



**EMERGENCY USE AUTHORIZATION (EUA) REQUEST
FOR
MODERNA COVID-19 VACCINE
(A NOVEL LIPID NANOPARTICLE-ENCAPSULATED MRNA-
BASED VACCINE AGAINST SARS-COV-2)**

EUA #27073

SPONSORED BY:

MODERNA THERAPEUTICS

TABLE OF CONTENTS

LIST OF ABBREVIATIONS.....	4
1. Description and Intended Use.....	5
1.1. Name of Product	5
1.2. Description of Product	5
1.3. Intended Use	5
2. UNMET NEED ADDRESSED BY THE EUA.....	5
3. APPROVAL/CLEARANCE STATUS	7
4. MANUFACTURING SITE/CGMP STATUS.....	7
5. ADEQUATE, APPROVED AND ALTERNATIVE PRODUCTS.....	8
6. SAFETY AND EFFICACY INFORMATION.....	8
6.1. Preclinical Safety and Efficacy	8
6.2. Clinical Safety and Efficacy	20
6.2.1. Bioassays for assessment of clinical endpoints.....	22
6.2.2. Efficacy	24
6.2.2.1. Phase 3	24
6.2.3. Immunogenicity	25
6.2.3.1. Phase 1	25
6.2.3.2. Phase 2a	26
6.2.4. Safety	26
6.2.4.1. Phase 3	26
7. POTENTIAL RISKS AND BENEFITS.....	27
7.1. Risk-Benefit Assessment	27
7.1.1. Benefits	27
7.1.2. Risks.....	28
7.1.3. Risk-Benefit Assessment	30
7.2. Contraindications	31
7.3. Important Precautions for Administering of the Moderna COVID-19 Vaccine Include: .	31
7.4. Special Populations	31
8. CHEMISTRY, MANUFACTURING, AND CONTROLS	32
9. FACT SHEET FOR HEALTHCARE PROVIDERS.....	33
10. FACT SHEET FOR RECIPIENTS	33
11. PROGRAM SCHEMA.....	33
11.1. Surge Capabilities	35
12. INSTRUCTIONS FOR USE.....	36

12.1.	Moderna COVID-19 Vaccine Preparation.....	36
12.2.	Storage and Packaging	36
12.3.	Dosage and Administration.....	37
13.	ADVERSE EVENT AND MEDICATION ERROR MONITORING	37
14.	LABELING	40
15.	RECORD KEEPING, REPORTING, AND RECORD ACCESS BY FDA ...	40
16.	References	41

LIST OF TABLES

Table 1:	Facilities and Responsibilities for Manufacture, Testing and Release of mRNA-1273 Vaccine.....	7
Table 2:	Summary of mRNA-1273 Pharmacology Studies Supporting EUA ...	11
Table 3:	Summary of mRNA-1273 Biodistribution and Toxicology Studies Supporting EUA.....	19
Table 4:	Safety Population, Size and Denominators (Safety Set).....	20
Table 5:	Overview of EUA Safety and Effectiveness Database for mRNA-1273 Development Program Included in Module 2.5.....	21
Table 6:	Overview of the Main Bioassays for the Assessment of Clinical Endpoints	22
Table 7:	Projected Doses of mRNA-1273 Vaccine Through Q1 2021.....	35

LIST OF ABBREVIATIONS

Acronym	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
bAb	Binding antibodies
BLA	Biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CGMP	Current Good Manufacturing Practice
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
DMID	Division of Microbiology and Infectious Diseases
DS	Data snapshot
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HHS	Health and Human Services
IA	Interim Analysis
LNP	lipid nanoparticle
MN	Microneutralization
mRNA	Messenger Ribonucleic Acid
NP	nucleoprotein
PEG2000-DMG	PEG2000-DMG=1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
PI	Package insert
PPQ	Process performance qualification
RT-PCR	Reverse transcription polymerase chain reaction
S	spike protein
S-2P	spike protein with 2 proline residues introduced for stability in a prefusion conformation
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
(b) (4)	(b) (4)
TFL	Table, Figure, Listing
UTR	Untranslated Region
VE	Vaccine Efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
YOA	Years of age

1. DESCRIPTION AND INTENDED USE

1.1. Name of Product

Moderna COVID-19 Vaccine

1.2. Description of Product

Suspension for injection in multidose container (medicinal product).

1.3. Intended Use

The intended use of investigational Moderna COVID-19 Vaccine under this Emergency Use Authorization (EUA) is to vaccinate persons 18 years of age and older to prevent COVID-19 in accordance with the Advisory Committee on Immunization Practices (ACIP) recommendations.ⁱ

Moderna is proposing the use of Moderna COVID-19 Vaccine under this EUA based on:

1) preclinical evidence of safety and effectiveness, 2) interim safety and immunogenicity results from Phase 1 and 2 clinical studies, 3) interim safety and efficacy results from the Phase 3 clinical study, and 4) sufficient data supporting drug substance (DS) and drug product (DP) manufacturing that ensures the quality and consistency of the vaccine processes, including critical process parameters and in-process controls of specific unit operations, appropriate method qualification/validation and comparability between manufacturing scales and sites.

The Moderna COVID-19 Vaccine will be allocated in a phased approach (i.e., Phase 1a, 1b, 2, 3) based on supply. Initial critical populations identified by ACIP, the National Institutes of Health, and the National Academies of Sciences, Engineering, and Medicine who may be prioritized for vaccination include: critical infrastructure workforce including healthcare personnel and other essential workers; people at risk for severe COVID-19 illness; people at increased risk of acquiring or transmitting COVID-19; people with limited access to routine services including rural communities; those with disability; and people under- or uninsured. These populations are described more fully in the COVID-19 Vaccination Program Playbook for Jurisdiction Operationsⁱⁱ.

2. UNMET NEED ADDRESSED BY THE EUA

On February 4, 2020, the Secretary of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens and that involves the virus that causes COVID-19 (virus later named as SARS-CoV-2)ⁱⁱⁱ. On the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 pandemic effective March 27, 2020^{iv}. Vaccination, including the use of

vaccines under an EUA, continues to be the most effective means of preventing COVID-19 during the ongoing pandemic.

The Food and Drug Administration (FDA) recently approved Veklury (remdesivir) for the treatment of COVID-19 in a hospitalized setting. EUAs have been granted for bamlanivimab for the treatment of mild to moderate COVID-19 and for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19. There are no vaccines authorized or approved by the FDA to prevent COVID-19, which is affecting millions of individuals in the nation.

Vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus. Immunization with a safe and effective COVID-19 vaccine is a critical component of the Nation's strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning. Early in the COVID-19 vaccination program, there may be a limited supply of COVID-19 vaccine, and vaccination efforts will be allocated in a phased approach as described above. The vaccine supply is projected to increase quickly over the proceeding months, allowing vaccination efforts to be expanded to additional critical populations and the general public.

Data from preclinical and clinical studies indicate that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks of the Moderna COVID-19 Vaccine. In the Phase 1 and 2 clinical studies, a consistent dose response was observed across age groups by several measures of humoral immunogenicity for both binding and neutralizing antibodies. The first interim analysis of the efficacy data for the Phase 3 study, which included evaluation of a total of 95 cases of COVID-19 confirmed by the Adjudication Committee and with date of onset beyond 14 days post-dose 2, indicated a point estimate of vaccine efficacy of 94.5% (95% CII: 86.5, 97.8), with a p-value<0.0001. The case split was 90 cases in the placebo group, and 5 cases in the mRNA-1273 group. There were also 11 cases of severe disease reported for evaluation in the first interim analysis, with all cases occurring in the placebo group and no cases occurring in the mRNA-1273, for a point estimate of vaccine efficacy of 100%. Injection site pain, headache, and fatigue were the most commonly reported solicited ARs after dose 1, and injection site pain, fatigue, headache, fatigue, myalgia and arthralgia were the most commonly reported solicited ARs after dose 2. The majority of reported solicited symptoms were mild-to-moderate in severity with a median duration ≤ 3 days. The independent Data and Safety Monitoring Board (DSMB) for the study has been reviewing safety information for this study in an ongoing manner, and has recommended that the study continue as planned, most recently on November 15, 2020. No safety signals have currently been identified.

As the ongoing COVID-19 pandemic continues, Moderna believes that the Moderna COVID-19 Vaccine should qualify for EUA as a part of the Nation's action plan to prevent COVID-19.

