Summary Basis for Regulatory Action

Date:	01/30/2022
From:	Sudhakar Agnihothram, PhD, Review Committee Chair, DVRPA/OVRR
BLA/NDA STN:	STN 125752/0
Applicant:	ModernaTX Inc.
Submission Receipt Date:	August 24, 2021
PDUFA Action Due Date:	April 24, 2022
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	SPIKEVAX
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

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

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
Chemistry Manufacturing and Controls (CMC)	
CMC Product (OVRR)	Alena Dabrazhynetskaya, PhD, OVRR/DVP Sara Gagneten, PhD, OVRR/DVP
Facilities Inspection (OCBQ/DMPQ and OVRR/DVP)	Pankaj (Pete) Amin, OCBQ/DMPQ Obinna Echeozo, MPH, MBA, OCBQ/DMPQ Christian Lynch, OCBQ/DMPQ Anissa Cheung, MS, OVRR/DVP
Facilities review (OCBQ/DMPQ)	Obinna Echeozo, MPH, MBA
Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC)	Marie Anderson, PhD Emnet Yitbarek, PhD Hsiaoling (Charlene) Wang, PhD Most Nahid Parvin, PhD LCDR Yen Phan, MLS(ASCP)
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Clinical (OVRR)	Rachel Zhang, MD, OVRR/DVRPA Jaya Goswami, MD, MA OVRR/DVRPA Anuja Rastogi, MD, OVRR/DVRPA
Clinical Diagnostic and Immunogenicity Assay Reviewers (OVRR)	Swati Verma, PhD, OVRR/DVP Keith Peden, PhD, OVRR/DVP Sara Gagneten, PhD, OVRR/DVP
Postmarketing safety epidemiological review (OBE/DE)	CDR Jane Baumblatt, MD, OBE/DE
Real World Evidence (OBE)	Yun Lu, PhD, OBE
Benefit Risk Assessment (OBE)	Hong Yang, PhD Osman Yogurtcu, PhD Patrick Funk, PhD
BIMO	Bhanu Kannan, MS, OCBQ/DIS
Statistical	
Statistical data (OBE/DB)	Ye Yang, PhD, OBE/DB
Non-Clinical/Pharmacology/Toxicology	
Non-Clinical Pharmacology Reviewers (OVRR)	Keith Peden, PhD, OVRR/DVP Li Sheng-Fowler, PhD, OVRR/DVP
Toxicology and developmental toxicology (OVRR)	Ching-Long (Joe) Sun, PhD, OVRR/DVRPA
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Promotional (OCBQ/APLB)	CAPT Oluchi Elekwachi, PharmD, MPH
Container and Carton/Package Insert Review (OVRR)	Daphne Stewart, OVRR/DVRPA Josephine Resnick, PhD, OVRR/DVRPA Joseph Kulinski, PhD, OVRR/DVRPA
Consults (CDISC, Datasets)	Brenda Baldwin, PhD, OVRR/DVRPA
Regulatory Project Management (OVRR)	Josephine Resnick, PhD, OVRR/DVRPA Joseph Kulinski, PhD, OVRR/DVRPA
Advisory Committee Summary	No Advisory Committee Meeting Held

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1. Introduction

ModernaTX, Inc. submitted an original Biologics License Application (BLA) STN BL 125752 for licensure of COVID-19 Vaccine, mRNA. The proprietary name of the vaccine is SPIKEVAX™. SPIKEVAX is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The vaccine is administered intramuscularly (IM) as a series of two doses (0.5 mL each) one month apart.

SPIKEVAX (also referred to in this document as "mRNA-1273 vaccine" in discussions related to non-clinical and clinical development, or as "Moderna COVID-19 Vaccine" during use under EUA) contains a nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized spike (S) glycoprotein of SARS-CoV-2 that is encapsulated in a lipid nanoparticle (LNP) composed of four lipids: SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]. The mode of action is based on delivery of the mRNA-LNPs into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

SPIKEVAX is provided as a sterile, white to off-white suspension for intramuscular injection. Each 0.5 mL vaccine dose is formulated to contain 0.1 mg mRNA in buffered sucrose. The vaccine does not contain preservatives, antibiotics, adjuvants, human-derived or animal-derived materials.

SPIKEVAX is supplied in two multiple-dose vial presentations in 10 mL vials that are closed with a rubber stopper and aluminum crimp flip-off seal. The two SPIKEVAX presentations are: a (b) (4)-mL fill volume containing a maximum of 11 doses per vial and an (b) (4)-mL fill volume containing a maximum of 15 doses per vial. The vaccine is stored frozen between -50 to -15ºC but can be stored refrigerated between 2 to 8°C for up to 30 days prior to first use. Prior to administration, the vaccine should be thawed in refrigerated conditions between 2 to 8°C for 2.5 hours (b) (4) mL fill volume) and 3 hours (b) (4) mL fill volume) and kept at room temperature for 15 minutes before administration. Alternatively, it can be thawed at room temperature between 15 to 25ºC for 1 hour (b) (4) mL fill volume) and 1.5 hours (b) (4) mL fill volume). After the first dose has been withdrawn, the vial should be held between 2 to 25ºC and should be used within 12 hours.

The expiry for SPIKEVAX supplied in multiple dose vials is 9 months from the date of manufacture when stored at -25 to -15°C. The date of manufacture is defined as the date of final sterile filtration of the formulated drug product (DP). Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the FDA.

2. Background

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of January,14, 2022, has caused approximately 318 million cases of COVID-19, including 5.58 million deaths worldwide. In the United States, more than 65 million cases and 847,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants such as the Delta variant and the more recently identified Omicron variant now predominant in the U.S., have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

In December 2020, the FDA issued emergency use authorizations (EUAs) for two mRNA vaccines which encode the SARS-CoV-2 S glycoprotein: Pfizer-BioNTech COVID-19 Vaccine (manufactured by Pfizer, Inc. in partnership with BioNTech Manufacturing GmbH) for use in individuals 16 years of age and older and Moderna COVID-19 Vaccine (manufactured by ModernaTX, Inc.) for use in individuals 18 years of age and older. In February 2021, the FDA issued an EUA for a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S glycoprotein, manufactured by Janssen Biotech, Inc. (Janssen COVID-19 Vaccine) for use in individuals 18 years of age and older.

In 2021, the FDA expanded the EUAs for:

- The Pfizer-BioNTech COVID-19 Vaccine to include a two-dose primary series in individuals 5 years of age and older, a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions, and a single booster dose in individuals 12 years of age and older.
- The Moderna COVID-19 Vaccine to include a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions, and a single booster dose in individuals 18 years of age and older.
- The Janssen COVID-19 Vaccine to include a single booster dose in individuals 18 years of age and older.

All three vaccines were also authorized for use as a heterologous (or “mix and match”) booster dose following completion of primary vaccination with an another available COVID-19 vaccine.

Several therapies, including antivirals, SARS-CoV-2 -targeting monoclonal antibodies, immune modulators and convalescent plasma, are available under emergency use.

On August 23, 2021, the Pfizer-BioNTech COVID-19 Vaccine was approved for use in individuals 16 years of age and older under the trade name COMIRNATY.

Following EUA of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 leading to the Delta variant-associated peak in September of 2021. Following the report of the first U.S. case of COVID-19 attributed to the Omicron variant on December 1, 2021, daily numbers of new cases in the U.S. increased sharply, rising by about 540% in 6 weeks. Given the current winter season with more indoor activities due to cold weather, there is concern that the trend of increasing cases may continue.

