1.5.1.3. Data cutoff 02 May 2024.
Abbreviations: N1=number of exposed participants who submitted any data for the event;
No grade 4 solicited adverse reactions were reported.
a. Fever: Grade 1: 38 – 38.4°C; Grade 2: 38.5 – 38.9°C; Grade 3: 39 – 40°C; Grade 4: >40°C
b. Headache: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
c. Fatigue: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
d. Myalgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
e. Arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
f. Nausea/Vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires emergency room visit or hospitalization for hypotensive shock.
g. Chills: Grade 1: No interference with activity; Grade 2: Some interference with activity not requiring medical attention; Grade 3: Prevents daily activity and requires medical attention; Grade 4: Requires emergency room visit or hospitalization.

The median day of onset for solicited systemic ARs was Day 2. The median duration for solicited systemic reactions was 2 days for recipients of both mRNA-1283.815 and Spikevax. Solicited systemic adverse reactions that persisted beyond 7 days were reported in 2.6% of mRNA-1283.815 recipients and 2.9% of Spikevax recipients. Fatigue was the most reported persistent solicited systemic ARs after either vaccine.

***Reviewer Comment**: Solicited systemic adverse reactions, including Grade 3 ARs, were reported less frequently in the mRNA-1283.815 group compared with the Spikevax group, with fewer participants requiring antipyretic or analgesic use. This difference was not observed in the main P301 study which showed similar solicited systemic AR profiles between the bivalent formulation of mRNA-1283 (mRNA-1283.222) and Moderna COVID-19 Vaccine, Bivalent. It is unclear if the solicited systemic AR data from the P301-Japan study represent true differences in the solicited safety profile between the bivalent and monovalent vaccine formulations, or if these findings are attributable to differences in study characteristics (e.g., smaller sample size contributing to these analyses, different populations).*

Subgroup analyses of solicited adverse reactions

Among mRNA-1283.815 recipients, the reported percentages of solicited local and systemic ARs were highest in the 12 to <18 years age cohort (91.4% and 72.4%, respectively) and lowest in the ≥65 years age cohort (77.1% and 50.0%, respectively). The percentage and severity of solicited local and systemic ARs in participants who had evidence of prior SARS-CoV-2 infection at baseline were generally similar to those of participants who had no evidence of prior SARS-CoV-2 infection at baseline. The solicited local and systemic adverse reaction percentages were similar regardless of the number of prior COVID-19 vaccine doses received.

***Reviewer Comment:** A lower percentage of older adult participants (≥65 years) reported any solicited AR after vaccination with mRNA-1283.815 compared with adolescent and younger adult participants, similar to the known reactogenicity profile of Spikevax. SARS-CoV-2 infection history and number of prior doses of COVID-19 vaccine did not appear to impact the solicited safety profile of mRNA-1283.815.*

6.2.12.4 Unsolicited Adverse Events

Unsolicited AEs through 28 days after vaccination

The percentage of unsolicited AEs through 28 days after vaccination was similar between the mRNA-1283.815 (7.0%) and Spikevax (6.9%) groups. There were no severe unsolicited AEs reported in either group.

Within 28 days of vaccination, AEs assessed as related to study vaccination by the investigators were reported for 0.9% of mRNA-1283.815 recipients and 0.6% of Spikevax recipients. These AEs were events consistent with vaccine reactogenicity (e.g., headache, myalgia, and injection site reactions).

Medically attended adverse events

Through the data cutoff, with a median follow-up of 35 days after vaccination, MAAEs were reported by a similar percentage of participants in the mRNA-1283.815 group (5.0%) and Spikevax group (4.0%). Of these, one MAAE (event of urticaria) in the mRNA-1283.815 group was assessed as related by the investigator and is further described below.

A 16-year-old male with no prior history of urticaria or hypersensitivity reported Grade 1 urticaria on Day 5 which resolved by Day 11. The event was considered possibly related to the vaccine by both the investigator and the Applicant, based on timing and lack of prior history. However, the report lacks information on other medical history, concomitant medications, or alternative exposures that could have contributed.

