



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Pharmacovigilance (DPV)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**To:** Joseph Kulinski, PhD  
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**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Moderna

**Product:** MNEXSPIKE (COVID-19 Vaccine, mRNA)\*

**Application Type / Number** BLA / STN 125835/0

**Proposed Indication** Active immunization to prevent COVID-19  
caused by SARS-CoV-2 in individuals 12 years  
of age and older.

**Submission Date:** September 30, 2024

**Action Due Date:** May 31, 2025

\*This product is referred to as mRNA-1283 throughout this memorandum.

## **1 OBJECTIVE**

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125835/0 based on the safety profile of MNEXSPIKE (COVID-19 Vaccine, mRNA). Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) are warranted and/or if there will be agreed-upon safety-related studies as Postmarketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for MNEXSPIKE, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

## **2 BACKGROUND**

COVID-19 is caused by the SARS-CoV-2 virus and has contributed significantly to global morbidity and mortality in the past several years. Coronaviruses, including SARS-CoV-2, are prone to high levels of genetic mutations due to the presence of an error-prone RNA-dependent RNA polymerase and the unique ability of coronaviruses to recombine to generate novel viral variants. Since the start of the pandemic, multiple SARS-CoV-2 variants have emerged and have been able to evade immunity induced by vaccines targeting prior variants or by prior natural infection.

Severe COVID-19 outcomes, such as hospitalization and death, occur with increased frequency in the elderly, those who have chronic kidney, heart, or lung disease, diabetes mellitus, obesity, or immunocompromise. In addition, long COVID has been recognized as a significant and serious consequence of symptomatic SARS-CoV-2 infection. In children, who generally have mild disease, multisystem inflammatory syndrome is a rare but serious condition associated with COVID-19 infection. Current interventions include prophylactic vaccination (including mRNA vaccines and protein subunit vaccines), antivirals, immune modulators, monoclonal antibodies, and supportive care for symptomatic infection.

MNEXSPIKE is designed using the membrane-bound, linked N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein from the SARS-CoV-2 strains. This differs from the current mRNA vaccines in that, instead of encoding the entire spike protein, it encodes only the two immune-dominant locations.

## **3 PRODUCT INFORMATION**

### **3.1 Product Description**

Each 0.2 mL dose of MNEXSPIKE contains 10 mcg nucleoside-modified messenger RNA (mRNA) encoding the subdomains of spike (RBD and NTD) protein of a SARS-CoV-2 variant lineage. Each dose also contains the following ingredients: a total lipid content of 0.2 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.09 mg tromethamine, 0.51 mg tromethamine hydrochloride, and 17 mg sucrose.

*Reviewer comment: This vaccine has so far been investigated in [REDACTED] formulations, three of which correspond to existing formulations of other mRNA vaccines marketed in the US (original, bivalent BA.4/5, and XBB.1.5), as well as [REDACTED] additional formulations.*

### 3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125835 is *active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS-CoV-2) in individuals 12 years of age and older.*

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

## 4 PERTINENT REGULATORY HISTORY

This is the first time this product has been submitted for regulatory approval in any country.

*Reviewer comment: Given that myocarditis and pericarditis are known serious risks for the current mRNA COVID-19 vaccines against SARS-CoV2, which encode for the entire spike protein, myocarditis and pericarditis are potential serious risks for this as well. This is relevant to the pharmacovigilance plan proposed for this product as well as product labeling.*

## 5 DESCRIPTION OF MNEXCOV CLINICAL TRIAL SAFETY DATABASE

### 5.1 Clinical studies

The clinical study safety data reviewed are from the Summary of Clinical Safety and the Clinical Study Reports for the relevant studies submitted to STN 125835/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125835/0 be approved. Please refer to the package insert for the final clinical safety data.

**Table 1. Summary of clinical studies supporting the safety of MNEXSPIKE**

Study	N exposed to MNEXSPIKE (dose)	Description
mRNA-1283-P301,	mRNA-1283.222 n = 5706 (10 mcg)	Phase 3 randomized, observer-blind, active-controlled study to investigate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283.222

Study	N exposed to MNEXSPIKE (dose)	Description
Part 1		<p>compared to mRNA-1273.222 (bivalent vaccine targeting Omicron BA.4/5 and original SARS-CoV-2).</p> <p>Study population: previously vaccinated individuals 12 years and older.</p>
mRNA-1283-P301, Japan	mRNA-1283.815 n = 343 (10 mcg)	<p>Phase 3 randomized, observer-blind, active-controlled study to investigate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283.815 compared to mRNA-1273.815 (monovalent vaccine targeting XBB.1.5 variant).</p> <p>Study population: Japanese participants 12 years and older</p>
mRNA-1283-P201	<p>Part A mRNA-1283 n = 57 (2.5 mcg) n = 63 (5 mcg) n = 56 (10 mcg)</p> <p>mRNA-1283.211 n = 53 (5 mcg) n = 54 (10 mcg)</p> <p>Part B mRNA-1283.529 n = 103 (5 mcg) n = 97 (10 mcg)</p>	<p>Phase 2a observer-blind, dose-ranging, single-dose study with two parts.</p> <p>Study population: Previously vaccinated healthy adults 18 years and older</p> <p>Part A: comparison of single dose of mRNA-1283 (original monovalent) or mRNA-1283.211 (bivalent vaccine candidate composed of equal amounts of 2 mRNAs; one encoding the linked RBD-NTD of the Spike protein of the original SARS-CoV-2 and the other mRNA encoding for the Spike protein of B.1.351 (Beta)), with active comparator mRNA-1273.</p> <p>Part B: open-label study that evaluated mRNA-1283.529 (monovalent mRNA-1283 vaccine candidate encoding the linked RBD-NTD of the Spike protein of Omicron B.1.1.529) with no comparator group</p>
mRNA-1283-P101	<p>Arm 1 n = 21 (2 doses, 10 mcg)</p> <p>Arm 2 n = 22 (2 doses, 30 mcg)</p> <p>Arm 3 n = 21 (2 doses, 100 mcg)</p> <p>Arm 4</p>	<p>Phase 1, randomized, observer-blind, dose-ranging study, investigating mRNA-1283 (initial monovalent). Single dose (arm 4) or 2 doses administered 28 days apart (arms 1-3), with comparator mRNA-1273, 2 doses (arm 5)</p> <p>Study population: unvaccinated adults aged 18-55 years</p>