The regulatory history of SPIKEVAX is summarized in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
Pre-IND meeting	February 19, 2020
IND submission	IND 19635 for Phase 1 Study: February 20, 2020 IND 19745 for Phase 2 Study: April 27, 2020
Fast Track designation granted	May 11, 2020
Pre-BLA meeting	April 28, 2021, Clinical July 1, 2021, CMC/Regulatory
BLA 125752/0 submission	August 24, 2021
BLA filed	October 14, 2021
Mid-Cycle communication	The Applicant cancelled
Late-Cycle meeting	The Applicant cancelled
Action Due Date	April 24, 2022

3. Chemistry Manufacturing and Controls

a. Product Quality

Description of Active Ingredient

SPIKEVAX is an mRNA-based vaccine indicated for active immunization for prevention of COVID-19. The mRNA in SPIKEVAX is called mRNA-1273 and is comprised of an open reading frame of 3819 nucleotides encoding the full-length S glycoprotein (from Wuhan-Hu-1 isolate of SARS-CoV-2 virus) modified to introduce two proline residues that stabilize the S glycoprotein in pre-fusion conformation. The mRNA also contains four regulatory elements: 5' and 3' untranslated regions (UTRs) which increase translational fidelity and confer robust protein expression, a 3' poly(A) tail sequence which promotes mRNA stability, and a 5' cap structure (b) (4) which mediates efficient translation. The mRNA is transcribed using N1-methyl-pseudoruridine instead of uridine nucleoside to minimize indiscriminate recognition of exogenous mRNA by pathogen-associated cellular receptors and to reduce the overall reactogenicity of synthetic mRNA. The in vitro transcribed single-stranded mRNA is encapsulated in a lipid nanoparticle (b) (4) composed of four lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; cholesterol, and DSPC. SPIKEVAX multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.

SPIKEVAX Manufacturing Overview

The manufacturing process for SPIKEVAX drug substance (DS) consists of (b) (4)

The SPIKEVAX DP is manufactured by (b) (4) filling of final containers, and labeling/packaging.

Drug Substance

Manufacture of CX-024414 mRNA

The CX-024414 mRNA manufacturing process consists of (b) (4)

(b) (4)

Manufacturing Process Development - CX-024414 mRNA

The manufacturing process for CX-024414 mRNA was developed progressively to support clinical development, emergency use authorization, and commercial supply. The initial process was developed in the ModernaTX (b) (4)

To support increases in manufacturing capacity, the process underwent scale-related changes, denoted as Scale A (b) (4) initial Scale B (b) (4) and commercial Scale B (b) (4) . The defined increases in scale included (b) (4) The major process changes implemented between the (b) (4) and Scale A include (b) (4) . Subsequent unit operations remained consistent from Scale A through commercial Scale B.

Comparability Assessment - CX-024414 mRNA

Comparability of Scale A, initial Scale B, and commercial Scale B processes was demonstrated through a) analytical comparability assessment by release, extended characterization, and stability testing and b) process performance comparability assessment by in-process controls (IPCs) and critical process parameters (CPPs) evaluated against expected ranges or proven acceptance ranges (PARs). All release results obtained for process performance qualification (PPQ) batches manufactured using commercial Scale B process (b) (4) conformed to both the specification and comparability acceptance criteria across all lots manufactured with different process trains at ModernaTX and Lonza sites. All results for extended analytical characterization conformed to the comparability expected range. The process comparability results showed that the Scale B manufacturing process parameters and quality attributes were comparable across the manufacturing sites.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Manufacture of mRNA-1273 LNP DS

The mRNA-1273 LNP DS manufacturing process consists of (b) (4)

Manufacturing Process Development - mRNA-1273 LNP DS

The mRNA-1273 LNP DS manufacturing process (b) (4)

To support increases in manufacturing capacity at ModernaTX, (b) (4)

To support the commercial supply, (b) (4)

. The analytical methods for the mRNA-1273 LNP DS release and stability testing were changed concurrently with process development.

Comparability Assessment - mRNA-1273 LNP DS

The comparability studies for mRNA-1273 LNP DS were performed (b) (4)

. Analytical comparability of commercial Scale B process was demonstrated through (b) (4)

ModernaTX and Lonza. All release results conformed to both the specification and comparability acceptance criteria for all PPQ lots tested. The extended characterization data conformed to the expected ranges for all attributes tested. All CPP, CIPC, and IPC values for all process comparability lots across the two manufacturing sites met their PARs and expected outcomes, supporting consistent performance for commercial production of mRNA-1273 LNP DS.

Drug Product

The SPIKEVAX DP, is an mRNA-lipid complex suspension of an mRNA encapsulated in lipid particles. The SPIKEVAX DP is a sterile, preservative-free solution that contains 0.20 mg/mL CX-024414 mRNA and 3.87 mg/mL SM-102 LNPs in a buffer containing 20 mM Tris; 87 g/L

sucrose; and (b) (4) mM acetate, pH 7.5 (Table 2). The SPIKEVAX DP is supplied as a multiple-dose, ready-to-use suspension for intramuscular administration in 10-mL vials that are closed with a rubber stopper and aluminum crimp flip-off seal.

Table 2. SPIKEVAX Drug Product Composition

Component		Function	Unit Formula (mg/mL)	Unit Formula (mg/vial) ((b) (4)-mL fill)	Unit Formula (mg/vial) ((b) (4)-mL fill)	Unit Formula (mg/dose) (0.5 mL dose)
CX-024414 mRNA		mRNA that encodes for the pre-fusion stabilized Spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2)	0.20	(b) (4)		0.10
SM-102 LNP	SM-102	Lipid Nanoparticles (The individual lipids make up the Lipid Components of the SM-102 LNP)	3.87	(b) (4)		
	Cholesterol					
	DSPC					
	PEG2000-DMG					
Tromethamine (Tris)		Components in Tris buffer	0.61	(b) (4)		0.31
Tromethamine HCl (Tris-HCl)			2.35	(b) (4)		1.18
Acetic acid (b) (4)		Buffer components for Sodium Acetate buffer in LNP	0.085	(b) (4)		0.043
Sodium acetate trihydrate			0.39	(b) (4)		0.20
Sucrose		Cryoprotection	87	(b) (4)		43.5
Water for injection		Diluent	q.s. 1.0 mL	(b) (4)		q.s. 0.5 mL

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; q.s. = quantum sufficit

Manufacture of SPIKEVAX DP

The SPIKEVAX DP manufacturing processes at Catalent and Baxter facilities are very similar and consist of the same unit operations, i.e., (b) (4) .

Manufacturing Process Development

Manufacturing process development for SPIKEVAX DP (b) (4) Scale A process, (b) (4) at ModernaTX and then scaled (b) (4) at Catalent (Bloomington, IN). To support emergency use authorization and commercial supply, the commercial Scale B process at Catalent (b) (4)). The analytical methods were developed concurrently with process development. No changes have been implemented that impact the comparison of data generated from the tests for the purpose of comparability assessment and comparison between the clinical development and commercial lots.

Comparability Assessment

For comparison between manufacturing scales, the SPIKEVAX DP analytical comparability was assessed using relevant release, stability, and extended characterization testing against pre-

defined acceptance criteria. CPP and IPC results were also evaluated against expected ranges for demonstration of the process performance comparability. To establish the expected analytical ranges, the initial baseline comparability studies (Phase 1) were performed using development, clinical, GMP, and PPQ batches.

The post-change comparability of the commercial Scale B process was assessed in Phase 2 and Phase 3 studies that were performed at Catalent and Baxter manufacturing sites. All CPP, CIPCs, and IPCs established for the commercial process met their PARs and expected ranges, demonstrating consistent performance for commercial production of SPIKEVAX DP using all filling lines at both manufacturing sites. Release testing of PPQ lots was performed in accordance with the specifications established for each fill presentation. Overall, the results from the Scale B (b) (4)-mL and (b) (4)-mL fill presentation DP batches manufactured at Catalent on all (b) (4) fill lines (b) (4) and the results from Scale B (b) (4)-mL fill presentation DP batches manufactured at Baxter on (b) (4) demonstrated that the pre-change and post-change manufacturing process and quality attributes are comparable.