Reviewer Comment*: The reviewer concurs with the assessment of relatedness for the MAAE of urticaria based on the available clinical details, temporal association with study product administration and the absence of alternative etiologies.*

Standard MedDRA Queries

FDA conduced standardized MedDRA queries (SMQs) using FDA-developed software to evaluate the Safety Set for constellations of unsolicited AEs with onset following vaccination through data cutoff. The SMQs were conducted on AE PTs that could represent various conditions, including but not limited to embolic & thrombotic events, convulsions, CNS vascular disorders, hypersensitivity, peripheral neuropathy, demyelination, cardiac arrhythmias, and cardiomyopathy. There were no notable imbalances observed between the mRNA-1283.815 and Spikevax groups based on analyses conducted using the SMQs.

Subgroup analyses

There were no safety concerns identified in subgroup analyses of safety by sex, age, prior SARS-CoV-2 infection, or number of prior COVID-19 vaccine doses received.

Pregnancy

At the time of the data cutoff, no participants reported pregnancies in either group.

6.2.12.3 Deaths

There were no deaths reported at the time of data cutoff.

6.2.12.4 Serious Adverse Events (SAEs)

There were no SAEs reported at the time of data cutoff.

6.2.12.5 Adverse Events of Special Interest (AESIs)

There were no AESIs reported at the time of data cutoff.

6.2.12.6 Dropouts and/or Discontinuations

There were no discontinuations due to AEs at the time of data cutoff.

6.2.13 Study Summary and Conclusions

Study P301-Japan evaluated the safety and immunogenicity of mRNA-1283.815 compared with Spikevax in COVID-19 experienced participants 12 years of age and older. The study met the pre-specified criterion for noninferiority of neutralizing antibody GMCs elicited by mRNA-1283.815 against the Omicron XBB.1.5 strain as compared with Spikevax. Descriptive analyses of seroresponse against Omicron XBB.1.5 showed similar seroresponse rates across the mRNA-1283.815 and Spikevax groups. Across all age groups, neutralizing antibody GMCs and SRRs were similar or higher among mRNA-1283.815 recipients compared with Spikevax recipients.

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 to Spikevax recipients. There were no notable imbalances in the overall percentages and types of unsolicited AEs 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.

6.3 Study mRNA-1283-P201

NCT05137236

Title: "A Phase 2a, Randomized, Stratified, Observer-Blind Study to Evaluate the Immunogenicity and Safety of mRNA-1283 Vaccine Boosters for SARS-CoV-2"

Overview: Study mRNA-1283-P201 (hereafter referred to as P201) is a dose-ranging study evaluating the immunogenicity and safety of monovalent and bivalent mRNA-1283 vaccine candidates, targeting various SARS-CoV-2 variants, when administered as a single dose in individuals previously vaccinated with Spikevax. The study was conducted from December 2021 to March 2023. The study informed dose selection and variant-specific formulation development for mRNA-1283.

6.3.1 Objectives (all descriptive)

Only study objectives with data submitted to this BLA and integral to the assessment of safety and effectiveness will be reviewed in this clinical memo.

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)

Endpoints:

- Frequency and severity of solicited ARs (Day 1 through 7)
- Frequency and severity of unsolicited AEs (Days 1 through 28)
- Frequency of SAEs, AESIs, MAAEs, and AEs leading to discontinuation (Day 1 through end of study)

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

Endpoints: Neutralizing antibody GMT, geometric mean fold-rise (GMFR), and SRR against SARS-CoV-2 D614G, Beta, and Omicron BA.1 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

Endpoints: GMT, GMFR, and SRR against SARS-CoV-2 D614G, Beta, and Omicron BA.1 at all timepoints (Days 91, 181, and 366)

Part B

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

Endpoints:

- Frequency and severity of solicited ARs (Day 1 through 7)
- Frequency and severity of unsolicited AEs (Days 1 through 8)

- Frequency of SAEs, AESIs, MAAEs, and AEs leading to discontinuation (Day 1 through end of study)

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.

Endpoints: Neutralizing antibody GMT, GMFR, and SRR against SARS-CoV-2 D614G and Omicron BA.1 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.

Endpoints: GMT, GMFR, and SRR against SARS-CoV-2 D614G and against SARS-CoV-2 variants at all timepoints (Days 91, 181, and 366)

6.3.2 Design Overview

Study Spikevax-P201 was 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 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. Participants were followed for safety for 12 months after vaccination.

6.3.3 Population

Adults ≥ 18 years of age in good health who have received the 2-dose Spikevax primary series, with last dose ≥6 months prior to study enrollment (Part A) or who have received the 2-dose Spikevax primary series and an additional booster dose of Spikevax as ≥3 months prior to study enrollment (Part B). Participants were excluded if history of SARS-CoV-2 infection within 14 days of screening or history of myocarditis or pericarditis within 2 months of screening.