Study	N exposed to MNEXSPIKE (dose)	Description
	n =18 (placebo + one dose 100 mcg)	

\*Adapted from Table 1, Core Risk Management Plan, STN 125835, Module 1.16.1

*Reviewer Comment: In total, the safety set constitutes 6614 individuals exposed to various doses and formulations of this vaccine product. Even if all individuals had been exposed to a single dose and formulation, the safety set would not be able to detect adverse events with a frequency of less than 1/1,000. This is mentioned in the limitations listed by the Sponsor in the Core Risk Management Plan. One of the Sponsor's stated anticipated benefits of this vaccine over the existing mRNA vaccines is that there is no creation of circulating Spike-S1 protein, which is hypothesized to mediate post-vaccination myocarditis/pericarditis. The number of individuals exposed to mRNA-1283 formulations within existing clinical studies is currently inadequate to determine whether this benefit is realized.*

## 5.2 Adverse events

Clinical Study mRNA-1283-P301 is the pivotal phase 3 study and all participants received the labeled dose of vaccine (10 mcg), using the bivalent formulation. Clinical Study mRNA-1283-P301, Japan is a second part of this study, using the labeled dose, but with the 2023-2024 formulation. Adverse events in these two studies will be described fully, and relevant additional information from the other studies in the safety database will be included.

### 5.2.1 Clinical study mRNA-1283-P301

i) Most common AEs: Solicited local AEs were mildly lower in the mRNA-1283.222 group at 70.3% (CI: 69.1 – 71.5) versus the mRNA-1273.222 group at 78.4% (CI: 77.3 – 79.5). However, solicited systemic AEs were similar in both groups. In both groups the most frequently reported local AE was injection site pain and the most frequently reported systemic AEs were fatigue and headache. Most of the adverse reactions were Grade 1 and 2 in severity. The incidence of unsolicited AEs was similar in both groups until day 28 after vaccination as well as until data cutoff. The most common unsolicited AEs in both groups were in the infections and infestations SOC. Specifically, upper respiratory tract infections were the most frequently reported PT, and the only PT reported in more than 1% of participants in either group.

ii) SAEs: The incidence of SAEs was similar in both groups through 28 days after vaccination (0.2% mRNA-1283.222 versus 0.3% mRNA-1273.222) and through data cutoff (2.7% mRNA-1283.222 versus 2.6% mRNA-1273.222).

Significant SAEs among the mRNA-1283.222 recipients include:

- A 41-year-old white female had a possible anaphylactic reaction 18 hours after vaccination. The Investigator considered this a possible delayed anaphylaxis, related to vaccination.
- A 37-year-old Asian male with HLA-B27 antigen and a history of TB exposure 10-14 years prior had acute septic arthritis on day 56 after vaccination. Initial TB culture was negative with one result pending. Rheumatology consultation resulted in treatment regimen for TB as well as disease modifying antirheumatic drug for possible ankylosing spondylitis. The Investigator assessed the event as related to study vaccine. The Sponsor assessed the events as unlikely related to study vaccine based on long latency, worsening course, and other possible etiologies.
- A 55-year-old developed polycythemia vera on day 67, which led to study discontinuation. This was assessed by the Investigator and Sponsor as not related to study vaccination.
- A 68-year-old white female had a suicide attempt on day 55, which led to study discontinuation. This was assessed by the Investigator and Sponsor as not related to study vaccination.
- A 69-year-old white female with a history of gastroesophageal reflux, was diagnosed with metastatic gastric cancer on day 99. This was assessed by the Investigator and Sponsor as not related to study vaccination.

*Reviewer comment: The Preferred Terms for SAEs were reviewed, and there were no trends or imbalances noted, overall or by age group (adolescents, adults  $\geq 18$ -<65,  $\geq 65$  years).*

iii) Deaths: There were a total of 15 deaths, of which five occurred in participants exposed to mRNA-1283.222. These were assessed as not related to study vaccination by the Investigator and Sponsor.