Stability Summary and Conclusion and Stability Data
An initial shelf life of 9 months is proposed for the SPIKEVAX DP lots stored in the commercial container-closure systems at the recommended long-term storage condition of -25 to -15°C (-20°C). The proposed shelf life includes up to 1 month (30 days) of storage at 2 to 8°C (5°C) and up to 24 hours at room temperature (25°C) to support administration of the vaccine at the point of care site.

b. Testing Specifications

The tests and specifications applied for routine release of SPIKEVAX are shown in Table 3.

Table 3. Testing Specifications for SPIKEVAX

Test	Method	Acceptance Criteria
Appearance	Visual	White to off-white dispersion. May contain visible, white or translucent product-related particulates
Identity	(b) (4)	
Total RNA Content	(b) (4)	
Purity Product-Related Impurities	(b) (4)	(b) (4)
%RNA (b) (4)	(b) (4)	
Particle Size		(b) (4)

Test	Method	Acceptance Criteria
(b) (4)		
SM-102 Cholesterol DSPC PEG2000-DMG	(b) (4)	(b) (4)
SM-102 Cholesterol DSPC PEG2000-DMG	(b) (4)	(b) (4) (b) (4) (b) (4) (b) (4)
Lipid Impurity		Individual Impurities: (b) (4) Total impurities: (b) (4)
(b) (4)		
pH	(b) (4)	
(b) (4)		
	(b) (4)	
Container Content[a]	(b) (4)	Maximum 11 Dose (0.5 mL per dose) Presentation Syringe/Needle: Option A: 11 doses of 0.5 mL from 1 vial Option B: 10 doses of 0.5 mL from 1 vial Maximum 15 Dose (0.5 mL per dose) Presentation Syringe/Needle: Option A: 15 doses of 0.5 mL from 1 vial Option B: 13 doses of 0.5 mL from 1 vial
Bacterial Endotoxins	(b) (4)	
Sterility	(b) (4)	Release No growth
Container-Closure Integrity (Stability only)	(b) (4)	End of Shelf Life Pass

[a] Container content is measured based on SOP-1229

Option A: (b) (4)

Option B: (b) (4)

The analytical methods and their validation and/or qualification for the SPIKEVAX DS and DP were found to be adequate for release testing and stability monitoring.

c. CBER Lot Release

The lot release protocol template was found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were found to be sufficient and acceptable. The facilities involved in the manufacture of the Moderna COVID-19 Vaccine are listed in Table 4. The activities performed and inspectional histories are noted in the table.

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

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Aldevron, LLC 4055 41st Avenue South Fargo, ND 58104 (b) (4)	3015047170	048764943	Pre-License Inspection (PLI)	CBER November 1 – 5, 2021 NAI
ModernaTX, Inc. One Moderna Way Norwood, MA 02062 *Drug Substance* mRNA and LNP manufacture *Drug Product* Release Testing	3014937058	116912313	PLI	CBER October 25 – 29, 2021 NAI
Lonza Biologics, Inc. 101 International Drive Portsmouth, NH 03801 *Drug Substance* mRNA and LNP manufacture	3001451441	093149750	PLI	CBER October 18 – 22, 2021 VAI
Catalent Indiana, LLC (subsidiary of Catalent Pharma Solutions, LLC) (Catalent) 1300 S Patterson Drive Bloomington, IN 47403 *Drug Product* Fill/finish, labeling, packaging and release testing (sterility)	3005949964	172209277	Waived	CDER August 27 – September 02, 2020 VAI
Baxter Pharmaceutical Solutions, LLC (Baxter) 927 S. Curry Pike Bloomington, IN 47403 *Drug Product* Fill/finish, labeling, packaging and release testing (sterility)	1000115571	604719430	Waived	ORA/OBPO November 02 – 10, 2021 VAI
(b) (4) *Drug Product* Release testing (bacterial endotoxin)	(b) (4)		Waived	ORA (b) (4) VAI

Abbreviations: DUNS = Data Universal Numbering System; FEI = FDA Establishment Identifier; LNP = lipid nanoparticle; NAI = no action indicated = ORA, Office of Regulatory Affairs; OBPO = Office of Biological Products Operations; VAI = voluntary action indicated

CBER conducted a Pre-License Inspection (PLI) of Aldevron, LLC in November 2021. No Form FDA 483 was issued, and the inspection was classified as no action indicated (NAI).

CBER performed a PLI of ModernaTX, Inc. in October 2021. No Form FDA 483 was issued, and the inspection was classified NAI.

CBER conducted a PLI of Lonza Biologics, Inc. in October 2021 and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified voluntary action indicated (VAI).

CDER inspected the Catalent facility in Bloomington, IN for a different drug product. This PLI was conducted in August/September 2020. Catalent is one of two Contract Manufacturing Organizations responsible for fill/finish operations, release, and stability testing of SPIKEVAX. A Form FDA 483 was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified VAI.

ORA/OBPO performed a surveillance inspection of the Baxter facility in Bloomington, IN in November 2021. A Form FDA 483 was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified VAI.

ORA performed a surveillance inspection of (b) (4) . A Form FDA 483 was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The commercial multiple-dose SPIKEVAX DP lots are supplied in a primary container closure system consisting of three components (vial, stopper, and seal) configured as shown in Table 5. The bulk DP is dispensed into vials and closed with a 20-mm stopper and 20-mm aluminum seal. Vials are then packaged in a secondary carton containing a total of 10 DP vials per carton. Each carton is then placed into a case containing a total of 12 cartons.

Table 5. Container Closure Configurations for Multiple Dose mRNA-1273 DP Vials

Container Closure Component	Description	Abbreviation
Vial	(b) (4) 10R clear Type 1 borosilicate glass vials	(b) (4)
Vial	(b) (4) 10-mL (b) (4) vial, RTU, sterile	
Vial	(b) (4) 10R clear Type 1 equivalent alkali aluminosilicate glass vial	
Vial	(b) (4) 10R clear Type 1 borosilicate glass vial	
Stopper	20 mm (b) (4) (b) (4) stopper (b) (4)	
Stopper	20 mm (b) (4) (b) (4) stopper (b) (4)	
Seal	(b) (4) 20 (b) (4) aluminum seal with flip-off plastic cap	20 mm aluminum seal

f. Environmental Assessment

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

4. Nonclinical Pharmacology/Toxicology

Developmental Assessment and Reproductive Toxicology (DART) Study
In a developmental toxicity study, 0.2 mL of a vaccine formulation containing nucleoside-modified mRNA (100 mcg) and other ingredients that are included in a 0.5-mL single human dose of SPIKEVAX was administered IM to female rats on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effect on postnatal development were observed in the study. Immunoglobulin G (IgG) responses to the pre-fusion stabilized spike protein antigen following immunization were observed in maternal samples and F1 generation rats indicating transfer of antibodies from mother to fetus and from mother to nursing pups.

Non-GLP Repeat Dose Toxicity and Immunogenicity Study
The report from a non-good laboratory practice (GLP) repeat-dose toxicity and immunogenicity study of IM injection of different dose levels of mRNA-1273 vaccine in rats was submitted and reviewed under the BLA. In this study, four groups of rats (5/sex/group) received two tri-weekly IM administrations of control article (Tris/sucrose buffer), 30, 60, or 100 mcg of mRNA-1273 vaccine. A dose-dependent finding of edema at the injection site with or without hindlimb impairment was noted in all treated animals starting 24 hours after each dose and resolved by end of the week. Dose-independent hematological changes consistent with inflammation included marked increases in neutrophil and eosinophil counts in all treatment animals. Slight, non-dose-dependent elevations of triglycerides and cholesterol were noted in male rats. Antibodies to the spike protein were demonstrated in sera obtained on day 13 post Dose 2. No organ weight, gross pathology, or histologic examinations were evaluated in this study. Findings from the intramuscular repeat dose rat toxicity study demonstrated that vaccine doses of up to 100 mcg (two doses given three weeks apart) were well-tolerated.