3. APPROVAL/CLEARANCE STATUS

mRNA-1273 is not FDA approved or approved in any other country. mRNA-1273 is being evaluated under an active investigational application (IND# 19745). IND# 19745 also cross references DMID IND# 19635 and MF# (b) (4).

4. MANUFACTURING SITE/CGMP STATUS

The following table provides the facilities and responsibilities for cGMP manufacture, testing and release of mRNA-1273 Vaccine. Excluding ModernaTX, Inc, all sites have US FDA establishment licenses as noted in the table.

Table 1: Facilities and Responsibilities for Manufacture, Testing and Release of mRNA-1273 Vaccine

Facility	Address	Responsibility
ModernaTX, Inc. DUNS# 116912313	One Moderna Way Norwood, MA 02062 USA	CX-024414 mRNA
		<ul style="list-style-type: none"> Manufacture of CX-024414 (b) (4) (b) (4) Release and stability testing of CX-024414 Lot release of CX-024414
		(b) (4)
		mRNA-1273 LNP
		<ul style="list-style-type: none"> Manufacture of mRNA-1273 LNP (b) (4) (b) (4) Release and stability testing of mRNA-1273 LNP (excludes bacterial endotoxin testing) Lot release of mRNA-1273 LNP
Lonza Biologics, Inc. FEI# 3001451441	101 International Drive Portsmouth,	mRNA-1273 Drug Product
		<ul style="list-style-type: none"> Release and stability testing of mRNA-1273 Drug Product (excludes bacterial endotoxin and sterility) Lot release of mRNA-1273 Drug Product
		CX-024414 mRNA
		<ul style="list-style-type: none"> Manufacture of CX-024414 (b) (4)

	NH 03801 USA	<p>scale)</p> <ul style="list-style-type: none"> • Bacterial endotoxin and bioburden release testing of CX-024414 • Bacterial endotoxin stability testing of CX-024414 <p>(b) (4)</p> <p>mRNA-1273 LNP</p> <ul style="list-style-type: none"> • Manufacture of mRNA-1273 LNP (b) (4) • Bioburden release testing of mRNA-1273 LNP
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(b) (4)

Catalent Indiana, LLC A wholly owned indirect subsidiary of Catalent Pharma Solutions, Inc. FEI# 3005949964	1300 South Patterson Drive Bloomington, IN 47403 USA	<ul style="list-style-type: none"> • Fill/Finish of mRNA-1273 Drug Product • Packaging of mRNA-1273 Drug Product • Labelling of mRNA-1273 Drug Product • Sterility release and stability testing of mRNA-1273 Drug Product
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Abbreviations: DUNS = data universal numbering system; FEI = FDA establishment Identifier; (b) (4) LNP = lipid nanoparticle; CX-024414 mRNA = mRNA coding for the full-length SARS-CoV-2 spike protein in the pre-fusion conformation; mRNA-1273 LNP = CX-024414 mRNA (b) (4) (b) (4)

5. ADEQUATE, APPROVED AND ALTERNATIVE PRODUCTS

There are no vaccines currently authorized or approved by the FDA to prevent COVID-19. The FDA recently approved Veklury (remdesivir) for the treatment of COVID-19 in a hospitalized setting. EUAs have been granted for bamlanivimab for the treatment of mild to moderate COVID-19 and for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19.

6. SAFETY AND EFFICACY INFORMATION

6.1. Preclinical Safety and Efficacy

In support of clinical development of mRNA-1273 against SARS-CoV-2, nonclinical immunogenicity, biodistribution, and safety studies were completed by the Sponsor using mRNA-1273 or similar mRNA-based vaccines formulated in (b) (4) LNPs.

To characterize the nonclinical immunogenicity and efficacy of mRNA-1273, the Sponsor and the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases performed nonclinical studies in mice, hamsters, and NHPs to evaluate mRNA-1273-induced immune responses, protection from high-dose virus SARS-CoV-2 challenge, and to address the theoretical concern of enhanced respiratory disease (ERD) mediated by vaccine-induced antibody responses and/or Th2-directed T-cell responses observed with other vaccines against viral respiratory diseases.

These studies demonstrated that mRNA-1273 is immunogenic in all species assessed, showing a dose-dependent response in IgG binding antibody titers and a significant correlation between binding and neutralizing antibody activity. In addition, antigen-specific T-cell responses were observed in studies in mice and in the NHP study. Th1-directed CD4 and CD8 T-cell responses were measured post-boost in animals that were vaccinated with mRNA-1273. Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of IgG2a/c/IgG1 antibody subclasses in mice, and the high levels of neutralizing antibody in all species lessens concerns regarding disease enhancement associated with administration of mRNA-1273.

In addition to measurements of the immune response, mice, NHPs, and hamsters were challenged with high-dose SARS-CoV-2 virus. In these studies, dose levels were included that were predicted to be optimal (fully protective) and suboptimal (subprotective). At higher doses, mice and NHPs were fully protected from viral replication in both lungs and nasal passages. At subprotective dose levels, animals either remained fully protected in the lungs or had reduced viral burden post-challenge versus control animals. There were no observations of increased viral load in vaccinated animals at protective or subprotective dose levels, further supports that mRNA-1273 does not drive enhanced disease.

The safety and tolerability of similar mRNA-based vaccines formulated in an (b) (4) (b) (4) LNP matrix encapsulating mRNA constructs encoding for various antigens have been evaluated in multiple GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats followed by a 2-week recovery period (Study 5002045, Study 5002231, Study 5002034, Study 5002158, Study 5002033, Study 5002400; CBER MF# 19622). The Sponsor proposes that the toxicity associated with mRNA vaccines formulated in LNP formulations are driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the expressed antigens of the mRNA vaccine. This is supported by the consistency of the aggregate rat repeat-dose toxicity profile observed in these GLP studies at IM doses ranging from 9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks and is considered to be representative of mRNA vaccines formulated in the same (b) (4) matrix, differing only by the encapsulated mRNA

sequence(s). Thus, the aggregate toxicity results from these studies support the development of mRNA-1273.

A developmental and reproductive toxicity (DART) study to assess potential fertility and pre and postnatal development effects of mRNA-1273 in pregnant and lactating female Sprague Dawley rats is currently on-going. A dose of 100 µg /dose was administered to female rats 28 and 14 days prior to mating and on gestation Days 1 and 13. Assessments include maternal function, embryo-fetal development, and postnatal development. Additionally, exposure to the SARS-CoV-2 antibody will be confirmed in the dams, embryo/fetuses, and pups. An audited draft report is expected to be submitted to IND# 19745 in early December.

Overall, nonclinical animal studies demonstrated that mRNA-1273 is safe and well tolerated, is immunogenic, fully protects animals from challenge at optimal dose levels, and does not drive ERD at protective or subprotective dose levels. These nonclinical studies supporting the development of mRNA-1273 are listed in [Table 2](#) and [Table 3](#), and the completed and preliminary results are described in Module 2.4 of IND# 19745. Study reports for the completed non-clinical studies are planned for submission to the BLA in December.

Table 2: Summary of mRNA-1273 Pharmacology Studies Supporting EUA

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Murine Studies								
BALB/cJ C57BL/6 B6C3F1/J	6-week-old/F	3/strain	10	Immunizations IM with 0.01, 0.1 or 1 µg of mRNA-1273 at W0 and W3. Sera were collected 2 weeks post-prime and post-boost.	N/A	ELISA and pseudovirus neutralization assay	0.01, 0.1, and 1 µg of mRNA-1273 elicits spike-binding IgG titers in a dose-driven manner. 1 µg of mRNA-1273 elicits a neutralizing response.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section I Murine Binding and Neutralizing Antibodies and Figure I.1.
BALB/c	6-8-week-old/F	14	8	Immunizations IM with 14 different doses ranging from 0.0025 - 20 µg of mRNA-1273 at W0 and W3. Sera were collected 2 weeks post-prime and post-boost.	N/A	ELISA and pseudovirus neutralization assay	mRNA-1273 elicits a dose-dependent antibody binding and neutralizing response and there is a strong positive correlation between binding and neutralizing titers.	IND 19745 Section 1.11.2 (MOD3938/40) and DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section I Murine Binding and Neutralizing Antibodies and Figure I.2.
BALB/cJ	6-8-week-old/F	3	10	Immunizations IM with 0.1, 1 or 10 µg of mRNA-1273. Sera were collected at 2- and 4-weeks postimmunization.	N/A	ELISA and pseudovirus neutralization assay	Single-dose immunization with mRNA-1273 elicits a robust antibody response.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section I Murine Binding and Neutralizing Antibodies and Figure I.3.