- a) 67-year-old white male, sudden death due to ruptured myocardial infarction and hemopericardium on study day 149. There had been a long history of epilepsy on phenytoin and levetiracetam but no prior cardiac issues or other known risk factors.
- b) 91-year-old white male with pre-existing COPD, death secondary to respiratory failure on study day 82
- c) 60-year-old African American male, with history of chronic heart failure, severe tricuspid regurgitation, coronary artery disease, status post recent percutaneous coronary intervention (PCI), left ventricle thrombus on apixaban, hypertension, chronic kidney disease stage 3, dilated cardiomyopathy, obesity, substance use (cocaine use), who had an acute myocardial infarction on day 156. After multiple subsequent episodes of acute heart failure, a cardiac arrest on day 251 resulted in death.
- d) 16-year-old white male, death on day 248 by homicide.
- e) 76-year-old white male, cardiac arrest and death on day 160. There was a previous history (since 2008) of hypertension, hyperlipidemia, cardiac failure, type 2 diabetes mellitus, and a cardiac pacemaker insertion in 2013.

One death occurred in a participant who received mRNA-1273.222 (Spikevax) and was assessed as related to vaccine by the Investigator due to temporality. This occurred on day 7 in a participant with significant cardiac history, whose cause of death was reported as unknown.

*Reviewer comment: The deaths among participants who were exposed to MNEXSPIKE were reviewed individually. All the participants had a long period of latency, had significant risk factors contributing to death, or had circumstances of death clearly unrelated to vaccine exposure.*

iv) Adverse events of special interest (AESIs): There were no myocarditis or pericarditis events in either group within 28 days post-injection or up to the data cutoff. Two participants had AESIs after receiving other off-study vaccines. The first participant in the mRNA-1283.222 group had Guillain-Barre Syndrome (GBS) with onset day 164, 13 days after receiving COVID-19 vaccination (tozinameran), RSV, and Pevnar vaccines. The second participant in the mRNA-1283.222 group had GBS with onset at day 269, and had received influenza vaccine on day 99, RSV vaccine on day 101, and an off study elasomeran vaccine on day 127. Both these cases were assessed as not related to study vaccine by the Investigator.

v) Safety in pregnancy: There were three pregnancies in the mRNA-1283.222 group that were pending outcomes at the time of the data lock point. In a response to an IR submitted to STN125835/0.27, the Sponsor stated that the three pregnancies in the mRNA-1283 group resulted in full-term births without complications.

## **5.2.2 Clinical study mRNA-1283-P301, Japan**

i) Most common AEs: Solicited local AEs were lower in the mRNA-1283.815 group at 86.3% (CI: 82.2 – 89.8) versus the mRNA-1273.815 group at 95.1% (CI: 92.2 – 97.1). However, solicited systemic AEs were similar in both groups. In both groups the most frequently reported local AE was injection site pain and axillary swelling or tenderness. The most frequently reported systemic AEs were fatigue and headache. The incidence of unsolicited AEs was similar in both groups until day 28 after vaccination as well as until data cutoff. The most common unsolicited AEs in both groups were in the infections and infestations SOC. Specifically, nasopharyngitis was the most frequently reported PT, and the only PT reported in more than 1% of participants in either group. Most of the adverse reactions were Grade 1 and 2 in severity.

ii) SAEs: There were no SAEs reported in this study in either vaccine group.

iii) Deaths: There were no deaths in this study in either vaccine group.

iv) Adverse events of special interest (AESIs): There were no myocarditis or pericarditis events or other AESIs in either group up to the data cutoff.

*Reviewer comment: The common and serious AEs are detailed in the pivotal studies (mRNA-1283-P301, and mRNA-1283-P301, Japan). Studies mRNA-1283-P201 and mRNA-1283-P101 are non-pivotal studies. The safety data from these studies was reviewed and the safety profile was similar to that in the pivotal studies. The common AEs for all the studies are related to reactogenicity. One serious event of delayed anaphylactic reaction is noted in study mRNA-1283-P301, which is a known AE for mRNA COVID-19 vaccines. The deaths are assessed as unrelated to study vaccination with alternate causes of death and long latencies. No myocarditis or pericarditis events occurred in any of the studies; however, the total number of participants exposed in all the studies would not be adequate to detect any adverse event with a frequency of <1/10,000.*

## 6 SPONSOR'S PHARMACOVIGILANCE PLAN

**Table 2. Sponsor's Pharmacovigilance Plan\***

Type of Concern	Safety Concern	Proposed Action
Identified	none	
Potential	Myocarditis	Routine pharmacovigilance Myocarditis/pericarditis questionnaire Expedited reporting to VAERS regardless of seriousness or label status Summary and analysis in periodic safety reports Ongoing Phase 3 study mRNA-1283-P301, parts 1, 3 Ongoing Phase 3 study mRNA-1283-P301, Japan Planned postmarketing retrospective US cohort study (mRNA-1283-P901) Planned postmarketing study for long-term followup of myocarditis (mRNA-1283-P904)
Potential	Pericarditis	Routine pharmacovigilance Expedited reporting to VAERS regardless of seriousness or label status Summary and analysis in periodic safety reports Ongoing Phase 3 study mRNA-1283-P301, parts 1, 3 Ongoing Phase 3 study mRNA-1283-P301, Japan Planned postmarketing retrospective database US cohort study (mRNA-1283-P901)
Missing	Use in pregnancy	Routine pharmacovigilance Planned postmarketing retrospective database US cohort study (mRNA-1283-P902)
Missing	Long-term safety	Routine pharmacovigilance Ongoing Phase 3 study mRNA-1283-P301, parts 1, 3 Ongoing Phase 3 study mRNA-1283-P301, Japan Planned postmarketing retrospective US cohort study (mRNA-1283-P901)

		Planned postmarketing study for long-term followup of myocarditis (mRNA-1283-P904)
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\*Adapted from Tables 24, 25, and 29, Core Risk Management Plan submitted to STN125835/0 and STN125835/0.27, Module 1.16.1

Routine pharmacovigilance includes adverse reaction reporting and signal detection.