Other Supportive Toxicology Studies
The safety of SPIKEVAX is further supported by the aggregate rat repeat-dose toxicity profiles observed in six GLP toxicity studies of five vaccines formulated in SM-102 lipid particles containing mRNAs encoding various viral glycoprotein antigens, demonstrating tolerance of repeat doses of these vaccines without any detrimental effects. Three other toxicology studies were also reviewed in support of safety of SPIKEVAX. A study report from an in vitro rat micronucleus assay evaluating the genotoxic potential of (b) (4) mRNA in SM-102 LNP revealed no genotoxic effects of SM-102 LNP. In addition, study reports from a bacterial reverse mutation test and an in vitro mammalian cell micronucleus test of PEG2000-DMG were also reviewed. No genotoxic effects of PEG2000-DMG were observed in these studies.

Biodistribution Study
A biodistribution study was not performed with mRNA-1273 vaccine. Results from the biodistribution study of a different vaccine, (b) (4) for an (b) (4), manufactured using the same procedure as SPIKEVAX and formulated with 100 µg mRNA in SM-102-containing LNPs, were submitted in support of SPIKEVAX. Because biodistribution and retention is a property of the LNP rather than the mRNA, results from this study were considered supportive for the approval of SPIKEVAX BLA.

Non-Clinical Effectiveness Pharmacology Studies
Non-clinical pharmacology studies were done in mice, rats, hamsters, and non-human primates. Collectively, these studies demonstrated that the mRNA-1273 vaccine elicited binding and neutralizing antibodies to Wuhan-Hu1 strain of SARS-CoV-2, a Th1-biased immune response, and protected animals from viral replication and weight loss upon challenge with SARS-CoV-2

virus, while no enhanced respiratory disease was observed. In addition, no other safety concerns were raised by these studies.

5. Clinical Pharmacology

Pharmacodynamic data obtained from the clinical studies demonstrated that SPIKEVAX induces a humoral immune response against the SARS-CoV-2 spike protein. The exact immunologic mechanism that confers protection against SARS-CoV-2 is unknown.

6. Clinical/Statistical

Clinical Diagnostic Assays Used to Support Primary Clinical Efficacy Endpoints

RT-qPCR Assay by Eurofins-Viracor for the Quantification of SARS-CoV-2 RNA

This reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay for the quantification of SARS-CoV-2 RNA received EUA from the FDA in 2020.The SARS-CoV-2-specific RT-qPCR assay was developed by Eurofins Genomics and validated by Eurofins-Viracor to detect SARS-CoV-2 RNA encoding the viral nucleocapsid (N) protein in upper respiratory (nasal/nasopharyngeal wash and swab) and bronchoalveolar lavage samples and in nasal swabs. The validation report included the extraction and RT-qPCR methods along with assessments of analytical sensitivity via limit of detection and lower limit of quantification, linearity and dynamic range, accuracy, intra-assay and inter-assay precision (reproducibility), and stability and acceptance criteria for each of these assay parameters. This assay was used to assess baseline SARS-CoV-2 status and asymptomatic/symptomatic SARS-CoV-2 infection. It was also used to quantify viral load as an exploratory endpoint after SARS-CoV-2 infection diagnosis over time to evaluate the effect of mRNA-1273 vaccine on the viral infection kinetics. The assay was adequately validated for the above described diagnostic and viral load assessments.

Immunogenicity Assays

Two anti-SARS-CoV-2 N protein immunoassays were used to assess baseline infection status by detecting anti-N protein IgG antibodies present in human serum and plasma.

- (b) (4) enzyme-linked immunosorbent assay (ELISA) anti-N protein (quantitative method)
- (b) (4) Anti-SARS-CoV-2 (b) (4)

Both assays were performed and validated at (b) (4). In addition, the (b) (4) anti-N ELISA was used to quantify anti-N titers as exploratory endpoints in studies P201 and P301.

Two anti-S immunoassays were used to quantify primary (study P201) or secondary (study P301) IgG S-protein binding antibody (bAb) immunogenicity endpoints in human sera:

- (b) (4) ELISA anti-S-2P (SARS-CoV-2 spike protein modified with 2 proline substitutions) to assess IgG antibodies against S-2P within the (b) (4).
- (b) (4) (b) (4) was developed to measure spike, receptor binding domain, and nucleocapsid proteins but the assay was only validated to measure binding IgG antibodies against the spike protein.

The (b) (4) ELISA was validated at (b) (4) and the (b) (4) assay was validated at the (b) (4)

Two neutralizing antibody assays were used to quantify neutralizing antibodies in serum or plasma samples:

- Live-Virus Microneutralization (MN) assay was validated at (b) (4).
- Pseudovirus Neutralization Assay was initially developed at the (b) (4) but was transferred and validated at the (b) (4).

Validation reports of all the assays described above were found to be acceptable. However, only the Pseudovirus Neutralization Assay was used for assessment of neutralizing antibodies in clinical study P301.

a. Clinical Program

Overview of Clinical Studies

Studies submitted in the BLA are summarized in Table 6. Study mRNA-1273-P301 is a multi-center, Phase 3, randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of this review. Study mRNA-1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 vaccine. Phase 1 Study 20-0003 is an open-label, dose-ranging, first-in-human study of mRNA-1273 vaccine.

Table 6. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study	Participants Randomized	Study Design, Type of Control	Dose Levels Assessed (amount of mRNA per dose)	Study Status
P301	Efficacy, safety, immunogenicity	30415	Phase 3, randomized, stratified, observer-blind, placebo-controlled study	100 mcg	Ongoing
P201	Safety, immunogenicity	600	Phase 2a randomized, observer-blind, placebo-controlled, dose-confirmation study	50 mcg, 100 mcg	Ongoing
20-0003[a]	Safety, immunogenicity	120	Phase 1 open-label dose-ranging study	25 mcg, 50 mcg, 100 mcg, 250 mcg	Ongoing

a. Sponsor: Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Study mRNA-1273-P301

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 vaccine administered as two doses 28 days apart to adults 18 years of age and older. The study includes 99 sites in the United States. Participants (N=30,415) were randomized 1:1 to receive IM injections of either mRNA-1273 vaccine containing 100 mcg of mRNA (n=15,206) or placebo (n=15,209) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to 64 years of age and not at risk for progression to severe COVID-19, 18 to 64 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups

consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. Approximately 25% of participants were healthcare workers. The expected duration of study participation for each participant is approximately 25 months.

Objectives

Primary efficacy objective: To demonstrate the efficacy of mRNA-1273 vaccine to prevent COVID-19 starting 14 days after the second dose.

Primary safety objective: To evaluate the safety and reactogenicity of 2 doses of the mRNA-1273 vaccine given 28 days apart.

Secondary efficacy objectives: To demonstrate the efficacy of mRNA-1273 vaccine to prevent:

- Severe COVID-19 starting 14 days after the second dose.
- Serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.
- COVID-19 as defined by a secondary definition.
- Death caused by COVID-19.
- COVID-19 starting 14 days after the first dose.
- COVID-19 regardless of evidence of prior SARS-CoV-2 infection.
- Asymptomatic SARS-CoV-2 infection.

Secondary immunogenicity objective: To evaluate the immunogenicity of 2 doses of mRNA-1273 vaccine given 28 days apart.