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Murine Studies								
BALB/cJ	6-8-week-old/F	3	3	Immunizations IM with 1 µg of (b) (4) SARS-CoV-2 S-2P at W0 and W3. Sera were collected 2 weeks post-boost and pooled.	N/A	Pseudovirus neutralization assay and PRNT	1 µg of (b) (4) SARS-CoV-2 S-2P elicits similar neutralizing activity to 1 µg of mRNA-1273.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section I Murine Binding and Neutralizing Antibodies and Table I.1
BALB/c	≥ 25-week-old/F	3	10	Immunizations IM with 0.1 or 1 µg of mRNA-1273 or SARS-CoV-1 DIV at W0 and W3. Sera were collected 2 weeks post-prime and post-boost.	N/A	ELISA and pseudovirus neutralization	mRNA-1273 elicits a dose-dependent antibody binding and neutralizing response in aged mice.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 “Immunogenicity and Efficacy of mRNA-1273 and SARS-CoV Double-Inactivated Virus (DIV) in Aged BALB/c Mice”, dated June 29, 2020
BALB/cJ C57BL/6 B6C3F1/J	6-8-week-old/F	6/strain	10	Immunizations IM with 0.01, 0.1 or 1 µg of mRNA-1273 or (b) (4) SARSCoV-2 S-2P at W0 and W3. Sera were collected at 2 weeks post boost.	N/A	ELISA	mRNA-1273 or (b) (4) SARS-CoV-2 S-2P elicit S-specific Th1-biased T-cell response.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section II Murine IgG2a/IgG1 and Figure II.1.

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Murine Studies								
BALB/cJ	6-8-week-old/F	6	10	Immunizations IM with 0.01 or 1 µg of mRNA-1273 or 0.2 and 1 µg of CDS or SARS-CoV-1 DIV adjuvanted with (b) (4) at W0 and W3. Sera were collected at 2 weeks post-boost.	N/A	ELISA	mRNA-1273 elicits a distinct profile of binding and neutralizing antibodies compared to inactivated virus or CDS delivered in (b) (4)	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section II Murine IgG2a/IgG1 and Figure II.2 and “Illness and lung hemorrhage scores following SARS-CoV-2 MA10 challenge of BALB/c immunized with mRNA1273 and Th2-skewing Vaccine Regimens”, dated June 26, 2020
BALB/c	≥ 25-week-old/F	3	10	Immunizations IM with 0.1 or 1 µg of mRNA-1273 or SARS-CoV-1 DIV at W0 and W3. Sera were collected 2 weeks post-prime and post-boost.	N/A	ELISA	mRNA-1273 elicits a balanced IgG2a and IgG1 response in aged mice.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 “Immunogenicity and Efficacy of mRNA-1273 and SARS-CoV Double-Inactivated Virus (DIV) in Aged BALB/c Mice”, dated June 29, 2020

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Murine Studies								
BALB/c	6-8-week-old/F	3	7	Immunizations IM with 1 or 10 µg of mRNA-1273 or 10 µg of SARS-CoV-2 S protein adjuvanted with (b) (4) at W0 and W2. Sera were collected at 2 weeks post-boost. At 4 weeks post-boost, splenocytes were collected and evaluated.	N/A	ELISA and cytokine measurement by (b) (4)	mRNA-1273 elicits Th1-skewed responses compared to S protein adjuvanted with (b) (4)	IND 19745 Section 1.11.2 (MOD-3937) and DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section II Murine IgG2a/IgG1 and Figure II.3 and Section III Murine IFN γ Production and Th1 vs Th2 Responses and Figure III.1.
B6C3F1/J	6-8-week-old/F	6	5	Immunizations IM with 0.1, 1 or 10 µg of mRNA-1273 or 0.1 or 1 µg of (b) (4) SARS-CoV-2 S2P. Splenocytes were collected 7 weeks later and analyzed.	N/A	ELISA and cytokine measurement by ICS	mRNA-1273 and S2P protein, delivered with (b) (4), elicit S-specific T-cell responses.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section III Murine IFN γ Production and Th1 vs Th2 Responses and Figure III.2

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Murine Studies								
BALB/cJ	6-8-week-old/F	7	10	Immunizations IM with 0.1 or 1 µg of mRNA-1273, or 0.2 or 1 µg of CDS or SARS-CoV-1 DIV adjuvanted with (b) (4) at W0 and W3. Splenocytes were collected at 2 weeks post-boost.	N/A	Cytokine measurement by ICS	mRNA-1273-elicited S protein-specific CD4+ T cells have a significantly different immune profile than those elicited by Th2skewing regimens, and high-dose mRNA-1273 immunization elicits CD8+ T-cell responses.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section III Murine IFN γ Production and Th1 vs Th2 Responses and Figure III.3 and “Illness and lung hemorrhage scores following SARS-CoV-2 MA10 challenge of BALB/c immunized with mRNA-1273 and Th2-skewing Vaccine Regimens”, dated June 26, 2020
BALB/c	≥ 25-week-old/F	4	5	Immunizations IM with 0.1 or 1 µg of mRNA-1273 or SARS-CoV-1 DIV. Four-weeks post-immunization mice were challenged. Four days post-challenge lung supernatants were collected.	Mouse-adapted SARS-CoV-2	Cytokine analysis by immunoassay	DIV induces increased levels of lung cytokines compared to mRNA-1273 in challenged aged mice.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 “Immunogenicity and Efficacy of mRNA-1273 and SARS-CoV Double-Inactivated Virus (DIV) in Aged BALB/c Mice”, dated June 29, 2020

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
BALB/c	≥ 25-week-old/F	4	5	Immunizations IM with 0.1 or 1 µg of mRNA-1273 or SARS-CoV-1 DIV. Four-weeks post-immunization mice were challenged. Two or 4 days post-challenge lung hemorrhage score was assessed.	Mouse-adapted SARS-CoV-2	Weight loss, viral load and lung hemorrhage score	mRNA-1273 protects aged mice from lethal SARS-CoV-2 infection.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section IV Protective Efficacy of mRNA-1273 in Mice and Figure IV.1
Murine Studies								
BALB/cJ	6-8-week-old/F	3	5	Immunizations IM with 0.1, 1 or 10 µg of mRNA-1273. Seven-weeks post-immunization mice were challenged. Two days post-challenge, mouse lungs were harvested.	Mouse-adapted SARS-CoV-2	Plaque assay	Single immunization of mRNA-1273 at 1 or 10 µg protects the murine lower airway.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section IV Protective Efficacy of mRNA-1273 in Mice and Figure IV.2(A)
BALB/c	≥ 25-week-old/F	4	5	Immunizations IM with 0.1 or 1 µg of mRNA-1273 or 0.2 µg and SARS-CoV-1 DIV. Four-weeks post-immunization mice were challenged. Two or 4 days post-challenge lung hemorrhage score was assessed.	Mouse-adapted SARS-CoV-2	Weight loss, viral load and lung hemorrhage score	mRNA-1273 protects aged mice from disease following SARS-CoV-2 challenge.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 “Immunogenicity and Efficacy of mRNA-1273 and SARS-CoV Double-Inactivated Virus (DIV) in Aged BALB/c Mice”, dated June 29, 2020