*Reviewer comment: The planned post-marketing studies for myocarditis, pericarditis, and safety in pregnancy were added to the PVP in a response to an IR submitted to STN125835/0.27.*

## 6.1 Enhanced Pharmacovigilance

The Sponsor will perform enhanced pharmacovigilance activities for myocarditis and pericarditis for three years post-approval including expedited reporting to VAERS regardless of seriousness or label status and a summary and analysis in periodic safety reports.

*Reviewer comment: The Sponsor agreed to FDA's requested enhanced pharmacovigilance activities in a response to an IR submitted to STN125835/0.35.*

## 6.2 Study mRNA 1283-P901 “Postmarketing safety of the mRNA-1283 vaccine in the United States”

### Primary Objectives:

- Describe the uptake of mRNA-1283 and characterize vaccine recipients
- Estimate the incidence of myocarditis and pericarditis among recipients of mRNA-1283
- Assess the risk of myocarditis and pericarditis using large-scale administrative claims data in the US, comparing the risk among the recipients of mRNA-1283 with the risk observed in persons who have not received a vaccine targeting SARS-CoV-2 within 90 days

### Secondary Objectives:

- Estimate the incidence of other safety topics of interest among recipients of mRNA-1283
- Assess the risk of other safety topics of interest using large-scale administrative claims data in the US, comparing the risk among the recipients of mRNA-1283 with the risk observed in persons who have not received a vaccine targeting SARS-CoV-2 within 90 days
- Where feasible, assess the risk of myocarditis, pericarditis, and other safety topics of interest among the following subgroups,
  - o Immunocompromised individuals
  - o Individuals of different age group and sex
  - o Individuals who were co-administered other selected vaccines to prevent diseases other than SARS-CoV-2 (e.g., influenza vaccine, RSV vaccine)

- Assess the risk of myocarditis, pericarditis, and other safety topics of interest using a self-control risk interval design when necessary analytic conditions are met.

*Reviewer comment: In an IR submitted to STN 125835/0.13 on January 24, 2025, the Sponsor clarified that though there were no primary or secondary objectives related to long-term safety, since the study is being conducted over three respiratory seasons, participants will be observed for up to three years.*

#### Study Design:

This retrospective US cohort study will actively monitor safety outcomes following administration of mRNA-1283 among individuals enrolled in commercial and Medicare claims databases. The study will descriptively monitor the utilization of mRNA-1283 and inferentially assess the risk of myocarditis, pericarditis and other safety topics of interest in recipients of these vaccines.

#### Study Population:

Exposed persons are defined as those who receive mRNA-1283 in routine clinical practice, and the cohort entry/index date will be the date of receipt. The comparator cohort will consist of both inactive and active comparators, which will be selected based on vaccine coadministration status and the specific vaccine(s) that are co-administered with mRNA-1283. Comparator index dates will be matched to the index dates of exposed individuals (i.e., the date of mRNA-1283 vaccination):

- For mRNA-1283 vaccine recipients with no co-administered vaccines, persons with  $\geq 1$  healthcare encounter for preventive care 365 days prior to and including the match day and no vaccinations on the match day will be eligible for selection as inactive comparators.
- For mRNA-1283 vaccine recipients with other vaccines co-administered on the same day, persons who have received the same other vaccine(s) without receiving a vaccine targeting SARS CoV-2 on the same calendar date will be eligible for selection as active comparators.

All eligible individuals will have >365 days of continuous medical and pharmacy claims enrollment prior to and including the index date, non-missing sex and age, and no vaccinations targeting SARS CoV-2 within 90 days prior to the index date. When assessing each individual safety topic of interest, individuals with a history of the specific safety topic of interest will be excluded in accordance with an outcome-specific washout window.

*Reviewer comment: The Sponsor was requested to provide an estimate of the sample size for Study mRNA-1283-P901. In a response to an IR submitted to STN125835/0.35, the Sponsor stated they will include all eligible individuals from data sources deemed fit-for-purpose. As vaccine uptake is unknown at this time, the Sponsor states a precise sample size cannot be determined at this time. The Sponsor's response is acceptable.*

Variables:

The exposure of interest will be defined as receipt of a dose of mRNA-1283 in routine clinical practice during the study period, identified via National Drug Code (NDC), Common Procedural Terminology (CPT), and/or Healthcare Common Procedure Coding System (HCPCS) codes.

Outcomes of interest include the following incident safety topics of interest, identified via International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes utilizing validated algorithms where available.