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative reverse transcription polymerase chain reaction [RT-PCR] and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The case definition for a confirmed COVID-19 case was defined as nasopharyngeal (NP) swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR along with:

- At least TWO of the following systemic symptoms: Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and NP swab. Presence of any one of these symptoms lasting at least 48 hours (except for fever and respiratory symptoms, which could be present for any duration) resulted in the site arranging an Illness Visit to collect an NP swab sample within 72 hours of symptom onset:

- Fever (temperature ≥ 38ºC) or chills (of any duration, including ≤48 hours)
- Shortness of breath or difficulty breathing (of any duration, including ≤48 hours)

- Cough (of any duration, including ≤48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition ("CDC definition"): a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38ºC), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level, or PaO_2/FiO_2 <300 mm Hg);
- Respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation);
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

In all cases, NP samples were tested for SARS-CoV-2 at a central laboratory using a RT-PCR test (Viracor; FDA authorized under EUA) or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result was used for the case definition, unless it was not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the primary efficacy analysis. Two interim analysis timepoints were pre-specified: the first upon accrual of 53 cases and the second upon accrual of 106 cases. The primary efficacy analysis supported issuance of the EUA, and the BLA submission also included an updated placebo-controlled efficacy analysis, with data cutoff of March 26, 2021, that included 799 primary endpoint cases.

Beginning December 28, 2020, per amended protocol following the issuance of the EUA for the Moderna COVID-19 Vaccine, all participants were asked to schedule a Participant Decision Visit (PDV), at which they would be given the option to be unblinded to their original treatment group. Investigators considered local and national public health guidance for administration of COVID-19 vaccines under EUA when determining the scheduling priority of participants, and thus the unblinding process occurred progressively over several months. Participants initially randomized to the placebo group were offered mRNA-1273 vaccination after unblinding. Participants who received only one dose of mRNA-1273 vaccine prior to unblinding were given a second dose in the open-label phase. For participants unblinded to his/her vaccine assignment, follow-up evaluations thereafter were conducted in an open-label manner.

Study Results

Protocol-Specified, Event-Driven Primary Efficacy Analysis

The primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after Dose 2. Cases were adjudicated by a blinded committee. The follow-up period for the primary analysis was from July 27, 2020 (date first participant was dosed), to the primary efficacy data cutoff date of November 21, 2020.

The primary efficacy analysis demonstrated a VE against COVID-19 occurring at least 14 days after the second dose of vaccine of 94.1% (95% confidence interval [CI]: 89.3%, 96.8%), which met the pre-specified success criterion. The case split was 11 COVID-19 cases in the mRNA-1273 vaccine group and 185 cases in the placebo group. This protocol-specified, event-driven primary efficacy analysis was the basis for issuance of the EUA for the Moderna COVID-19 Vaccine on December 18, 2020. Please refer to the EUA Review Memo for the Moderna COVID-19 Vaccine for additional details from that analysis time point.

Updated Efficacy Analyses

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up phase of the study (Part A) through data cutoff of March 26, 2021, with a median follow-up duration of approximately 4 months after Dose 2 for participants in the efficacy population. In the updated analysis of the primary endpoint of vaccine efficacy to prevent protocol-defined COVID-19 based on adjudication committee assessment starting 14 days after Dose 2, there were 55 cases in the mRNA-1273 vaccine group versus 744 cases in the placebo group, for a VE of 93.2% (95% CI: 91.0, 94.8), see Table 7**.**

Table 7. Updated Part A Analysis of Vaccine Efficacy to Prevent COVID-19 Starting 14 Days After Dose 2, Per Protocol Set, Data cutoff March 26, 2021

Pre-Specified Age Group	mRNA-1273 Vaccine Cases/N (%) Incidence rate per 1,000 person-years[a]	Placebo Cases/N (%) Incidence rate per 1,000 person-years[a]	Vaccine Efficacy % (95% CI)[b]
All participants	55/14287 (0.4) 9.6	744/14164 (5.3) 136.6	93.2 (91.0, 94.8)
18-64 years	46/10661 (0.4) 10.7	644/10569 (6.1) 159.0	93.4 (91.1, 95.1)
≥65 years	9/3626 (0.2) 6.2	100/3595 (2.8) 71.7	91.5 (83.2, 95.7)

Source: Adapted from STN 125752.1_P301Clinical Study Report, Table 14.2.2.1.3.1.1, 14.2.2.1.3.6.1.1.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; N=number of participants in the per-protocol set;
a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.
b. Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vaccine versus placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor

Most COVID-19 cases in the study were identified by sequencing as SARS-CoV-2 variant B.1.2. Additional SARS-CoV-2 variants identified included B.1.427/B.1.429 (Epsilon), P.1 (Gamma), and P.2 (Zeta), though the numbers were too small to conclude on VE specifically against these variants. The data cutoff for the blinded phase occurred prior to the widespread circulation of the B.1.617.2 (Delta) variant within the U.S. and prior to the emergence of the B.1.1.529 (Omicron) variant.

Subgroup Analyses

The updated vaccine efficacy analyses included subgroup analyses by age, sex, race and ethnicity, demographics and risk for severe COVID-19, and provide additional information on the applicability of these results across the general population. Similar to the results obtained in the primary analysis, in the updated efficacy analyses, VE point estimates were consistent across subgroups (although limited by smaller number of participants and cases in certain subgroups) and were comparable to the VE seen in the overall study population.

Efficacy Against Severe COVID-19

The Applicant conducted updated analyses of the secondary efficacy endpoint of prevention of severe COVID-19 with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 26, 2021 (Table 8). In the updated analysis, the estimated VE against severe COVID-19 occurring at least 14 days after Dose 2 was 98.2% (95% CI: 92.8, 99.6) with 2 severe COVID-19 cases in the mRNA-1273 vaccine group and 106 severe COVID-19 cases in the placebo group. The VE estimate was similarly high among participants ≥65 years of age as those 18 through 64 years of age.

Table 8. Updated Vaccine Efficacy to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Dose 2, Per Protocol Set, Data Cutoff March 26, 2021

Pre-Specified Age Group	mRNA-1273 Vaccine Cases/N (%) Incidence rate per 1,000 person-years[a]	Placebo Cases/N (%) Incidence rate per 1,000 person-years[a]	Vaccine Efficacy % (95% CI)[b]
All participants	2/14287 (<0.1) 0.3	106/14164 (0.7) 19.1	98.2 (92.8, 99.6)
18-64 years	1/10661 (<0.1) 0.2	76/10569 (0.7) 18.4	98.7 (91.0, 99.8)
≥65 years	1/3626 (<0.1) 0.7	30/3595 (0.8) 21.4	96.9 (77.1, 99.6)

Source: Adapted from STN 125752.0, CSR Table 6-4, Table 14.2.2.2.3.6.1
N = number of participants in the specified group.
a. Person-years is defined as the total years from randomization date to the date of COVID-19, the date of earliest positive RT-PCR or Elecsys at scheduled visits, last date of study participation, or efficacy data cutoff date, whichever is earlier. Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group.
b. Vaccine efficacy (VE), defined as 1−hazard ratio (mRNA-1273 vaccine versus placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

Asymptomatic Infection

Asymptomatic SARS-CoV-2 cases were identified by absence of symptomatic COVID-19 (based on either the primary efficacy endpoint COVID-19 definition or secondary definition of COVID-19) and either seroconversion as measured by binding antibody specific to SARS-CoV-2 nucleocapsid (N-serology) at scheduled visits (Months 1, 2, 7, 13, 25, PDV) or positive SARS-CoV-2 RT-PCR at scheduled visits (D29, PDV). The protocol-specified asymptomatic infection endpoint was infection starting 14 days after Dose 2, which required a positive PCR and/or positive N-serology at the Day 57 (Month 2) visit or later. The results from the tests collected at the PDV (occurring at or before the data cutoff date of March 26, 2021) are included in this analysis. Due to study unblinding after EUA, few participants reached Month 7 of blinded follow-up (and no participant reached Month 13 or Month 25), and thus most cases as determined by positive N-serology came from the Month 2 visit or PDV. The date of the asymptomatic infection is the earlier date of seroconversion or positive RT-PCR, with absence of symptoms. Participants who had symptomatic infection prior to an asymptomatic infection were censored at the time of the symptomatic infection for the analysis.