6.3.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1283 (2.5µg, 5µg, 10µg)

- Dose and route of administration: 0.25 mL IM
- Description: Monovalent formulation encoding the linked NTD-RBD of the S-protein of the Wuhan-Hu 1 strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol (DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 8522600101

mRNA-1283.211 (5 µg, 10 µg)

- Dose and route of administration: 0.25 mL IM
- Description: Monovalent formulation encoding the linked NTD-RBD of the S-protein of B.1.351 (Beta) and the Wuhan-Hu 1 strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol (DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 8522800101

mRNA-1283.529 (5 µg, 10 µg)

- Dose and route of administration: 0.25 mL IM
- Description: Monovalent formulation encoding the linked NTD-RBD of the S-protein of Omicron BA.1 (B.1.1.529) strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol (DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 8523200101

Spikevax (50 µg) (COVID-19 Vaccine, mRNA)

- Dose and route of administration: 0.5 mL IM
- Description: 50 µg of mRNA encoding the full length S protein of the Wuhan-Hu 1 strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 7008121001, 7006121003

6.3.5. Directions for Use

A single IM injection administered in the deltoid muscle.

6.3.6 Sites and Centers

Part A was conducted at 13 study sites in the United States and Part B was conducted at 10 study sites in the United States.

6.3.7 Surveillance/Monitoring

Safety

Solicited ARs through Day 7 were collected by eDiary. Unsolicited AEs were monitored through Day 28, and SAEs, MAAEs, AESIs were continuously monitoring until end of study (Day 366). Safety telephone calls and site visits were conducted per protocol.

Immunogenicity

Blood samples collected at baseline and multiple timepoints up to Day 366 to measure neutralizing antibody GMTs using PsVNA (validated; Duke).

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1.

6.3.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive without formal hypothesis testing.

6.3.10 Study Population and Disposition

Part A: A total of 340 participants were randomized across 6 groups (53-63 participants per group). The median age ranged from 41 to 47 years of age across the study groups. Most of the participants identified as White (68.5-82.5%) and not Hispanic or Latino (78.1-83.9%). Across the study groups, 32.8-53.7% of participants had evidence of prior SAR-CoV-2 infection. The median interval from the second dose of the 2-dose series to receipt of the study vaccine was 8.4-9.0 months.

Part B: 200 participants were enrolled (5 µg: 103; 10 µg: 97)

For both parts, the demographics and baseline characteristics were generally balanced across the study groups.

6.3.11 Effectiveness Analyses

Immunogenicity

Part A

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 B

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.

6.3.12 Safety Analyses

Part A

Solicited 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.

Part B

Through the entire study period of 12 months after vaccination, there were no SAEs assessed as related to study vaccine by the investigator. No cases of myocarditis, pericarditis, or anaphylaxis were observed.

Deaths reported in Part B:
Two deaths were reported during the study, both were assessed as not related to study vaccine by the investigator and described below.

- One death occurred in a 50-year-old woman with a past medical history of hyperlipidemia, Ehlers-Danlos syndrome, and Sjogren's syndrome, on Day 99 after vaccination with mRNA-1283.529 (10µg) of unknown cause (autopsy not performed).

- One death occurred in a 40-year-old man with a past medical history of hypertension, hyperlipidemia, and coronary artery disease who died on Day 96 after administration of mRNA-1283.529 (10µg). An autopsy revealed that the participant had died from atherosclerotic and hypertensive heart disease. He was reportedly to be noncompliant with medications for these chronic diseases.

Clinical Reviewer Comment: *This clinical reviewer agrees with the investigators' assessment that these two deaths were unlikely to be related to study vaccine due to onset >3 months after receipt of study vaccine and the participants' underlying medical conditions which were more likely to have contributed to the deaths.*

Pregnancies reported in Part B:

- One pregnancy occurred in a 31-year-old participant with estimated date of conception 222 days after vaccination. The pregnancy outcome is unknown as the participant was unable to be contacted after study completion (approximately 4 months after conception).
- One pregnancy occurred in a 35-year-old participant with estimated date of conception approximately 4 months after vaccination. No pregnancy complications were reported, and the participant delivered a full term infant.

6.3.13 Study Summary and Conclusions

A single dose of any formulation of mRNA-1283 was well tolerated and immunogenic in previously vaccinated adults. The 10-µg dose level of mRNA-1283 demonstrated the most favorable balance of safety and immunogenicity, supporting further evaluation in Phase 3.