Primary safety topics of interest:

- Myocarditis
- Pericarditis

Secondary safety topics of interest:

- Neurological outcomes
  - o Acute disseminated encephalomyelitis
  - o Bell's palsy
  - o Guillain-Barré Syndrome
  - o Transverse myelitis
- Cardiovascular outcomes
  - o Acute myocardial infarction
  - o Atrial fibrillation
- Thromboembolic outcomes
  - o Venous thromboembolism
  - o Stroke, non-hemorrhagic
- Other outcomes
  - o Stroke, hemorrhagic
  - o Anaphylaxis
  - o Myositis
  - o Single organ cutaneous vasculitis

Additional safety topics of interest may be added during the study as identified by the Sponsor, based on literature reports, regulator inquiries, or other surveillance systems.

Covariates of interest include demographics, baseline comorbidities including immunocompromised status, baseline co-medications including use of other vaccines, and baseline healthcare utilization. Covariates will be identified through ICD-10-CM, NDC, and/or CPT/HCPCS codes. Validated algorithms will be utilized where available.

Data Sources: May include:

- Blue Health Intelligence (BHI) commercial claims for persons aged <65 years old
- Optum Clinformatics DataMart (CDM) including commercial claims for persons aged <65 years old
- Medicare Advantage claims for persons aged ≥65 years old
- Humana Medicare Advantage claims for persons aged ≥65 years old, and

- Fee for Service Medicare parts A, B, and D.

*Reviewer comment: The Sponsor states that fit-for-purpose data sources will be selected for use in this study at the point of protocol development. The Sponsor was requested to clarify what criteria will be used for selection of data sources. In a response to an IR submitted to STN125835/0.27, the Sponsor states that data sources should allow for detection of individuals with at least 365 days of continuous enrollment for baseline analysis. Data sources should have quality assurance and control measures. Data lag times will also be considered. The Sponsor's response is acceptable.*

#### Data Analyses:

- Analyses will be conducted within each database, and results will be pooled through a meta-analysis when appropriate.
- Descriptive analyses will characterize vaccine recipients and estimate incidence rate per 100,000 person-years (with a 95% CI) of each safety topic of interest.
- Propensity score will be estimated using a multivariable logistic regression model, from which inverse probability of treatment weights will be calculated.
- Cox proportional hazards regression will then be used to evaluate the association between the exposure to the vaccine and each safety topic of interest.
- Subgroup analyses will be conducted when sample size allows.
- As a secondary analysis, potential signals will be further evaluated using self-controlled risk interval analyses when thresholds are met.

The sponsor proposed the following milestones:

- Final protocol submission: June 30, 2025
- Study completion date: May 31, 2028
- Final study report (FSR) submission: September 30, 2028

*Reviewer comment: The above milestones were confirmed in a response to an IR submitted to STN125835/0.27.*

### **6.3 Study mRNA-1283-P904 Long-term outcomes of myocarditis following administration of the mRNA-1283 vaccine**

#### Primary Objectives:

- To characterize the presentation and clinical course of vaccine-associated myocarditis
- To characterize the potential long-term outcomes following vaccine-associated myocarditis

#### Secondary Objectives:

- To compare presentation, clinical course, and long-term outcomes following vaccine-associated myocarditis with those of non-vaccine myocarditis

### Study Design:

This is an observational, retrospective cohort study in which patients with myocarditis will be followed for at least five years to determine the long-term outcomes of vaccine-associated myocarditis compared to non-vaccine myocarditis.

*Reviewer comment: In an IR response submitted to STN125835/40, the Sponsor agreed to change the followup of myocarditis cases from “up to” to “at least” five years of followup.*

### Study Population:

This study will use administrative claims data and medical records from health systems. The exposed cohort will include individuals diagnosed with myocarditis within 30 days of mRNA-1283 vaccination. The comparison group will comprise contemporaneous sex and age matched myocarditis patients who did not receive a COVID-19 vaccine within 30 days of diagnosis.

*Reviewer comment: The Sponsor was requested to provide an estimated sample size for study mRNA-1283-P904. In a response to an IR submitted to STN125835/0.35, the Sponsor stated that it is not feasible to estimate a sample size because vaccine uptake is unknown at this time. Instead, the Sponsor plans to include all eligible cases during the study period. The Sponsor’s response is acceptable.*

### Variables:

NDCs, CPTs, and HCPCS will be used to identify mRNA-1283 receipt.

### Outcomes of interest

An adjudication committee of cardiologists for myocarditis case ascertainment will be used. Additional outcomes of interest will include the following:

- Acute myocardial infarction
- Acute coronary syndrome
- Stroke
- Systemic embolism
- Hospitalization for heart failure, cardiomyopathy, arrhythmia, or myocarditis recurrence.
- Cardiac MRIs for late gadolinium enhancement will be evaluated as feasible

### Covariates of interest

Covariates will include demographics, comorbidities, medications, receipt of other vaccines, and general healthcare utilization. ICD-10-CM, NDC, CPT, HCPS codes will be used for covariate identification.

### Data Sources:

The Sponsor anticipates the use of large administrative healthcare databases with options for obtaining medical records with specification at protocol development.

#### Data Analyses:

The first stage of analysis will evaluate mRNA-1283 uptake and myocarditis cases. The second state of analysis will link cases adjudicated as confirmed myocarditis with medical records with follow-up for five years.