Since asymptomatic cases were defined in the protocol as those without COVID-19 symptoms prior to a positive test, it was possible for participants to be counted as an asymptomatic case but then have documented COVID-19 symptoms at a later timepoint. It was also possible for participants to be included in the asymptomatic infection endpoint if they reported COVID-19 symptoms at an earlier timepoint but did not have an accompanying positive RT-PCR (and thus did not meet the protocol-specified criteria for a COVID-19 or secondary COVID-19 case). Following an information request by CBER, the Applicant conducted a sensitivity analysis excluding participants with any documented protocol-defined COVID-19 symptoms at any time during the study. The sensitivity analysis of asymptomatic infections in the mRNA-1273 vaccine and placebo groups is shown in Table 9 below. Limitations of this analysis include the infrequently-scheduled assessments for serology and PCR testing, which may not have captured all cases of asymptomatic infections which occurred during the study.

Table 9. Sensitivity Analysis of Asymptomatic SARS-CoV-2 Infection Starting 14 Days After Dose 2 in the Blinded Phase, Per Protocol Set

Participants With Asymptomatic Infection	mRNA-1273 Vaccine N=14287	Placebo N=14164
Number	180	399
IR/1000 person-years (95% CI)	31.3 (26.9, 36.2)	73.3 (66.3, 80.9)

Source: Applicant's response to Information Request dated December 6, 2021
Asymptomatic cases of COVID-19 defined as positive SARS-CoV-2 serology or PCR in the absence of protocol-defined COVID-19 symptoms reported at any time during the study
Abbreviations: IR = incidence rate

Study mRNA-1273-P201

Study P201 is an ongoing, phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 vaccine in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older. Participants were randomized equally to three groups to receive 2 doses of either mRNA-1273 vaccine containing 50 mcg of mRNA-1273, mRNA-1273 vaccine containing 100 mcg of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months after the last vaccination.

All participants were followed for solicited adverse reactions (ARs) through 7 days after each vaccination. Unsolicited adverse events (AEs) were collected through 28 days after each vaccination. Serious adverse events (SAEs) and medically attended adverse events (MAAEs) will be collected through the end of the study.

Objectives

Primary safety objective: To evaluate the safety and reactogenicity of 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart.

Primary immunogenicity objective: To evaluate 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart, as assessed by the level of specific bAb at baseline and at various time points after vaccination.

Secondary immunogenicity objective: to evaluate 2 dose levels of the mRNA-1273 vaccine, each administered in 2 doses given 28 days apart, as assessed by the nAb titer at baseline and at various time points after vaccination.

Study Results

The immune response as assessed by bAb IgG ELISA after two doses was slightly higher in the 100-mcg group compared to the 50-mcg group (Day 57 geometric mean titer [GMT]: 657.2 versus 519.5). This difference persisted at 6 months after Dose 2 (Day 209 GMT: 128.0 versus 97.0 for the 100-mcg and 50-mcg groups, respectively). Immune responses measured by MN antibody titers were comparable between the 100-mcg and 50-mcg groups (MN50 at Day 57 of 1656.1 and 1632.4, respectively) at 28 days after Dose 2. At 6 months after Dose 2, the 100-mcg group had a slightly higher antibody level compared to the 50-mcg group (MN50 at Day 209 of 538.8 versus 401.5, respectively). In both the 50-mcg and 100-mcg dose groups, the older age cohort (≥55 years) had slightly lower antibody titers when compared to the younger age cohort (18 to <55 years) at 28 days and 6 months post-Dose 2.

In addition to immunogenicity assessments, participants were swabbed for SARS-CoV-2 RT-PCR testing during scheduled study visits per protocol (Days 1, 29, 57), as well as at unscheduled illness visits if they reported suspected COVID-19 symptoms or after potential exposure to a SARS-CoV-2-infected individual. During the blinded phase of the study, the

following participants were found to have a positive SARS-CoV-2 RT-PCR as collected in the study or a positive diagnostic test outside of the study by a local laboratory:

- 24 participants in the placebo group (12 with symptomatic COVID-19)
- 4 participants in the 50-mcg mRNA-1273 vaccine group (1 with symptomatic COVID-19)
- 2 participants in the 100-mcg mRNA-1273 vaccine group (1 with symptomatic COVID-19)

As there is currently no immunologic correlate of protection, and the study design did not include a direct comparison between the 50-mcg and 100-mcg dose levels, it is not possible to draw firm conclusions about the clinical benefit of the 50-mcg dose when administered as a 2-dose primary dose series. While neutralizing antibody titers at 28 days post Dose-2 were only slightly higher in the 100-mcg dose group compared with the 50-mcg dose group, and the 50-mcg dose group had numerically fewer SARS-CoV-2 infection/COVID-19 cases identified during the study compared to the placebo group, based on the data in this study alone it is unclear if efficacy following the 2-dose 50-mcg primary series would be numerically as high or as durable as that for the 2-dose 100-mcg primary series.

Two doses of mRNA-1273 vaccine at either the 50-mcg or 100-mcg dose level were immunogenic, with a slightly higher immune response as measured by bAb and MN antibody titers after the 100-mcg dose compared to 50-mcg dose, and a slightly higher response in the younger age cohort (18 to <55 years) than the older cohort (≥55 years). The safety profile of both dose levels was comparable and there were no major safety concerns identified in the study.

Study 20-0003

Study Design

Study 20-0003 (sponsored by the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health) is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 vaccine in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 groups (based on age and dose) to receive 2 doses of mRNA-1273 vaccine 28 days apart. The dose groups were 25 mcg, 50 mcg, 100 mcg, and 250 mcg and the age groups were 18 through 55 years, 56 through 70 years, and 71 years and older. Participants will be followed for safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the BLA

The immunogenicity objectives are to evaluate the bAb concentrations for spike IgG as measured by ELISA and nAb titers as measured by Pseudovirus Neutralizing Antibodies for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants were followed for solicited adverse reactions through 7 days after each vaccination. Unsolicited AEs were collected through 28 days after each vaccination. All SAEs and MAAEs will be collected through the end of the study.

Study Results

In an evaluation of 60 participants 18 to 55 years of age, 30 participants 56 to 70 years of age, and 30 participants ≥71 years, dose response was measured by both bAb and nAb after 2 doses. Comparable antibody responses were observed in the 100-mcg and 250-mcg dose groups, and greater immune responses were observed in both dose groups compared to the 50-mcg and 25-mcg groups. The bAb and nAb levels seen after 2 doses of either the 100-mcg or 250-mcg doses of mRNA-1273 vaccine were similar in magnitude compared to those seen in pooled convalescent sera from patients who had recovered from COVID-19. At 6 months post

Dose 2, nAb titers across all dose levels were lower compared to the respective levels observed at 1 month post Dose 2, though some had overlapping intervals. For all dose levels, participants in the younger age cohorts had a higher immune response compared to participants in the older age cohorts. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines with minimal Th2 cytokine expression, suggestive of decreased risk of vaccine-induced enhanced disease. Safety data showed lower frequencies of solicited adverse reactions in the 100-mcg group compared to the 250-mcg group. No safety concerns were identified in this study. Based on both the immunogenicity and safety data, the 100-mcg dose was selected for further evaluation in Phase 2 and 3 studies.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

One BIMO inspection was performed for a domestic clinical investigator participating in the conduct of study Protocol: mRNA-1273-P301. The inspection did not reveal any issues impacting the data submitted in support of this BLA.

c. Pediatrics

To address requirements of the Pediatric Research Equity Act, the Applicant submitted a request for deferral of the following studies in pediatric individuals <18 years of age because the mRNA-1273 vaccine would be ready for approval for use in adults before such studies could be completed. The deferred studies are:

- Deferred pediatric study P203 to evaluate the safety and effectiveness of mRNA-1273 vaccine in children 12 years through 17 years of age
- Deferred pediatric study P204 to evaluate the safety and effectiveness of mRNA-1273 vaccine in children 6 months to <12 years of age
- Deferred pediatric study to evaluate the safety and effectiveness of mRNA-1273 vaccine in infants <6 months of age

The deferral request and pediatric plans were accepted without revisions by the FDA Pediatric Review Committee on December 14, 2021.

d. Other Special Populations

Study P301 enrolled 185 participants with stable HIV infection (CD4 count >350 cells/mm^3 and undetectable HIV virus in past 1 year) who received at least one dose of mRNA-1273 vaccine (n=94) or placebo (n=91). Among participants in the Per Protocol Set with HIV infection (n=82 placebo; n=85 mRNA-1273), there were 4 cases of COVID-19 starting 14 days after Dose 2 in the placebo group compared to none in the mRNA-1273 vaccine group. The safety profile in this subgroup was comparable to the overall study population. Given the small number of participants considered immunocompromised included in the study, data in the BLA submission are insufficient to inform vaccine safety and effectiveness in immunocompromised populations.