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
BALB/cJ	6-8-week-old/F	10	5	Immunizations IM with 0.01, 0.1 or 1 µg of mRNA-1273 at W0 and W3. Five- or 13-weeks post-boost mice were challenged. Two days post-challenge nasal turbinates and lungs were harvested.	Mouse-adapted SARS-CoV-2	Plaque assay	Prime boost immunization regime of mRNA-1273 at 1 µg protects the murine lower and upper airway.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section IV Protective Efficacy of mRNA-1273 in Mice and Figure IV.2(B-E)
Murine Studies								
BALB/cJ	6-8-week-old/F	4	5	Immunizations IM with 0.01 or 0.1 µg of mRNA-1273 at W0 and W3 or a single immunization with 0.1 µg. Seven-weeks post-immunization or 5-weeks post-boost mice were challenged. At Days 2 or 4, post-challenge lungs were harvested.	Mouse-adapted SARS-CoV-2	Histology	Subprotective doses of mRNA-1273 do not induce immunopathology in lungs.	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section IV Protective Efficacy of mRNA-1273 in Mice and Figure IV.3.
Hamster Studies								
Syrian golden hamster	12-14-week-old/F	5	15	Immunizations IM with 25, 5, or 1 µg of mRNA-1273 at W0 and W3 or 25 µg of mRNA-1273 W0 only. Sera were collected pre-immunization, 3- and 6-weeks post-prime and post-boost.	SARS-related coronavirus 2, Isolate USA-WA1/2020, 10 ⁵ PFU/100 µL challenge	ELISA, LV PRNT, viral load in lung and nasal turbinates by plaque assay (D2, D4, D14, post-challenge)	mRNA-1273 elicits robust binding antibody responses in hamsters.	IND 19745 Section 1.11.2 (UTMB01)

Test Animal	Age/Sex	No. of Cohorts	No of Animals /Cohort	Interventions	Challenge	Experimental Assessment	Outcome	Reference
Nonhuman Primates								
Rhesus macaque	3-5-years of age/4F and 4M	3	8	Immunizations IM with 10 or 100 µg of mRNA-1273 at W0 and W4. Sera were collected pre-immunization, 2- and 4-weeks post-prime and post-boost.	N/A	ELISA, pseudovirus neutralization assay, live virus neutralization by NanoLuc reporter assay and cytokine measurement by ICS	mRNA-1273 elicits robust binding and neutralizing antibody responses in non-human primates	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 Section V “Immunogenicity and Protective Efficacy of mRNA-1273 in Rhesus Macaques”, dated July 02, 2020 and Figure V.1
Nonhuman Primates								
Rhesus macaque	3-5-years of age/4F and 4M	3	8	Immunizations IM with 10 or 100 µg of mRNA-1273 at W0 and W4. Sera were collected pre-immunization, 2- and 4-weeks post-prime and post-boost and Days 0, 7, and 14 post-challenge. Nasal swabs were collected Days 1, 2, 4, and 7 post-challenge. BALs were collected days 2, 4, and 7 post-challenge.	SARS-CoV-2 USA-WA 1/2020	ELISA, PCR, histology, chemokine and cytokine assessment by Luminex	mRNA-1273 limits SARS-CoV-2 replication upper and lower airways of rhesus macaques	DMID IND #19635 SN00020 Section 1.11.2 VRC mRNA-1273 Nonclinical Study Update v2.0 July 2, 2020 “Immunogenicity and Protective Efficacy of mRNA-1273 in Rhesus Macaques”, dated July 02, 2020

Abbreviations: BAL = bronchoalveolar lavage; CDS = conformationally-disrupted spike protein; DIV = double inactivated; ELISA = enzyme-linked immunosorbent assay; F = female; ICS = intracellular staining; IgG = immunoglobulin G; IM = intramuscular; IN = intranasal(ly); IND = Investigational New Drug; IT = intratracheal; LV = live virus plaque reduction assay; M = male; N/A = not applicable; NHP = nonhuman primate; PCR = polymerase chain reaction; PFU = plaque-forming unit; PRNT = plaque reduction neutralization test; PV = pseudovirus neutralization assay; S = spike; S2P = spike protein with 2 proline residues introduced for stability in a prefusion conformation; SARS = severe acute respiratory syndrome; SARS-CoV-2 = 2019 novel coronavirus; (b) (4) Th = T-helper ; VRC = Vaccine Research Center; W = week.

Table 3: Summary of mRNA-1273 Biodistribution and Toxicology Studies Supporting EUA

Study Type/Description	Test Article/ Viral Antigen (if not SARS- CoV-2) ^a	Species, Strain	Method of Administration; Dosing Schedule	GL P	Reference
Biodistribution Studies					
Single dose tissue distribution study	mRNA-1647 (CMV)	Rat, Sprague Dawley	IM 1 single dose	No	5002121 Amendment 1 CBER MF #19622
Toxicology Studies					
Repeat-Dose Toxicity					
1-month (3 doses) repeat- dose study with 2week recovery	mRNA-1706 (Zika)	Rat, Sprague Dawley	IM; (Days 1, 15, 29)	Yes	5002045 CBER MF #19622
1-month (3 doses) repeat- dose study with 2week recovery	mRNA-1706 (Zika)	Rat, Sprague Dawley	IM; (Days 1, 15, 29)	Yes	5002231 CBER MF #19622
1-month (3 doses) repeat- dose study with 2week recovery	mRNA-1653 (human metapneumovirus and PIV3)	Rat, Sprague Dawley	IM; (Days 1, 15, 29)	Yes	5002033 CBER MF #19622
1-month (3 doses) repeat- dose study with 2week recovery	mRNA-1893 (Zika)	Rat, Sprague Dawley	IM; (Days 1, 15, 29)	Yes	5002400 CBER MF #19622
6-week (4 doses) repeat- dose study with 2-week recovery	mRNA-1647 (CMV)	Rat, Sprague Dawley	IM; (Days 1, 15, 29, 43)	Yes	5002034 CBER MF #19622
6-week (4 doses) repeat- dose study with 2week recovery	mRNA-1443 (CMV)	Rat, Sprague Dawley	IM; (Days 1, 15, 29, 43)	Yes	5002158 CBER MF #19622
In Vitro Genotoxicity					
Bacterial reverse mutation test	(b) (4)	Salmonella typhimurium, Escherichia coli	Incubation for 67 hours 29 minutes	Yes	9601567 CBER MF #19622
Mammalian cell micronucleus test		Human peripheral blood lymphocytes	Incubation for 4 and 24 hours	Yes	9601568 CBER MF #19622
In Vivo Genotoxicity					
In vivo mammalian erythrocyte micronucleus test	mRNA-1706 (Zika)	Rat, Sprague Dawley	Single IV	Yes	9800399 CBER MF #19622
Other Toxicology					

5-week (2 doses) repeat-dose immunogenicity and toxicity study	mRNA-1273	Rat, Sprague Dawley	IM; (Days 1 and 22)	No	2308123 IND 19745 4.2.3.7
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Abbreviations: alum = aluminum hydroxide; CDS = conformationally disrupted severe acute respiratory syndrome coronavirus-2 S protein; CMV = cytomegalovirus; g = glycoprotein; GLP = Good Laboratory Practice; IM = intramuscular; IV = intravenous; mRNA = messenger ribonucleic acid; NHP = nonhuman primate; SARSCoV-1 DIV = double-inactivated severe acute respiratory syndrome coronavirus1; WT = wildtype.

^aThe viral antigen comprising non-mRNA-1273 products is shown in the table. Additional IP formulation information is included in the study report. The same LNP formulation was used for each study.

^bThe NPI luciferase mRNA is combined in a mixture of 4 lipids ((b) (4)), PEG2000-DMG, cholesterol, and DSPC) and formulated in 25 mM Tris, 123 g/L sucrose, 1 mM DTPA, pH 7.5.

6.2. Clinical Safety and Efficacy

The clinical safety and efficacy are being evaluated in 3 ongoing clinical studies: a dose ranging- Phase 1 safety and immunogenicity study; a dose confirmation Phase 2a safety and immunogenicity study; and a pivotal Phase 3 efficacy, safety, and immunogenicity study. Across the 3 studies, 15,419 participants have been dosed with the 100 µg dose of mRNA-1273 (Table 4). These studies and the available data summarized in detail Module 2.5 are described in Table 5, and summarized in the clinical safety and efficacy sections below.

Table 4: Safety Population, Size and Denominators (Safety Set)

Safety Database for the Study Vaccine ¹		
N=15419		
Clinical Trial Groups	Vaccine Group	Placebo Group
Controlled trials conducted for this indication ²		
Study P301	15,184	15,165
Study P201	200 ²	200
Study P101 (DMID 20-0003)	35	0

¹ study vaccine means the vaccine being considered for approval.

² In Study P201, 200 subjects on mRNA-1273 100µg, 200 subjects on mRNA-1273 50µg

At the time of this submission, safety and efficacy data from all 3 studies support a positive benefit-risk profile.