The clinical course for myocarditis cases by exposure status will be described, including procedures, outcomes, healthcare utilization, and other cardiac events during follow-up. Summary statistics such as the mean, standard deviation, median, and interquartile range will be used for continuous variables. Counts and proportions will be used for categorical variables. The relative risk for long-term outcomes among exposed cases compared to comparator cases will be assessed by regression models.

The sponsor proposed the following milestones:

- Final protocol submission: November 30, 2025
- Study completion date: March 31, 2033
- Final study report (FSR) submission: March 31, 2034

*Reviewer comment: The Sponsor was requested to propose a post-market safety study to evaluate the potential for long-term sequelae of myocarditis after vaccination with five years of follow-up with the suggestion to evaluate for persistent late gadolinium enhancement using cardiac MRI. The Sponsor proposed study mRNA-1283-P904 in a response to an IR submitted to STN125835/0.27.*

*The Sponsor originally proposed March 31, 2026 for the Final Protocol Submission. FDA requested a protocol submission date closer to anticipated product approval. In a response to an IR submitted to STN125835/0.35, the Sponsor proposed November 30, 2025 as the Final Protocol Submission because this study requires the use of multiple data sources with medical record review, which will take some time for feasibility assessment. The Sponsor's response is acceptable.*

*The study milestones were further revised in an IR response submitted to STN125835/0.40 to allow a two-year data collection period with adequate follow-up time. The Sponsor also provided dates for interim report submissions, which will occur annually from June 30, 2027 to June 30, 2032. The Sponsor response is acceptable.*

*The sponsor submitted draft study protocols to evaluate the known serious risks of myocarditis and pericarditis, and the long-term sequelae of myocarditis after vaccination with five years of follow-up. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the Important Risk of myocarditis and pericarditis.*

*The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to assess the serious risks of myocarditis and pericarditis following vaccination with*

*MNEXSPIKE in lieu of a postmarketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, [Postmarketing Studies and Clinical Trials—Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#), this determination “takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).” At this time, the data sources in the CBER BEST Program are not sufficient to identify the safety outcomes due to uncertainties in vaccine uptake in the post-approval period. Of note, the BEST Program does not include foreign data sources. Should there be future use of the product outside U.S., then the Sponsor may access foreign data sources in addition to U.S. data sources, for assessment of such rare serious risks. A finding of insufficiency based on uncertainty at the time of approval is consistent with current Guidance.*

*Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, if MNEXSPIKE is approved, the Sponsor will be required to conduct PMR safety studies under FDAAA Title IX to characterize the Important Risk of myocarditis and pericarditis.*

*DPV presented the PMRs to the CBER Safety Working Group (SWG) on March 27, 2025 and the Sponsor was notified that the post-marketing studies will be PMRs on April 11, 2025 (acknowledged in IR response submitted to STN125835/0.43).*

#### **6.4 Study mRNA 1283-P902 “An Observational Cohort Study to Assess Maternal and Infant Outcomes Following Exposure to mRNA-1283 During Pregnancy”**

##### Primary Objectives:

- 1) To describe the utilization of the mRNA-1283 vaccine in routine clinical practice and estimate incidence rates of pregnancy complications (gestational hypertensive disorders and gestational diabetes), adverse pregnancy outcomes (medically attended spontaneous abortion, stillbirth, and preterm birth), and infant major congenital malformations among mRNA-1283 vaccine recipients using large-scale administrative claims data in the US.
- 2) Upon accrual of a sufficient number of exposed pregnancies (defined as sample size with 80% power to detect an effect estimate of 2.5 with 1:4 matching):
  - a. To assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of pregnancy complications.
  - b. To assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of adverse pregnancy outcomes.
  - c. To assess whether exposure to mRNA-1283 during pregnancy is associated with an increased prevalence of infant major congenital malformation (MCM).

### Secondary Objectives:

- 1) To estimate the incidence of infant hospitalization due to COVID-19 in the first 6 months of life among mRNA-1283 vaccine recipients.
- 2) To assess whether exposure to mRNA-1283 during pregnancy is associated with a change in the rate of infant hospitalization due to COVID-19 in the first 6 months of life.

### Study Population:

A defined population of pregnant women and their linked infants from a large administrative database.

#### Exclusion criteria:

- a) Lack of an adequate database enrollment period
- b) Known exposure to major teratogenic infections or medications

### Data Collection:

Exposures and study outcomes will be identified using relevant ICD, CPT, and NDC codes in the administrative database.

### Data Analysis:

#### Stage one: uptake monitoring

Monitor accrual of eligible study participants by identifying the number of mRNA-1283-exposed pregnancies meeting study entry criteria. The rate of each study outcome (gestational hypertensive disorders, gestational diabetes, medically attended spontaneous abortion, stillbirth, preterm birth, major congenital malformations, and infant hospitalization due to COVID-19), described as proportion of pregnancies affected for pregnancy complications and outcomes, birth prevalence for major congenital malformation, and incidence for infant hospitalization due to COVID-19, will be estimated.

#### Stage 2: accrual of a sufficient number of exposed pregnancies to detect a risk ratio of 2.5 with 80% power (defined at an outcome specific level)

Comparative analyses using a sequential matched cohort design that aligns cohort entry by gestational week. Pregnancies exposed to mRNA-1283 will be matched to unexposed pregnancies based on maternal age, gestational week of mRNA-1283 vaccination, calendar time at cohort entry, and propensity score.