6.4 Study mRNA-1283-P101

NCT0481796

Title: "A Phase 1, Randomized, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1283 and Spikevax SARS-CoV-2 Vaccine in Adults Aged 18-55 years"

Overview: The mRNA-1283-P101 study (hereafter referred to as P101) was a Phase 1, randomized, observer blind, dose-ranging trial evaluating the safety, reactogenicity, and immunogenicity of mRNA-1283 in COVID-19 vaccine-naïve adults 18 through 55. The study was designed to determine the optimal dose level and dosing regimen of mRNA-1283. The study was initiated in March 2021 and completed in July 2023.

6.4.1 Objectives

Primary Objective

Safety

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

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 Objectives

Secondary Immunogenicity Objective

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

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 seroresponse (≥LLOQ if baseline <LLOQ, or ≥4-fold rise from baseline)

Exploratory objectives:

To assess cell-mediated responses, subclass-specific antibody binding, and immune profile of participants infected during the study.

6.4.2 Design Overview

Study P101 was a Phase 1, randomized, observer-blind, dose-ranging study in 105 healthy adults 18-55 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.

6.4.3 Population

Healthy adults 18-55 years of age, SARS-CoV-2 naïve by PCR and serology, and no prior COVID-19 vaccination.

6.4.4 Study Treatments or Agents Mandated by the Protocol

mRNA-1283 at 10 µg, 30 µg, or 100 µg

- Dose and route of administration: 0.25 mL IM
- Description: Monovalent vaccine encoding the linked NTD-RBD of the S-protein of the Wuhan-Hu 1 strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 8520700101

Spikevax (100 µg) (COVID-19 Vaccine, mRNA)

- Dose and route of administration: 0.5 mL IM
- Description: 100 µg mRNA encoding the full length S protein of the Wuhan-Hu 1 strain of SARS-CoV-2 formulated in lipid nanoparticles composed of 4 lipids [SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG) 2000 - dimyristoyl glycerol(DMG) (PEG2000-DMG)]
- Presentation: suspension for intramuscular injection
- Lot number: 700632008

Placebo

- Dose and route of administration: 0.5 mL IM
- Description: normal saline
- Lot number: 14001DK, 10097DK

6.4.5 Directions for Use

IM injection administered in the deltoid muscle on Days 1 and 29.

6.4.6 Sites and Centers

The study was conducted at 5 clinical sites in the United States.

6.4.7 Surveillance/Monitoring

Safety

Solicited ARs through Day 7 were collected by eDiary. Unsolicited AEs were monitored through Day 29, and SAEs, MAAEs, AESIs were continuously monitoring until end of study. Safety telephone calls and site visits were conducted per protocol.

Immunogenicity

Blood samples collected on Days 1, 29, 57, 209, 394 (and optionally 574, 754) to assess nAb titers using PsVNA (validated; Duke), binding antibody levels (enzyme-linked immunosorbent assay; ELISA), and S-specific T-cell responses ((b) (4))

6.4.8 Endpoints and Criteria for Study Success

See Section 6.4.1.

6.4.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive without formal hypothesis testing.

6.4.10 Study Population and Disposition

A total of 105 participants were randomized (18-23 per group). The demographics and baseline characteristics were similar across the study groups, with a median age of 30.5 to 43 years. The majority of participants identified as White (55.6%-76.2%) and not Hispanic or Latino (63.6%-76.2%). All participants had no evidence of prior SARS-CoV-2 infection at baseline.

6.4.11 Effectiveness Analyses

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, after the first and second vaccination. A single dose of mRNA-1283 (placebo at baseline, 100ug on Day 29) resulted in a numerically lower GMC ratio and lower seroresponse rate at Day 57 compared with participants who received two doses of mRNA-1283, regardless of dose level. The 10-ug dose of mRNA-1283 elicited GMTs and SRR that were comparable to or numerically higher than those observed with Spikevax at 100ug. Responses were detectable through Day 394. Binding antibody responses and T-cell analyses were consistent with neutralizing antibody results.