The initial EUA package includes efficacy analyses from the first interim analysis that demonstrated the vaccine efficacy of mRNA-1273 based on the pre-specified success criterion

on efficacy with VE of 94.5% (95% CI: 86.5%, 97.8%). The total number of COVID-19 cases for IA#1 confirmed by the Adjudication committee is 95. At the time of IA1, the median follow-up was 7 weeks safety for the full cohort. Additional safety data with a median follow-up of 2 months, and additional efficacy data with the final efficacy analysis will be submitted as a follow-up to the initial EUA submission. The following clinical information have been submitted to the IND in support of this EUA application:

- Study mRNA-1273-P301 Efficacy Tables and Figures are provided in Module 5.3.5.1 – (IND 19745, SN0071)
- Study mRNA-1273-P301 Safety TFLs are provided in Module 5.3.5.1 – (IND 19745, SN0080)
- Study mRNA-1273-P301 Datasets are provided in Module 5.3.5.1 – (IND 19745, SN0080)
- Study mRNA-1273-P201 TFLs are provided in Module 5.3.5.1 – (IND 19745, SN0078)
- [Module 2.5](#) with summaries of the data is provided in Module 2– (EUA 27073)
- DMID Phase 1 Study 20-0003 20-0003 Safety Summary Report (dated 26 Oct 2020) is provided in Module 1.11.3– (IND 19745, SN0080)
- DMID Phase 1 Study 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020) and 20-0003 Immunogenicity Summary Report (dated 24 Sep 2020) are provided in Module 1.11.3– (IND 19745, SN0080)
- SOPs and Validation Assays for clinical biomarkers (IND 19745, SN0036 and SN0073)

Table 5: Overview of EUA Safety and Effectiveness Database for mRNA-1273 Development Program Included in Module 2.5

mRNA-1273 Clinical Study	Population	Scope of Data Set	Endpoints
Phase 1 Study (DMID 20-0003)	Healthy adults 18 to 55 years age (n=60), 56 to 70 years age (n=30) or 71+ years age (n=30) receiving 25, 50, 100 or 250 µg	Safety Data through 07 Oct for 100 µg dose	solicited and unsolicited AE, AE leading to w/d, SAE, MAAE
		Immunogenicity Data through Day 119 for 100 µg dose	Binding Ab responses (ELISA)
			Neutralizing Ab responses
		Cell mediated immunity	Intracellular T cell cytokine profile (Th1 vs Th2) for CD8+ and CD4+ T cells

mRNA-1273 Clinical Study	Population	Scope of Data Set	Endpoints
Phase 2 Study (mRNA-1273-P201)	Healthy adults between 18 to <55 years age (n=300) and 55+ years age (n=300) years randomized 1:1:1 to placebo, 50 or 100 µg	Safety Data through Day 57	solicited AR and unsolicited AE, AE leading to w/d, SAE, MAAE
		Immunogenicity Data through Day 57	Binding Ab responses (ELISA)
			Neutralizing Ab responses
Phase 3 Study (mRNA-1273-P301)	Adults >18 years age (n=30,000) randomized 1:1 to placebo or 100 µg	Efficacy Data from IA#1 (95 cases for the primary efficacy endpoint in the PP Set)	<ul style="list-style-type: none"> Analysis of Primary efficacy endpoint to demonstrate the efficacy of mRNA-1273 to prevent COVID-19 <ul style="list-style-type: none"> Available subgroup analyses Analysis of select secondary efficacy endpoints including prevention of severe COVID-19 and secondary case definition of COVID-19
		Safety data (median follow-up time: 49 days data)	Solicited AR and unsolicited AE, AE leading to w/d, SAE, MAAE up to data snapshot 2

Abbreviations: Ab = antibody; AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; ELISA = enzyme-linked immunosorbent assay; IA = interim analysis; MAAE = medically attended adverse event; SAE = severe adverse event; w/d = withdrawal

6.2.1. Bioassays for assessment of clinical endpoints

The clinical biomarker strategy to support clinical development under our IND (#19745) includes an extensive panel of assays to assess infection and characterize the immune response induced by mRNA-1273. The context of use, assay name, brief description, development status, and supporting available information available in IND #19745 is summarized in [Table 6](#) below.

Table 6: Overview of the Main Bioassays for the Assessment of Clinical Endpoints

Assay Name	Methodology	Context of Use	Development Status (Vendor)	Supporting Documentation
SARS-CoV-2 RT-PCR	RT-PCR	Baseline serostatus and asymptomatic/symptomatic SARS-CoV-2 infection for study	Commercial (LDT), Validated at Performing CLIA Lab (Viracor)	EUA https://www.fda.gov/media/136740/download LoA: EUA200124 21120-9142 21120-9152 21120-9184

Assay Name	Methodology	Context of Use	Development Status (Vendor)	Supporting Documentation
		participants P201 and P301		21120-9201 21120-9204 21120-9249 21120-9457 COVID PCR Control LJ Trending Hi Pos COVID PCR Control LJ Trending Lo Pos
Roche's Elecsys Anti-SARS-CoV-2	Antibody-based electrochemiluminescence	Baseline serostatus and asymptomatic/symptomatic SARS-CoV-2 infection for study participants P301	Commercial, Validated at Performing CLIA Lab (PPD GCL)	EUA, PI https://www.fda.gov/media/137603/download https://www.fda.gov/media/137605/download LoA: EUA200514 Elecsys SARSCOV2 cut-off determination GCL-LAB-0172r14 GCL-LAB-0699r02 GCL-LAB-0957ar04 AMR Tab GCL-LAB-0957ar04 Change Log Tab GCL-LAB-0957ar04 Info Tab GCL-LAB-0957ar04 ReagentCalQC Tab GCL-LAB-0957ar04 RefRange Tab GCL-LAB-0957ar04 StabInt Tab GCL-LAB-0957ar04
Anti-Spike IgG ELISA	ELISA	Immunogenicity Assessments P201	Qualified (PPD Vaccines Laboratories)	Qualification Statistical report (VSDVAC 58)
Anti-Spike IgG ELISA	ELISA	Immunogenicity Assessments P301	Validated (PPD Vaccines Laboratories)	Validation Statistical Report and SOP Method VSDVAC 65
Anti-NP IgG ELISA	ELISA	Infection Assessment (Qualitative) P201 and P301	Qualified (PPD Vaccines Laboratories)	Qualification report VSDVAC 64 Validation Plan VSDVAC 66

Assay Name	Methodology	Context of Use	Development Status (Vendor)	Supporting Documentation
				Validation Statistical Report will be available End of Nov.
SARS-CoV-2 Virus Neutralization 1	Live virus Micro-Neutralization (MN)	Immunogenicity Assessment P201 and P301	Qualified (Battelle)	Qualification report (QA-5858) Validation report not yet available.
	PseudoVirus-Based Neutralization (PsV)	Immunogenicity Assessment P201 and P301	Validation Report pending. (TBC)	Validation report not yet available.

Abbreviations: EUA = emergency use authorization; ELISA = enzyme-linked immunosorbent assay; PI = package insert; RT-PCR = reverse transcriptase polymerase chain reaction

6.2.2. Efficacy

6.2.2.1. Phase 3

The primary efficacy endpoint was VE of mRNA-1273 to prevent the first occurrence of COVID-19, and the primary endpoint analysis included cases starting 14 days after the second injection in the PP Set, as adjudicated by an independent adjudication committee that was blinded to vaccine group assignment. Symptomatic COVID-19 was defined as the presence of two systemic symptoms including fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory or taste disorders; OR one respiratory symptom including cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND the participant had to have at least one nasopharyngeal (NP) swab, nasal swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

At IA1, there was a total of 95 cases of COVID-19 starting 14 days after the 2nd dose confirmed by the Adjudication Committee based on the per-protocol Set, the primary analysis population for efficacy. There were 5 cases on mRNA-1273 and 90 cases on Placebo. The VE of mRNA-1273 based on hazard ratio was 94.5% compared to placebo, with a 95% CI of 86.5%, 97.8%. The 1-sided p value was $< .0001$ to reject the null hypothesis of $\text{VE} \leq 30\%$, achieving the prespecified efficacy boundary based on the 1-sided nominal alpha of 0.0047 using the Lan-DeMets O'Brien-Fleming spending function using the O'Brien-Fleming boundary.

There were 11 cases of severe disease cases starting 14 days after the 2nd dose based on adjudication committee assessment at IA1, with all cases occurring in the placebo group and no cases occurring in the mRNA-1273. The point estimate of vaccine efficacy for preventing severe disease was 100%.