The sponsor proposed the following milestones:

- Final protocol submission: August 31, 2025
- Study completion date: December 15, 2031
- Final study report (FSR) submission: December 15, 2032

*Reviewer comment: The Sponsor submitted the protocol synopsis for Study mRNA-1283-P902 to STN125835/0.27. The Sponsor has not yet defined which administrative database will be used; however, it is expected that this will be part of the final protocol*

*submission. Because it is not known at this time what the uptake of this new vaccine will be, this staged approach is acceptable.*

*The Sponsor originally proposed a Final Protocol Submission date of December 15, 2025, which is prolonged relative to anticipated product approval. The Sponsor agreed to move up the Final Protocol Submission date to August 31, 2025 in a response to an IR submitted to STN125835/0.35.*

*The Sponsor was notified of this Postmarketing Commitment on April 11, 2025 (acknowledged in IR response submitted to STN125835/0.43).*

## **7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN**

### **7.1 Important Identified Risks**

There were no important identified risks included in the pharmacovigilance plan for this vaccine product.

*Reviewer comment: Based on review of the pivotal Phase 3 study data, there were no significant trends or imbalances with regard to SAEs, AESIs or deaths.*

### **7.2 Important Potential Risks**

#### **7.2.1 Risk 1: Myocarditis**

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

*Reviewer comment: The following are planned to minimize the risk of myocarditis in recipients of mRNA-1283, as well as to further characterize and quantify the risk.*

- Enhanced pharmacovigilance activities including expedited reporting to VAERS regardless of seriousness or label status, and a summary and analysis in periodic safety reports based on interval and cumulative data.*
- Myocarditis is included in the Special Warnings and Precautions section of the USPI; proposed sponsor draft language as follows: "Increased risks of myocarditis and pericarditis have been observed with authorized or approved COVID-19 vaccines, particularly within the first week following vaccination with the observed risk highest in males 12 through 24 years of age, particularly within the first week following vaccination with the observed risk highest in males 12 through 24 years of age". Please see section below on ongoing regulatory action for class safety labeling change (SLC) for mRNA COVID-19 vaccines.*
- Study mRNA-1283-P301 and Study mRNA-1283-P301, Japan are ongoing studies and will continue to evaluate adverse events, including myocarditis*

- *Post-marketing study mRNA-1283-P901 will evaluate myocarditis after receipt of vaccination.*
- *Post-marketing study mRNA-1284-P904 will evaluate long-term outcomes of myocarditis with five years of follow-up.*

*At this time, routine pharmacovigilance, enhanced pharmacovigilance, ongoing clinical trials, and post-marketing studies are adequate to evaluate the risk of myocarditis in recipients of MNEXSPIKE.*

### **Class safety labeling change (SLC) for new safety information (NSI)**

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and licensed biological product applications to make safety-related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

In a safety labeling change (SLC) notification letter dated April 17, 2025, under STN 125752/272, FDA notified Moderna of class SLC for mRNA COVID-19 vaccines including Moderna COVID-19 Vaccine (SPIKEVAX). FDA has become aware of the following: (1) data from the Biologics Effectiveness and Safety System on the estimated incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines, and (2) results from a postapproval study<sup>1</sup> in patients with COVID-19 vaccine-associated myocarditis showing persistence of abnormal cardiac magnetic resonance imaging findings that are a marker for myocardial injury at a median follow-up of approximately 5 months. FDA considers this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA. Please see the SLC notification letter under STN 125752/272 for specific labeling language to include NSI in the labeling under Warnings and Precautions – Myocarditis and Pericarditis, Adverse Reactions – Postmarketing Experience, References, Patient Package Insert.

The above NSI and SLC is pertinent to the serious risk of myocarditis following MNEXSPIKE. Please see the final version of the USPI for the agreed upon language.

*Reviewer comment: The Sponsor submitted a response to STN125835/0.55 regarding the labeling changes detailed in the SLC notification letter. Labeling negotiations are underway and will be detailed in a separate memorandum.*

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<sup>1</sup> Jain SS, Anderson SA, Steele JM, et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study. Lancet. 2024;76:1-13.  
<https://doi.org/10.1016/j.eclinm.2024.102809>

### 7.2.2 Risk 2: Pericarditis

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

*Reviewer comment: The following are planned to minimize the risk of pericarditis in recipients of mRNA-1283, as well as to further characterize and quantify the risk.*

- Enhanced pharmacovigilance activities including expedited reporting to VAERS regardless of seriousness or label status, and a summary and analysis in periodic safety reports based on interval and cumulative data.*
- Pericarditis is included in the Special Warnings and Precautions section of the USPI: "Increased risks of myocarditis and pericarditis have been observed with authorized or approved COVID-19 vaccines, particularly within the first week following vaccination with the observed risk highest in males 12 through 24 years of age, particularly within the first week following vaccination with the observed risk highest in males 12 through 24 years of age."*
- Study mRNA-1283-P301 and Study mRNA-1283-P301, Japan are ongoing studies and will continue to evaluate adverse events*
- Post-marketing study mRNA-1283-P901 will evaluate pericarditis after receipt of vaccination.*

*At this time, routine pharmacovigilance, enhanced pharmacovigilance, ongoing clinical trials, and post-marketing studies are adequate to evaluate the risk of pericarditis in recipients of MNEXSPIKE.*

## 7.3 Important Missing Information

### 7.3.1 Missing Information 1: Use in pregnancy.

In the safety dataset, three participants in Study mRNA-1283-P301 were exposed to MNEXSPIKE during pregnancy, all of which resulted in full-term births with no complications (response to IR submitted to STN125835/0.27). All three pregnancies were pending outcomes at the time of the data cutoff date of May 6, 2024. There were no pregnancies reported in studies mRNA-1283-P301/Japan, mRNA-1283-P201, and mRNA-1283-P101.