6.4.12 Safety Analyses

The overall safety profile of mRNA-1283 was consistent with Spikevax at all dose levels. Most solicited adverse reactions (ARs) were mild to moderate. The 10-µg dose of mRNA-1283 had the lowest percentages of solicited ARs among all mRNA-1283 dose levels. Unsolicited AEs within 28 days were reported at similar percentages (22.2-23.8%) across the 10-µg mRNA-1283 (2-dose series), 100-µg mRNA-1283 (single dose) and 100-µg Spikevax (2-dose series) groups, and at higher rates (38.1%-40.9%) in the 30-µg mRNA-1283 (2-dose series) and 100-µg mRNA-1283 (2-dose series) groups. There was one SAE, which was fatal, reported in the study: a gunshot wound leading to death in a participant in the Spikevax group which occurred 677 days after the last vaccination. This event was assessed as unrelated to the study vaccine by the investigator. No events of myocarditis or anaphylaxis were reported in the study.

6.4.13 Study Summary and Conclusions

Among COVID-19 vaccine naïve participants, a single dose or 2-dose series of mRNA-1283 was generally well tolerated across all dose levels tested and demonstrated comparable immunogenicity to a 2-dose series of Spikevax. Among the dose levels evaluated, the 10-ug mRNA-1283 group had the most favorable reactogenicity profile while eliciting neutralizing and binding antibody responses similar to Spikevax. These results supported continued clinical development of 10-ug of mRNA-1283.

7. INTEGRATED OVERVIEW OF EFFICACY

Study P301 was the only study with evaluation of clinical efficacy endpoints. Therefore, an integrated overview of efficacy is not applicable to this review.

8. INTEGRATED OVERVIEW OF SAFETY

The safety data reviewed in this application to support the final mRNA-1283 vaccine 10-ug dose were primarily from Study P301 and included 5706 vaccine recipients. The safety database from the other studies included 908 participants who received any dose level of mRNA-1283.

The overall safety conclusions for mRNA-1283 are sufficiently characterized by data from Study P301 and reflect the safety findings from the other 3 studies. Therefore, an integrated overview of safety is not applicable to this review.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were excluded from enrollment in clinical studies of mRNA-1283. Female participants of childbearing potential were required to practice adequate contraception for ≥28 days prior to vaccination through 90 days following vaccination and to have a negative pregnancy test prior to receipt of study vaccine. Participants were followed for outcomes for all reported pregnancies that occurred after vaccination. See Section 6.1.12.8 for summary of pregnancies reported in Study P301 and Section 6.3.12 for summary of pregnancies reported in Study P201. There were no pregnancies reported in the other 2 clinical studies of mRNA-1283.

9.1.2 Use During Lactation

Breastfeeding women were excluded from enrollment in clinical studies of mRNA-1283. Data are not available to assess the effects of mRNA-1283 on the breastfed infant or on milk production.

9.1.3 Pediatric Use and PREA Considerations

Adolescents 12 through 17 years of age were included in Study P301 and Study P301-Japan. The Applicant has addressed the Pediatric Research Equity Act (PREA) requirements for individuals 12 through 17 years of age with this BLA. For further discussion of these data, see Section 6.1 and Section 6.2.

To address PREA requirements, the Applicant has proposed the following deferred studies in individuals <12 years of age because mRNA-1283 vaccine would be ready for approval for use before such studies could be completed.

- 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 accepted by the Pediatric Review Committee (PeRC) on March 18, 2025.

9.1.4 Immunocompromised Individuals

The clinical studies of mRNA-1283 excluded enrollment of immunocompromised individuals. Data are not available on the safety and effectiveness of mRNA-1283 specifically in immunocompromised individuals.

9.1.5 Geriatric Use

Of the 5706 study participants in Study P301 who received mRNA-1283.222, 28.6% (n=1634) were ≥65 years of age and 5.6% (n=322) were ≥75 years of age. The relative vaccine efficacy

and relative immunogenicity of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent were higher in participants ≥65 years of age compared with those in adolescents and younger adult participants. Study P301-Japan included an additional 70 mRNA-1283.815 recipients ≥65 years of age. Across both Study P301 and Study P301-Japan, solicited local and systemic adverse reactions after mRNA-1283 were lower in the older adult age cohort compared with the adolescent and younger adult cohorts, and no safety concerns specific to the older adult age cohort were identified.