For the full description of the Phase 3 efficacy data, refer to [Module 2.5.4.2](#). Module 2.5 contains the data and corresponding summaries for the Phase 3 efficacy data, including:

- Analysis of Primary efficacy endpoint to demonstrate the efficacy of mRNA-1273 to prevent COVID-19
- Subgroup analysis of the primary efficacy endpoint by:
 - age
 - age and health risk for severe COVID-19 (18 to <65 not at risk, 18 to <65 at risk for severe COVID-19, and ≥65)
 - sex
 - race and ethnicity group (white as compared to a pooled group of communities of color)
- Analysis of Secondary efficacy endpoints:
 - to demonstrate the efficacy of mRNA-1273 to prevent **severe** COVID-19
 - to demonstrate the efficacy of mRNA-1273 to prevent symptomatic COVID-19 disease by a broader, secondary definition
 - to evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose
 - To evaluate the efficacy of mRNA-1273 to prevent COVID-19 regardless of prior SARS-COV-2 infection status (using Full Analysis Set)

6.2.3. Immunogenicity

6.2.3.1. Phase 1

Immunogenicity results in Study 20-0003 indicated that the 100 µg dose administered as 2 injections 28 days apart resulted in the induction of neutralizing antibodies in all participants across three age strata (18-55, 56-70, and ≥71 YOA) as of 1 week after the second injection.^{v vi} After a single injection of 100 µg of mRNA-1273, bAb for Spike glycoprotein were detectable two weeks later in all participants in all 3 age strata, with further increases observed at the second injection. The immune response was consistent across age groups and persisted 3 months after the second injection (20-0003 Immunogenicity Summary Report [29 Oct 2020]). A similar response was observed across all doses in all age cohorts, but higher responses were observed with the second injection in older adults at doses of 100 µg as compared to the 25 µg dose. Further, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited, if any, indication of a Th2-directed response.

For the full description of the Phase 1 immunogenicity data, refer to [Module 2.5](#), the 20-0003 Immunogenicity Summary Report (dated 29 Oct 2020), and 20-0003 Immunogenicity Summary Report (dated 24 Sep 2020) (IND 19745 Module 1.11.3, SN0080).

6.2.3.2. Phase 2a

Participants who received 2 doses of either 50 µg or 100 µg of mRNA-1273 separated by 28 days developed both binding and neutralizing antibodies against the SARS-CoV-2 virus, with GMFRs >20-fold (binding antibody) and >50-fold (MN assay), regardless of dose level. These data are supportive because of the magnitude of the antibody response to 2 doses of mRNA-1273 and confirm the selection of the 100-µg dose brought forward in the pivotal Phase 3 efficacy study.

For the full description of the Phase 2 immunogenicity data, refer to [Module 2.5.4.2.4.1](#).

6.2.4. Safety

The observed safety profiles in the Phase 1 and Phase 2 studies were consistent with observations in the Phase 3 study, and neither study resulted in any emerging safety concerns. The 100 µg dose was generally well tolerated in both studies. Solicited adverse reactions (AR) were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site for all age groups. Solicited ARs were dose dependent and were more common after the second immunization. No vaccine-related SAEs were reported and no holding rules were met. Unsolicited AEs related to vaccination were mostly mild in severity and all resolved without sequelae. Both studies employed independent Safety Monitoring Committees, and both committees have recommended that the studies continue as planned.

For the full summaries of Phase 1 and Phase 2 safety data, refer to [Module 2.5.5.2](#) and [Module 2.5.5.3](#).

6.2.4.1. Phase 3

In the Phase 3 study, the safety and reactogenicity of mRNA-1273 100 µg compared with placebo administered 28 days apart were assessed in participants 18 years of age and older at increased risk for acquiring COVID-19 based on occupation or location and living circumstances. Reactogenicity (solicited local and/or systemic ARs) was observed in the majority of participants in the mRNA-1273 group and generally increased after the second injection. The rates of local and systemic reactions were higher in the mRNA-1273 group than in the placebo group after each injection. Injection site pain, headache, and fatigue were the most commonly reported solicited ARs after dose 1, and injection site pain, fatigue, headache, myalgia and arthralgia were the most commonly reported solicited ARs after dose 2. The majority of solicited ARs in the mRNA-1273 group were grade 1 to grade 2 in severity and generally

resolved within 3 days or less. The overall incidence of unsolicited treatment-emergent adverse events (TEAEs), severe TEAEs, and MAAEs during the 28 days after injection were also generally similar in participants who received mRNA-1273 and those who received placebo.

The independent Data and Safety Monitoring Board (DSMB) has been reviewing safety information for this study in an ongoing manner, and has recommended that the study continue as planned, most recently on November 15, 2020. No safety signals have currently been identified.

Deaths and SAEs were generally reported at a similar incidence in the mRNA 1273 and placebo groups. There was no evidence of enhanced disease as fewer cases (n=0) of severe COVID-19 and COVID-19 were observed in participants who received mRNA-1273 than those who received placebo (n=11). Deaths and SAEs were generally reported at a similar incidence in the mRNA-1273 and placebo groups.

For the full summaries of the Phase 3 safety data, refer to [Module 2.5.5.1](#).

7. POTENTIAL RISKS AND BENEFITS

7.1. Risk-Benefit Assessment

7.1.1. Benefits

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study mRNA-1273-P301. The primary efficacy endpoint in Study mRNA-1273-P301 was met: mRNA-1273 prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the mRNA-1273 group and 90 cases in the placebo group). The VE was 94.5% (95% CI: 86.5%, 97.8%; one-sided p value < 0.0001), rejecting the null hypothesis of $VE \leq 30\%$ and achieving the prespecified efficacy boundary based on the 1-sided nominal alpha of 0.0047 using the Lan-DeMets O'Brien-Fleming spending function.

The vaccine was effective in preventing severe COVID-19, with 11 cases in the placebo group and 0 cases in the mRNA-1273 group. In addition, the vaccine was efficacious in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second injection (VE of 93.5% based on HR).

The mRNA-1273-P301 study population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of mRNA-1273 was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females,

and in White participants and those from communities of color. There was a limited number of participants in each ethnic group in the subgroup analysis who contributed to the primary efficacy endpoint, and therefore efficacy analyses were not performed for each specific racial and ethnic subgroup.

The efficacy of mRNA-1273 in the PPS was consistent across several sensitivity analyses, including those using the mITT population and FAS populations, as well as COVID-19 cases from randomization and 14 days after the first injection. The vaccine efficacy to prevent COVID-19 starting 14 days after the first dose of vaccine was 95.4%, and to prevent COVID-19 after randomization was 94.6%. However, these analyses must be interpreted with caution because the follow-up period was limited (approximately 28 days), the vast majority (>90%) of participants received a second dose, and cases were not censored from the analysis if they occurred after the second dose.

The immunogenicity of the mRNA-1273 vaccine was evaluated in Studies DMID 20-0003 and mRNA-1273-P201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal Phase 3 study. In Study 20 0003 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of neutralizing or binding antibody and this observation was the basis for selecting the 100-µg dose for use in the pivotal Phase 3 study. Importantly, the antibody levels after 2 doses of mRNA 1273 exceeded those in a pool of convalescent sera. Neutralizing activity was observed for the 100 µg mRNA-1273 dose as of Day 36, which was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. Additionally, in Study 20-0003, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response and similar responses were observed among all age groups for the 100-µg dose. In the dose-confirming study, mRNA-1273-P201, generally comparable neutralizing and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of mRNA-1273 administered 28 days apart.

7.1.2. Risks

Moderna COVID-19 Vaccine is an investigational vaccine and is not FDA-approved for prevention of COVID-19.

The safety of mRNA-1273 is largely based on data from the pivotal Phase 3 study using an 11 Nov 2020 data snapshot taken at the time of the interim analysis. The safety analysis set included 30,350 study participants: 15,184 received mRNA-1273 and 15,165 received placebo. The median study duration from first injection was 78 days (range: 1 to 108 days or more) for 30,350

participants and the median study duration from second injection was 49 days (range: 0 to 83 days or more).

Solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and systemic ARs were more common after the second injection. The most common solicited local AR was pain and the incidence was similar between the first and second injections of mRNA-1273. The majority of the solicited local ARs occurred within the first 1 to 2 days after administration of mRNA 1273 and generally persisted for a median of 1 to 3 days. Solicited systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and the majority of these solicited systemic ARs were mild to moderate in severity. The most common solicited systemic ARs were headache and fatigue after the first injection and, headache and fatigue, myalgia, arthralgia and chills after second injection. The majority of solicited systemic reactions also occurred within the first 1 to 2 days after administration of IP and persisted for a median of 3 days or less.

Solicited local and systemic ARs were more commonly reported by younger adults (18 to < 65 years) compared with older adults (≥ 65 years) after the first and second injections. There was no difference in the incidence of solicited local and systemic ARs based on baseline SARS CoV-2 status. The solicited AR profile in the pivotal Study mRNA-1273-P301 was similar to the profile observed in the 100 μ g mRNA-1273 treatment group in Study mRNA 1273-P201.

The overall incidence of unsolicited TEAEs and MAAEs reported up to 28 days after vaccination were comparable in participants who received mRNA-1273 or placebo. The overall incidence of related TEAEs was higher in participants who received mRNA-1273 compared with placebo. This difference is a consequence of more frequently reported solicited adverse reactions by participants who received mRNA-1273 either persisting beyond Day 7 or were severe reactions and/or required medical attention, since these were also reported as unsolicited AE. The incidence of unsolicited TEAEs leading to discontinuation from study vaccine was greater in participants who received placebo compared with mRNA-1273 (85 participants [0.6%] vs 45 participants [0.3%], respectively), largely due to a diagnosis of COVID-19 prior to Day 29 which rendered them ineligible to receive the second injection.

The incidence of unsolicited TEAEs within 28 days after any injection regardless of relationship was comparable in adults 18 to <65 years of age compared with participants 65 years of age and older who received mRNA-1273 (21.5% versus 23.1%, respectively). There was no apparent effect of age on the relative incidence of these TEAEs by vaccine group. There was no difference in the incidence of unsolicited TEAEs based on SARS-CoV-2 serology at baseline.

The incidence and absolute number of SAEs and treatment-related SAEs in the 28 days after vaccination was comparable between mRNA-1273 and placebo groups. A total of 8 deaths occurred in Study mRNA-1273-P301, with 4 deaths occurring in the mRNA-1273 group and 4

deaths occurring in the placebo group. None were attributed to COVID-19 nor considered related to study product. The causes of death were consistent those that are expected in the population enrolled in the study.

There were fewer cases of severe COVID-19 or COVID-19 from the time of randomization amongst participants who received mRNA-1273 compared with placebo, and thus no evidence of vaccine-associated enhanced respiratory disease.

In the Phase 2a Study mRNA 1273-P201, the incidence of unsolicited TEAEs, related unsolicited TEAEs, and MAAEs were comparable between the mRNA-1273 and placebo groups. One SAE was reported and assessed as unrelated to IP in Study mRNA-1273-P201 and no SAEs have been reported through Day 119 in Study 20 0003.

7.1.3. Risk-Benefit Assessment

There is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Based on the interim results from the pivotal Phase 3 study, mRNA-1273 prevents COVID-19 and severe COVID-19. The demonstrated clinical benefit of mRNA-1273 is supported by evidence of a robust immune response both in terms of bAbs and nAbs as well as the induction of CD4+ T-cells with a Th-1 dominant phenotype. Based on administration of mRNA-1273 to 15,693 adults across all 3 clinical studies to date, there have been no emergent safety concerns and the AE profile is manifested largely by mild to moderate reactogenicity lasting 2 to 3 days.

Statistically significant vaccine efficacy to prevent COVID-19 was demonstrated in adults ≥ 18 years of age during the ongoing pandemic. The clinical benefit was consistent in older and younger adults, with or without risk factors for complications of COVID-19, in males and females, and in participants who were white as compared to those from communities of color. Importantly, mRNA-1273 was demonstrated to be effective in preventing severe COVID-19. The efficacy of mRNA-1273 to prevent COVID-19 and severe COVID-19 demonstrated in the study to date also mitigates concern about the risk of enhanced disease during the 28-day period following 2 doses of vaccine. The results from the pivotal efficacy study are supported by the substantial immune response observed in the Phase 1 and Phase 2 studies that was consistent across age groups and persisted over 3 months after the second injection of mRNA-1273.

Vaccination with mRNA-1273 generally results in transient local injection site and systemic reactions. The incidence of local and systemic ARs was lower in older adults compared with younger adults. The incidence of unsolicited TEAEs, MAAEs, and TEAEs leading to discontinuation of IP, were similar between the treatment groups but unsolicited related TEAEs were more common in participants who received mRNA-1273. This difference is explained by an increase in local and systemic ARs which were assessed as severe or persisted beyond 7 days.

Less common but clinically significant AEs, such as SAE and deaths were reported at comparable rates for placebo and vaccine recipients. The overall safety profile observed in the Phase 3 large-scale safety and efficacy study was generally consistent with the safety profile observed to date in the Phase 1 and Phase 2 studies.

Based on the data presented in this submission, mRNA-1273 administered as two 100 µg doses 28 days apart is an effective vaccine with an acceptable safety profile for the prevention of COVID-19 in adults 18 years of age and older. The safety and immunogenicity data from the Phase 1 and Phase 2 studies and the efficacy data from the Phase 3 study support the use of the 100-µg dose of mRNA 1273. Considering the ongoing public health emergency due to SARS-CoV-2, the lack of approved preventative vaccines, as well as the available safety and efficacy data from the 3 clinical studies presented herein, the Sponsor considers that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks for the Moderna COVID-19 Vaccine and warrant consideration for EUA under Section 564 (b)(1)(C) of the FD&C Act.

7.2. Contraindications

Moderna COVID-19 Vaccine is contraindicated in individuals with known severe allergic reactions (e.g. anaphylaxis) to any component of the vaccine or to a previous dose of Moderna COVID-19 Vaccine.

7.3. Important Precautions for Administering of the Moderna COVID-19 Vaccine Include:

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine.

As with other intramuscular injections, the Moderna COVID-19 Vaccine should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

Consideration should be given to postponing immunization in persons with severe febrile illness or severe acute infection. Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.

Vaccination with the Moderna COVID-19 Vaccine may not protect all recipients.

7.4. Special Populations

Special populations such the pediatric group (<18-year-old), pregnant and breastfeeding women and immunocompromised patients have not been included in the clinical development program

and data are not available at this time. Until more information is available in these populations the Fact Sheet will describe the lack of experience in these special populations (refer to the Fact Sheet for additional information for each group below).

Vaccination in Pediatrics

The safety and efficacy of Moderna COVID-19 Vaccine in individuals less than 18 years of age have not yet been established. No data are available.

Vaccination during Pregnancy and Lactation

A developmental and reproductive study with the Moderna mRNA-1273 Vaccine in female Sprague-Dawley rats is underway. It is not known whether the Moderna COVID-19 Vaccine is excreted in human milk. Therefore, during the early period of the use of the Moderna COVID-19 Vaccine is not recommended in pregnant and lactating women.

Moderna is planning to enhance pharmacovigilance for that special population and is establishing an observational pregnancy cohort study, (e.g., with the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) Mother to Baby cohort [<https://aaaai.org/VAMPSS>]). Unlike a traditional passive pregnancy registry this approach will enable the calculation of incidence rates for adverse pregnancy and birth outcomes. It will also enable the identification of key confounders and non-medically attended outcomes (e.g., spontaneous abortions) that are incompletely recorded in secondary healthcare records (see [Section 13](#). ADVERSE EVENT AND MEDICATION ERROR MONITORING).

Vaccination in those experiencing Immunosuppression

If the Moderna COVID-19 Vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Vaccination in Geriatrics

In an ongoing Phase 3 clinical study, the safety and efficacy of the Moderna COVID-19 Vaccine was assessed in individuals 18 years of age and older, including 3,527 subjects 65 years of age and older. The efficacy of the Moderna COVID-19 Vaccine was consistent between older subjects (≥ 65 years) and younger subjects (18-64 years). Older subjects 65 years of age and older reported solicited local and systemic adverse reactions at a lower rate than younger subjects 18-64 years of age.