In August 2021, FDA re-issued the EUA for Moderna COVID-19 Vaccine to authorize administration of a third primary series dose, at least 28 days following the second dose, in individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; authorization was supported by data from published reports of low antibody responses and breakthrough infections among significantly immunocompromised individuals (mainly solid organ transplant recipients) who received the two-dose vaccination series (See the EUA memorandum for third dose in certain immunocompromised individuals).

7. Safety and Pharmacovigilance

Clinical Trials

The focus of the clinical trial safety data review was Study P301 Part A which provides blinded safety data for 30,346 participants who received at least one dose of dose of mRNA-1273 vaccine (N=15,184) or placebo (N=15,162).

In participants 18 through 64 years of age, the most frequently reported (≥10%) adverse reactions were pain at injection site (93.3%), fatigue (71.9%), headache (68.7%), myalgia (64.8%), chills (49.7%), arthralgia (48.6%), nausea/vomiting (25.7%), axillary swelling/tenderness (22.2%), fever (17.3%), swelling at the injection site (15.4%), and erythema at the injection site (10.5%). In participants 65 years of age and older, the most frequently reported (≥10%) adverse reactions were pain at injection site (88.3%), fatigue (64.8%), headache (53.3%), myalgia (51.8%), arthralgia (40.2%), chills (32.7%), nausea/vomiting (15.0%), swelling at the injection site (13.0%), and axillary swelling/tenderness (12.7%). Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

In Study P301, numerical imbalances in unsolicited AEs between treatment groups (with greater number in the mRNA-1273 vaccine group compared to placebo) from Dose 1 through 1 month after Dose 2 included lymphadenopathy-related events (264 versus 167), herpes zoster (22 versus 15), and facial paralysis (2 versus 1). In the blinded phase of the study which included a median duration of follow-up of 4 months after Dose 2, facial paralysis was reported in 8 participants in the mRNA-1273 vaccine group and 3 in the placebo group. The imbalance in lymphadenopathy-related events is consistent with the data on solicited axillary swelling/tenderness of the injected arm. For facial paralysis and herpes zoster, available information is insufficient to determine a causal relationship with vaccination. During the 7-day follow-up period after any vaccination, hypersensitivity events of injection site rash or injection site urticaria, likely related to vaccination, were reported by 6 participants in the mRNA-1273 vaccine group and none in the placebo group. Delayed injection site reactions that began >7 days after vaccination, likely related to vaccination, were reported by 219 participants in the mRNA-1273 vaccine group and 100 in the placebo group.

The SAE data from the blinded phase of Study P301 included a median duration follow up of 4 months after Dose 2. Overall, SAEs were reported by a similar proportion of participants after vaccination: 1.8% (401 events in 268 participants) in the vaccine group and 1.9% (439 events in 292 participants) in the placebo group. There were 32 deaths during the blinded phase of the study: 16 deaths in the vaccine group, and 16 in the placebo group. None of the unsolicited AEs leading to death were considered vaccine-related. COVID-19 was reported as the event leading to death for 1 participant in the vaccine group and 3 in the placebo group.

There were three serious adverse events of angioedema/facial swelling in the vaccine group in recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 to 2 days after the second dose and was likely related to vaccination. There were no other notable patterns or imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273 vaccine. Additionally, SAEs reported during the open-label phase of the study were reviewed and did not raise any new safety concerns.

Post-Authorization Safety Surveillance

The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following administration of the Moderna COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of

doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was due to the vaccine.

From December 18, 2020 (date of EUA), to November 30, 2021, a total of 348,505 reports to VAERS related to the Moderna COVID-19 Vaccine were received and processed (coded, redacted, and quality assurance performed). Among these 18% (61,474 reports) were reports of SAEs. The most common SAEs reported to VAERS were pyrexia (n=10,606, 3.0%), headache (n=9,410, 2.7%), fatigue (n=8,387 2.4%), dyspnea (n=6,612, 1.9%), nausea (n=6,387, 1.8%), chills (5,849, 1.7%), myalgia (n=4,993, 1.4%), dizziness (n=4,948 1.4%), pain in extremity (n=4,487, 1.3%), and COVID-19 (n=4,461, 1.3%). VAERS received 5,203 reports of death (1.5% of all AE reports for Moderna Covid-19 Vaccine). Of note, FDA requires vaccination providers to report any deaths after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. FDA review of U.S. death reports, including review of available medical records and/or autopsy reports, has not identified any new safety concerns.

FDA review of VAERS reports identified anaphylaxis and myocarditis and pericarditis as safety concerns, which are included as important identified risks in the current Pharmacovigilance Plan. Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine is included as a contraindication in the Prescribing Information. The Warnings and Precautions section of the Prescribing Information also includes subsections on the Management of Acute Allergic Reactions and on Myocarditis and Pericarditis. These risks are also addressed in the Prescribing Information. Specific safety concerns are discussed in more detail below.

Anaphylaxis
There were no cases of anaphylaxis within 30 minutes of administration of mRNA-1273 vaccine reported in clinical trials through the cutoff date of May 4, 2021; however, anaphylaxis has been reported to VAERS following use of Moderna COVID-19 Vaccine under EUA. Based on automated query of VAERS (which includes cases for which diagnosis and outcomes were not confirmed) with November 30, 2021 data lock point, the estimated crude reporting rate for anaphylaxis in the U.S. is 5.1 cases per million doses. This reporting rate is similar in magnitude to that following other approved preventive vaccines. A contraindication for individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of SPIKEVAX is included in section 4 of the Prescribing Information. Additionally, a warning statement is included in section 5.1 of the Prescribing Information instructing that "*Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of SPIKEVAX*."

Myocarditis/Pericarditis
Although evaluation of adverse events in the P301 safety database (N=30,346) did not identify cases of post-vaccination myocarditis, post-authorization safety surveillance has identified serious risks of myocarditis and pericarditis, particularly within 7 days following the second dose of Moderna COVID-19 Vaccine. The observed risk is higher in males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age; an analysis of VAERS data from passive surveillance indicated a reporting rate of 40 cases per 1 million second doses administered to males 18 to 24 years of age, while an FDA meta-analysis of four healthcare claims databases in CBER's Biologics Effectiveness and Safety System estimated a rate of 148 cases per 1 million males 18 to 25 years of age vaccinated with the 2-dose primary series. Although some reported cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of

symptoms with conservative management. Information is not yet available about potential long-term sequelae.