10. CONCLUSIONS

The primary data to support the effectiveness of mRNA-1283 are from Study P301, which evaluated the relative vaccine efficacy and immunogenicity of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent in participants 12 years of age and older who have previously received any COVID-19 vaccine. The primary efficacy objective to demonstrate the noninferior rVE of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent to prevent symptomatic COVID-19 was met, with a rVE of 9.3% (99.4% confidence interval [CI]: −6.6, 22.8), based on a median follow-up for efficacy of 8 months after vaccination. The study also met the pre-specified criteria for demonstration of noninferior immunogenicity of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent based on neutralizing antibody GMCs and SRRs against the SARS-CoV-2 strains encoded for in the vaccine. Although not powered for subgroup analyses by age, there was a trend observed of increasing rVE and relative immunogenicity with increasing age, with the highest rVE and neutralizing antibody GMC ratios observed in the ≥65 years age cohort. Data from Study P301-Japan demonstrated the noninferior immunogenicity of a monovalent formula of mRNA-1283 (mRNA-1283.815) compared with Spikevax, further supporting mRNA-1283 vaccine effectiveness.

Study P301 provided the primary data to support the safety of mRNA-1283 and included 5,706 mRNA-1283.22 recipients with a median follow-up of 8.8 months postvaccination. In general, solicited local adverse reactions were less frequently reported in participants who received mRNA-1283.222 compared with those who received Moderna COVID-19 Vaccine, Bivalent, while solicited systemic adverse reactions were reported by a similar percentage of participants across the two groups. Overall, the reported rates of unsolicited AEs, including SAEs, were comparable across the two groups. There were no SAEs or deaths assessed as related to mRNA-1283.222 by FDA. Review of safety data from studies P301-Japan, P201, and P101 did not reveal any safety concerns and supported the overall safety findings of Study P301. Although no vaccine-related cases of myocarditis or pericarditis were reported in the clinical studies of mRNA-1283, the safety database was not large enough to evaluate for rare adverse events. The Applicant will be required to conduct additional postmarketing required studies to evaluate the risk of myocarditis after mRNA-1283 vaccination.