*Reviewer comment: Since the age indication for this product includes women of child-bearing age, the Sponsor was asked to propose a post-marketing study to evaluate the safety of mRNA-1283 in pregnancy. In an IR response submitted to STN 125835.0.13 on January 24, 2025, the Sponsor proposed an observational cohort study assessing maternal and infant outcomes following exposure to mRNA-1283 during pregnancy. This study is detailed in section 6.2 earlier in this memo.*

### 7.3.2 Missing Information 2: Long-term safety

The median and maximum follow-up time after receipt of mRNA-1283 in the four studies is listed below in Table 3.

**Table 3: Followup Times after Exposure to MNEXSPIKE in Clinical Studies**

Study ID	Number of participants	Median Follow-up	Maximum Follow-up
mRNA-1283-P101	82 (all doses)	397 days	768 days
mRNA-1283-P201 part A	283 (all doses and formulations)	359-365 days	434 days
mRNA-1283-P201 part B	200 (all doses)	359-360 days	378 days
mRNA-1283-P301	5706	8.772 months	10.68 months
mRNA-1283-P301, Japan	343	36 days	49 days

Adapted from:

Table 8, Final Clinical Study Report, Study mRNA-1283-P101

Tables 14.1.6.1 and 14.1.6.2, Final Clinical Study Report, Study mRNA-1283-P201

Table 13, Final Clinical Study Report, Study mRNA-1283-P301

Table 9, Final Clinical Study Report, Study mRNA-1283-P301, Japan

Submitted to STN 125835/0 Module 5.3.5.1 on September 30, 2024.

*Reviewer comment: To date, the maximum observed time after exposure to any formulation of mRNA-1283 has been less than a year. There have not been long-term adverse effects noted thus far. The observation time of up to three respiratory seasons in the proposed postmarketing study mRNA-1283-P901 will provide additional information about any additional long-term adverse effects. Study mRNA-1283-P901 will provide five years of follow-up of myocarditis cases.*

*The planned pharmacovigilance activities are acceptable for evaluation of safety of MNEXSPIKE.*

## 8 DPV ASSESSMENT

In the clinical trials to date, adverse events have all been consistent with reactogenicity. Though there have been no consistent serious adverse events, the safety dataset is small. The pharmacovigilance activities, including the described PMR study evaluating vaccine-associated myocarditis and pericarditis, the long-term follow-up of myocarditis PMR study, and the described PMC study evaluating safety in pregnancy will be adequate to evaluate safety of MNEXSPIKE on an ongoing basis.

## 9 DPV RECOMMENDATIONS

Should MNEXSPIKE be approved for the indication of active immunization against SARS-CoV-2 in ages 12 years and older, the proposed PVP, version 2.0, dated March 6, 2025, including the following activities is adequate to monitor post-marketing safety of MNEXSPIKE.

- Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
- Expedited reporting to VAERS and sponsor assessments for myocarditis and/or pericarditis in the periodic safety reports
- Postmarketing Requirement for a safety-related study for evaluation of vaccine-associated myocarditis and pericarditis (Study mRNA-1283-P901)
- Postmarketing Requirement for long-term outcomes of myocarditis (Study mRNA-1283-P904)
- Postmarketing Commitment for a safety-related study for pregnancy (Study mRNA-1283-P902)

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

## APPENDIX

**Table A1: Materials reviewed in support of this assessment**

<b>Date</b>	<b>Source</b>	<b>STN</b>	<b>Document(s) Reviewed</b>
Sept 30, 2024	Sponsor	125835/0	Module 1.16.1, Risk Management Plan
Sept 30, 2024	Sponsor	125835/0	Module 5.3.5.1, Study mRNA-1283-P301
Sept 30, 2024	Sponsor	125835/0	Module 5.3.5.1, Study mRNA-1283-P201
Sept 30, 2024	Sponsor	125835/0	Module 5.3.5.1, Study mRNA-1283-P101
Jan 24, 2025	Sponsor	125835/0.13	Module 1.11.3 Response to IR dated January 10, 2025
March 7, 2025	Sponsor	125835/0.27	Module 1.11.3 Response to IR dated February 20, 2025 Module 1.16 Revised Risk Management Plan, version 2.0, dated March 6, 2025 Module 5.3.6, Studies P901, P902, and P904
March 21, 2025	Sponsor	125835/0.35	Module 1.11.3 Response to IR
April 4, 2025	Sponsor	125835/0.40	Module 1.11.3 Response to IR Module 5.3.6 Revised study mRNA-1283-P904
April 18, 2025	Sponsor	125835/0.43	Module 1.11.4 Sponsor acknowledgement of PMR and PMC notification
May 8, 2025	Sponsor	125835/0.55	Module 1.11.3 Response to myocarditis/pericarditis labeling changes