To address the identified risk of myocarditis/pericarditis with mRNA-1273 vaccine, FDA conducted a quantitative, age-stratified benefit-risk analysis in males ≥18 years of age, using healthcare claims and CDC surveillance databases, to evaluate the balance of benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths against the risk of vaccine-related myocarditis/pericarditis cases, hospitalizations, ICU admissions, and deaths under various conditions of COVID-19 incidence and vaccine effectiveness informed by real-world data. The modeling attempted to account for preliminary estimates of Omicron-specific vaccine efficacy. While COVID-19 is known to cause myocarditis, and COVID-19-associated myocarditis may be more severe than vaccine-associated myocarditis, the model does not specifically estimate the number of COVID-19-associated cases of myocarditis that would have resulted in hospitalizations, ICU admission, or deaths in the absence of COVID-19 vaccination. Modeling for individuals ≥65 years and for females was not conducted due to limited number of cases of vaccine-related myocarditis/pericarditis for these populations. However, this evidence indicates a more favorable benefit-risk profile in individuals ≥65 years of age and in females as compared with males 18 to 64 years of age. Based on the current understanding of vaccine-associated myocarditis, the analyses support the benefits of vaccination over the risks of myocarditis/pericarditis for individuals ≥18 years of age. Mitigation of the observed risks of myocarditis/pericarditis and associated uncertainties will be accomplished through labeling (with inclusion of information about the risks of myocarditis and pericarditis in the Warnings and Precautions section of the Prescribing Information), continued safety surveillance, and postmarketing studies.

Thrombosis with Thrombocytopenia
An increased risk for thrombosis with thrombocytopenia syndrome (TTS) has been identified following administration of adenovirus-vectored COVID-19 vaccines, including the Janssen COVID-19 Vaccine. This prompted the VAERS analyses for reports of TTS that occurred following administration of Moderna COVID-19 Vaccine. As of January 20, 2022, three cases of TTS following vaccination with the Moderna COVID-19 Vaccine have been reported to VAERS and confirmed based on expert adjudication with a standardized case definition. The low reporting rate suggests that these cases represent the background rate of thrombosis with thrombocytopenia rather than signaling a risk of TTS attributable to the Moderna COVID-19 Vaccine.

Pharmacovigilance Plan
The Applicant's Risk Management Plan version 2.2 includes the following important risks and missing information in the pharmacovigilance plan:

- Important identified risks: Anaphylaxis; Myocarditis; Pericarditis
- Important potential risks: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Long term safety and long-term effectiveness; Use with concomitant vaccines; Use in immunocompromised patients; Interaction with other vaccines; Use in frail subjects with unstable health conditions and comorbidities (COPD, T2DM, CVD, chronic neurological disease), Use in subjects with autoimmune or inflammatory disorders; Use in pediatric individuals < 18 years of age.

In addition to routine pharmacovigilance, the Sponsor will conduct the postmarketing studies as postmarketing requirements and commitments as listed in Section 11c Recommendation for

Postmarketing Activities. Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 11c are adequate to monitor the postmarketing safety for SPIKEVAX.

8. Labeling

The proprietary name, SPIKEVAX, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) and found to be acceptable. CBER communicated this decision to the Applicant on October 15, 2021. The APLB found the Package Insert (PI), Patient Package Insert (PPI) and carton/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, PPI, and package/container labels with ModernaTX Inc. Six versions of the PI (submitted in amendments 24,35,43,48,51 and 52), two versions of carton/container labels (submitted in amendments 24 and 35), and one version of the PPI (submitted in amendment 37) were submitted to STN 125752 by ModernaTX Inc. during labeling negotiations. The PI submitted on January 28, 2022 (amendment 52), the package/container labels submitted on December 15, 2021 (amendment 35) and the PPI submitted on December 16, 2021 (amendment 37) were considered final for approval.

9. Advisory Committee Meeting

The most critical issues involving data to support safety and effectiveness of this vaccine were considered during the October 2020, December 2020, and October 2021 meetings of the Vaccines and Related Biological Products Advisory Committee (VRBPAC). Information concerning the risk of myocarditis/pericarditis continued to be updated during the BLA review through ongoing post-EUA surveillance and observational studies. FDA's assessment of this information did not impact the overall benefit/risk considerations to an extent that VRBPAC input was needed to guide a licensure decision for use in individuals ages 18 years and older.

10. Other Relevant Regulatory Issues

Due to the urgent need to make licensed vaccines available to combat the ongoing COVID-19 pandemic, the SPIKEVAX BLA was granted priority review. CBER reviewed the material threat medical countermeasure priority review voucher (PRV) request from the Applicant, and a PRV was granted for SPIKEVAX.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the BLA, the Review Committee recommends approval of SPIKEVAX for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of SPIKEVAX that have been presented and discussed in this document, as well as the quantitative benefit/risk analysis conducted by FDA, the Review Committee agrees that the benefit/risk balance for SPIKEVAX is favorable and supports approval for use of a 2-dose primary series in individuals 18 years of age and older. Despite evidence from published observational studies of waning protection following primary vaccination and evidence of decreased effectiveness against some SARS-CoV-2 variants such as Omicron, the clinical benefits of primary vaccination with SPIKEVAX remain clear especially with regard to protection against more severe COVID-19 and its serious sequelae (see CDC's Morbidity and Mortality Weekly Report of January 28, 2022). Additional doses (e.g., 3rd primary series dose for certain immunocompromised adults and booster dose for

the general adult population) improve upon the benefits provided by the primary series and are currently available under EUA, with the potential for approval in a future BLA supplement.

c. Recommendation for Postmarketing Activities

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

POSTMARKETING REQUIREMENTS UNDER SECTION 505B(a)

1. Deferred pediatric study under PREA (Study mRNA-1273-P203) to evaluate the safety and effectiveness of SPIKEVAX in children 12 years through 17 years of age.

   Final Protocol Submission: January 31, 2022
   Study Completion Date: April 30, 2024
   Final Report Submission: July 31, 2024

2. Deferred pediatric study under PREA (Study mRNA-1273-P204) to evaluate the safety and effectiveness of SPIKEVAX in children 6 months through <12 years of age.

   Final Protocol Submission: February 28, 2022
   Study Completion Date: December 31, 2023
   Final Report Submission: March 31, 2024

3. Deferred pediatric study under PREA (Study mRNA-1273-P206) to evaluate the safety and effectiveness of SPIKEVAX in infants < 6 months of age.

   Final Protocol Submission: June 30, 2022
   Study Completion Date: June 30, 2024
   Final Report Submission: December 31, 2024

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

4. Study mRNA-1273-P903, entitled "Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity", to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

   Final Protocol Submission: January 31, 2022
   Study Completion Date: December 31, 2022
   Final Report Submission: June 30, 2023

5. Study mRNA-1273-P904, entitled "Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe," to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

   Final Protocol Submission: November 4, 2021 (completed)
   Study Completion Date: March 31, 2023
   Final Report Submission: December 31, 2023

6. Study mRNA-1273-P911, entitled "Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273)," to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.

   Final Protocol Submission: April 30, 2022
   Study Completion Date: October 31, 2027
   Final Report Submission: October 31, 2028

7. Study mRNA-1273-P301: sub study to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older.

   Final Protocol Submission: September 14, 2021 (completed)
   Study Completion Date: December 31, 2022
   Final Report Submission: June 30, 2023

8. Study mRNA-1273-P203: sub study to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 years through <18 years of age.

   Final Protocol Submission: November 12, 2021 (completed)
   Study Completion Date: April 30, 2024
   Final Report Submission: July 31, 2024

9. Study mRNA-1273-P204: substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months through <12 years of age.

   Final Protocol Submission: October 6, 2021 (completed)
   Study Completion Date: December 31, 2023
   Final Report Submission: March 31, 2024

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

10. Study mRNA-1273-P901, entitled "Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine."

    Final Protocol Submission: December 20, 2021 (completed)
    Study Completion Date: January 31, 2024
    Final Report Submission: April 14, 2025

11. Study mRNA-1273-P902, entitled "Moderna mRNA-1273 Observational Pregnancy Outcome Study."

    Final Protocol Submission: July 31, 2022
    Study Completion Date: September 30, 2023
    Final Report Submission: June 30, 2024

12. Study mRNA-1273-P905, entitled "Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries."

    Final Protocol Submission: November 4, 2021 (completed)
    Study Completion Date: March 31, 2023
    Final Report Submission: December 31, 2023