Based on the totality of available data and the risk-benefit considerations as described in Section 11, the clinical review team concludes that the clinical data submitted in this application support approval of mRNA-1283 for the proposed indication of 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.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 39. STN 125835: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19, caused by SARS-CoV-2, has led to almost 104 million confirmed cases and approximately 1.1 million deaths in the United States alone since 2020. Globally, the impact has been even larger, with over 770 million cases and approximately 7 million deaths reported as of February 2025. • SARS-CoV-2 continues to evolve, particularly in the spike protein's receptor-binding domain. Successive waves of variants, including Delta, Omicron BA.1, BA.5, XBB.1.5, and JN.1, have demonstrated increased transmissibility and, in some cases, greater ability to evade immunity from prior infection or vaccination. The trajectory of SARS-CoV-2 continues to remain unpredictable, including the potential emergence of variants with greater immune escape or virulence. • A large proportion of the United States population has developed "hybrid immunity" through some combination of vaccination and prior infection. While this has contributed to reduced rates of severe disease, it complicates assessments of vaccine effectiveness over time. The durability of hybrid immunity and the impact of waning immune protection on future disease burden are not fully known. In vitro immunological assessments of the neutralizing antibody responses against emerging variants show increased neutralization by antibodies induced by updated vaccine formulas in both nonclinical and clinical studies.	• COVID-19 continues to pose a substantial public health threat, both from acute infections and long-term complications. • Vaccination remains a cornerstone of the public health response, with updated formulations improving neutralization of currently circulating variants. • High initial vaccine efficacy and improvements in updated vaccines support continued use and updating of vaccination strategies to maintain protection at the individual and population level. • Despite widespread hybrid immunity, ongoing viral evolution necessitates continued surveillance and flexibility in vaccine development and public health planning.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	• COVID-19 remains a serious illness, particularly for older adults and individuals with underlying health conditions. While many individuals recover within 1-2 weeks, some experience prolonged symptoms or develop post-acute sequelae known as Long-COVID, contributing to long-term morbidity. The ability of current treatments to prevent Long-COVID remains unclear. • Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; these therapeutics are more effective when taken soon after disease onset and are generally more effective against mild to moderate COVID-19 cases. The age of the patient and the presence or absence of hybrid immunity from natural infection and prior COVID-19 immunization may also affect the benefit of using these treatments for COVID-19. • The rise of new variants has been associated with an increase in breakthrough infections among vaccinated individuals. While some vaccines continue to strongly protect against severe disease and death, evidence suggests some decline in vaccine effectiveness over time. • Currently, three COVID-19 vaccines (Spikevax, Comirnaty, and Nuvaxovid) have received FDA approval for prevention of COVID-19. Additional FDA-approved vaccines are needed to expand prevention options.	• Current antiviral and therapeutic options are limited in their ability to manage severe COVID-19 and to prevent long-term complications. • There is an ongoing need for additional FDA-approved COVID-19 vaccines to diversify and strength preventive efforts.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• In a randomized, observer-blind, active-controlled Phase 3 study (P301) of approximately 11,000 participants ≥12 years of age who have received at least one prior dose of any prior COVID-19 vaccine, the pre-specified criterion for noninferior relative vaccine efficacy (rVE) of mRNA-1283.222 compared with Moderna COVID-19 Vaccine, Bivalent was met, with a rVE of 9.31% (99.4% CI: −6.6, 22.8) against symptomatic COVID-19 clinical disease over a median duration of 8 months follow-up. • In study P301, mRNA-1283.222 demonstrated noninferior immunogenicity as compared with Moderna COVID-19 Vaccine, Bivalent, based on neutralizing antibody responses against both Omicron BA.4/BA.5 and ancestral SARS-CoV-2 D614G at Day 29. The postvaccination neutralizing antibody GMTs and seroresponse rates were numerically higher among mRNA-1283.222 recipients compared with Moderna COVID-19 Vaccine, Bivalent recipients, without overlapping CIs. • In a randomized, observer-blind, active-controlled Phase 3 safety and immunogenicity study in Japan (P301-Japan) of 692 participants ≥12 years of age who have received at least one dose of any prior COVID-19 vaccine, mRNA-1283.815 demonstrated noninferior immunogenicity compared with Spikevax (2023-2024 Formula), based on neutralizing antibody responses against Omicron XBB.1.5 at Day 29. • Uncertainties in clinical benefit include: precise estimate of relative vaccine efficacy in adolescents 12 through 17 years of age, effectiveness in COVID-19 vaccine-naïve individuals, effectiveness against severe disease, durability of protection beyond 8-12 months; effectiveness in preventing asymptomatic infection or transmission, effectiveness in immunocompromised populations, and effectiveness in pregnant women.	• The evidence for clinical benefit of mRNA-1283 meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 12 years of age and older, based on noninferior relative vaccine efficacy and noninferior immunogenicity compared with an authorized/approved COVID-19 vaccine. • Data from additional studies, including ongoing follow-up and real-world evidence, are needed to address uncertainties such as the duration of protection, effectiveness against severe disease, and effectiveness in special populations (e.g., immunocompromised individuals)
Risk	• The most commonly reported adverse reactions following mRNA-1283 vaccination were injection site pain, fatigue, headache, and myalgia. These reactions were generally mild to moderate in severity, occurred within 1-2 days after vaccination, and resolved quickly. Unsolicited AEs within 28 days postvaccination and SAEs through the study duration occurred at similar rates across the mRNA-1283 and the comparator vaccine groups. There were no SAEs assessed as related to mRNA-1283 by the FDA. • Although no cases of vaccine-related myocarditis, pericarditis, or anaphylaxis were observed in the mRNA-1283 study population, these events remain recognized potential risks for the vaccine class.	• The safety and reactogenicity profile of mRNA-1283, is acceptable for its intended use of prevention against COVID-19. • Most adverse reactions were mild to moderate and of short duration. • No new or unexpected safety concerns were identified that differed from the known safety profile of other mRNA COVID-19 vaccines, including Spikevax. • Important risks recognized for mRNA COVID-19 vaccines overall, such as myocarditis, pericarditis, and anaphylaxis, will require ongoing monitoring.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Postmarketing monitoring for AEs using both passive and active surveillance systems will be used to assess for emergence of any new safety concerns.	○ Safety monitoring through active and passive surveillance systems will continue to be essential to identify rare AEs post-approval

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of mRNA-1283 in preventing symptomatic COVID-19 in individuals 12 years and older who have received a previous dose of any COVID-19 vaccine is favorable compared with potential risks associated with vaccination. In a global Phase 3 study (Study P301), a single 10-µg dose of a bivalent formulation of mRNA-1283 (mRNA-1283.222) met all pre-specified primary endpoints, demonstrating noninferior relative vaccine efficacy against symptomatic COVID-19 and noninferior neutralizing antibody responses against SARS-CoV-2 strains encoded for in the vaccine compared with Moderna COVID-19 Vaccine, Bivalent. In Study P301-Japan, the noninferior immunogenicity of a monovalent formulation of mRNA-1283 (mRNA-1283.815) was demonstrated when compared with Spikevax. The safety of mRNA-1283 is adequately described in the product's prescribing information. The Applicant's routine pharmacovigilance and the additional PMR studies to assess for the risk of myocarditis and pericarditis after vaccination are adequate for monitoring of AEs postmarketing.

11.3 Discussion of Regulatory Options

The data submitted in the BLA indicate the safety and efficacy of mRNA-1283 (mNexspike) meet the statutory requirements to support its use to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received any COVID-19 vaccine. The totality of clinical data provide evidence to support the safety and effectiveness of mNexspike with updates to the strain composition and/or valency.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of mNexspike (2024-2025 Formula) for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, and that this independent assessment of the submitted clinical data serve as the basis to support the safety and effectiveness of future periodic strain updates to mNexspike.

11.5 Labeling Review and Recommendations

The proprietary name mNexspike was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

The Applicant will be required to conduct the following postmarketing requirement (PMR) studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to assess the known serious risks of myocarditis and pericarditis:

1. 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

2. 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

The Applicant has made the following postmarketing commitment subject to reporting requirements under Section 506B:

1. 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 Completion Date: December 15, 2031
   Final Report Submission: December 15, 2032

As summarized in Section 9.1.3, the Applicant is required to conduct the following PREA deferred studies:

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-P3XX) 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

12. APPENDICES

12.1 Appendix A: Adverse Events of Special Interest (Study mRNA-1283-P301)

Adverse Events of Special Interest That Were Pre-Specified in the Protocol of Study P301

- anosmia
- ageusia
- subacute thyroiditis
- acute pancreatitis
- appendicitis

- rhabdomyolysis
- ARDS
- coagulation disorders
- acute cardiovascular injury
- acute kidney injury
- acute liver injury
- dermatologic findings (chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme, bullous rashes, severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, fixed drug eruptions, and necrotic or exfoliative reactions)
- systemic inflammatory syndromes
- thrombocytopenia
- acute aseptic arthritis
- new onset or worsening of neurological disease (e.g., immune-mediated neurological disorders, Guillain-Barre syndrome, acute disseminated encephalomyelitis, peripheral facial nerve palsy (Bell's palsy), transverse myelitis, encephalitis/encephalomyelitis, aseptic meningitis, seizures/convulsions/epilepsy, narcolepsy/hypersomnia)
- anaphylaxis, and other syndromes (e.g., fibromyalgia, postural orthostatic tachycardia syndrome, chronic fatigue syndrome, myalgic encephalomyelitis, post viral fatigue syndrome, myasthenia gravis).

12.2 Appendix B: CDC Criteria for Probable and Confirmed Cases of Myocarditis, Pericarditis, and Myopericarditis

Table 40. CDC Criteria for Probable and Confirmed Cases of Myocarditis, Pericarditis, and Myopericarditis

Condition	Probable Case Definition	Confirmed Case Definition
Acute myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms:[a] chest pain, pressure, or discomfort dyspnea, shortness of breath, or pain with breathing palpitations syncope OR infants and children aged <12 years might instead have ≥2 of the following symptoms: irritability vomiting poor feeding tachypnea lethargy AND ≥1 new finding of troponin level above upper limit of normal (any type of troponin) abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[b] abnormal cardiac function or wall motion abnormalities on echocardiogram cMRI findings consistent with myocarditis[c] AND No other identifiable cause of the symptoms and findings	Presence of ≥1 new or worsening of the following clinical symptoms:[a] chest pain, pressure, or discomfort dyspnea, shortness of breath, or pain with breathing palpitations syncope OR infants and children aged <12 years might instead have ≥2 of the following symptoms: irritability vomiting poor feeding tachypnea lethargy AND ≥1 new finding of histopathologic confirmation of myocarditis[d] cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin) AND No other identifiable cause of the symptoms and findings
Acute pericarditis[e]	Presence of ≥2 new or worsening of the following clinical features: acute chest pain[f] pericardial rub on exam new ST-elevation or PR-depression on EKG new or worsening pericardial effusion on echocardiogram or MRI	-
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	-

Source: Applicant's mRNA-1083-P301 Protocol Amendment 1, Appendix 7.
Abbreviations: AV=atrioventricular; cMRI=cardiac magnetic resonance imaging; ECG/EKG=electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Applicant. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
b. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.
c. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d. Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
e. Adler et al 2015.
f. Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur. (Gargano et al 2021).