8. CHEMISTRY, MANUFACTURING, AND CONTROLS

Information concerning the Chemistry, Manufacturing and Controls (CMC) information for mRNA-1273 vaccine is located in IND 19745. As of December 1, 2020, IND 19745 contains:

- Drug Substance PPQ information conducted at ModernaTX, Inc. (Norwood, MA). The Drug Substance process consists of (b) (4) IVT scale for CX-024414 (SN0041), (b) (4) and (b) (4) (b) (4) (b) (4) (b) (4) (SN0039, SN0066) and (b) (4) and (b) (4) scales for mRNA-1273 LNP (SN0039, SN0066).
- Drug Substance Comparability conducted at ModernaTX, Inc. (Norwood, MA). Comparability for Drug Substance consists of manufacturing lots at the (b) (4) IVT scale for CX-024414, (b) (4) (b) (4) (b) (4) and (b) (4) mRNA scale for mRNA-1273 LNP. ((b) (4) IVT in SN0066, (b) (4) and mRNA-1273 LNP in SN0070 with the additional submission planned 30 Nov).
- Drug Substance PPQ information conducted at Lonza Biologics, Inc. (Portsmouth, NH). The Drug Substance process consists of (b) (4) IVT scale for CX-024414 (SN0041).
- Drug Substance Comparability conducted at Lonza Biologics, Inc. (Portsmouth, NH). Comparability for Drug Substance Process consists of manufacturing lots at the (b) (4) IVT scale for CX-024414, (b) (4) (b) (4) (b) (4) and (b) (4) mRNA scale for mRNA-1273 LNP. (Planned Submission 30 Nov).
- Drug Product PPQ complete information conducted at Catalent Biologics, LLC (Bloomington, IN). Drug Product process represents a fill/finish output of up to (b) (4) (b) (4) per run (SN0039).
- Drug Product initial PPQ information (1st lot) conducted at Catalent Biologics, LLC (Bloomington, IN). Drug Product process represents a fill/finish output of up to (b) (4) (b) (4) per run (SN0070).

The Sponsor will continue to submit periodic updates to IND 19745 as additional data becomes available. The Sponsor will submit the Certificate of Analysis of each batch of Drug Product to IND 19745 prior to distribution.

9. FACT SHEET FOR HEALTHCARE PROVIDERS

Refer to [Module 1.14.1.3](#).

10. FACT SHEET FOR RECIPIENTS

Refer to [Module 1.14.1.3](#).

11. PROGRAM SCHEMA

This EUA is to be implemented only upon issuance by the Commissioner of the FDA, and in accordance with the terms and conditions of the EUA.

COVID-19 vaccines and ancillary supplies will be procured and distributed by the federal government at no cost to enrolled COVID-19 vaccination providers^{vii}. The US Government will use centralized distribution to fulfill orders for most vaccine products and associated ancillary supplies. It is also possible that vaccines may be procured by entities directly from manufacturers, depending on the supply and regulatory status of available COVID-19 vaccines.

As determined by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) and stakeholder recommendations, COVID-19 vaccine initial allocation will be focused prioritized populations (e.g., critical infrastructure workforce including healthcare personnel and other essential workers, people at risk for severe COVID-19 illness, people at increased risk of acquiring or transmitting COVID-19, people with limited access to routine services), prior to broad distribution to the U.S. population at large. As vaccine supply increases, a phased approach will be taken to expand access beyond the initial populations. This approach will include distribution plans to allocate vaccine to state, territorial, and local health departments, tribal communities, and federal and commercial partners (e.g., pharmacy partners, some Indian Health Service locations, Veterans Administration clinics and hospitals, and other federal providers). State, territorial, and local health departments, tribal communities, and federal and commercial partners receiving direct COVID-19 vaccine allocations from CDC will be responsible for subsequent vaccine distribution according to their internal response plans and procedures. Ultimately, if there is a public health need for an ongoing vaccination program, FDA-licensed COVID-19 vaccines will be made available through routine vaccination programs.

The Biomedical Research and Development Authority (BARDA) will direct the shipment of bulk vaccines product from Moderna Therapeutics to designated CDC distributor depot sites.

CDC will coordinate the allocation, distribution, and administration of vaccine to states, jurisdictions and partners through McKesson, the centralized distributor, using HHS's Vaccine Tracking System (VTrckS). Enrolled COVID-19 vaccination providers will order COVID-19 vaccine through VTrckS. Through collaborative planning with state and local jurisdictions and private sector provider partners such as pharmacies, vaccine administration sites will be selected to optimize access to vaccines throughout a distribution process developed by the US Government.

All COVID-19 vaccination providers (providers enrolled by jurisdictions, commercial pharmacies, and federal partners) will be required to report inventory of COVID-19 vaccines, and dose level administration information as determined by CDC reporting requirements.

Data will be available both federally and at the state, territorial, local, and tribal level to ensure efficient management of the vaccination program. Immunization Information Systems used by state, territory, and city entities that deliver public vaccinations will be central to the IT infrastructure. Each vaccine administration site will have capabilities for tracking, storing,

handling, and administering vaccine product in accordance with the specific distribution and administration requirements. Data will be reported into a common US Government managed IT infrastructure that will support analysis and reporting. The IT infrastructure will support partners with a broad range of tools for record-keeping, supply information, data on who is being vaccinated, monitoring, and reminders for second doses.

11.1. Surge Capabilities

To date ~7.8M dose equivalents have been manufactured (mRNA 1273 LNP) of which ~2.1M doses have completed filling as well as EUA labeling and packaging. The projected number of doses available through Q1 2021 are provided in [Table 7](#).

Table 7: Projected Doses of mRNA-1273 Vaccine Through Q1 2021

	November 30	December 31	January 31	February 28	March 30
Total # doses per month	2.1M	15-20M	18-20M	30-32M	30- 33M

Information concerning the lots (including yield) and batch release data will be located in IND 19745 Section 3.2.P.5.4. Actual vial quantities will be coordinated through distribution logistics for exact number of available vials.

As outlined in Section 4, the manufacturing sites for the mRNA-1273 Drug Substances (CX-024414 mRNA, (b) (4) and mRNA-1273 LNP) will be:

- ModernaTX, Inc in Norwood, MA
- Lonza Biologics, Inc. in Portsmouth, NH.

The manufacturing site for the mRNA-1273 Drug Product will be:

- Catalent Biologics, Inc in Bloomington, IN.

Please note that the Sponsor will be enabling an additional mRNA-1273 Drug Product manufacturing facility in late Q4 2020 (Baxter, Bloomington, IN). Information concerning these manufacturing activities will be submitted as an amendment to IND 19745 when the information become available.

Information concerning the Chemistry, Manufacturing and Controls (CMC) information for mRNA-1273 vaccine is located in Module 3 of IND 19745.

12. INSTRUCTIONS FOR USE

12.1. Moderna COVID-19 Vaccine Preparation

- The Moderna COVID-19 Vaccine multiple-dose vial contains a frozen suspension that is preservative-free and must be thawed prior to administration.
- Thaw in refrigerated conditions between 2° to 8°C (36° to 46°F) for 2 hours and 30 minutes. Let vial stand at room temperature for 15 minutes before administering.
- Alternatively, thaw at room temperature between 15° to 25°C (59° to 77°F) for 1 hour.
- After thawing, do not return the vial to the freezer.
- Swirl vial gently after thawing and between each withdrawal. Do not shake. Do not dilute the vaccine.
- Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Inspect Moderna COVID-19 Vaccine vials visually for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
- A maximum of 10 doses can be withdrawn from the multiple-dose vial.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 6 hours. Do not refreeze.

12.2. Storage and Packaging

Moderna COVID-19 Vaccine multiple-dose vials contain a maximum of 10 doses. Ten multiple-dose vials are packaged in a carton.

Storage Prior to Use

The Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -25° to -15°C (-13° to 5°F). Store in the original carton to protect from light. Do not store on dry ice or below -40°C (-40°F).

Remove the required number of vial(s) from storage and thaw each vial before use. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Do not refreeze.

Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. Do not refreeze.

Storage After First Puncture of the Vaccine Vial

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Discard vial after 6 hours. Do not refreeze.

12.3. Dosage and Administration

The Moderna COVID-19 Vaccine is administered intramuscularly as two doses (0.5 mL each). The second dose is administered 1 month after the first dose.

There are no data available on the interchangeability of the Moderna COVID-19 Vaccine with other COVID-19 vaccines. Individuals who have received one dose of Moderna COVID-19 Vaccine should receive a second dose of Moderna COVID-19 Vaccine to complete the vaccination series.

13. ADVERSE EVENT AND MEDICATION ERROR MONITORING

Moderna plans to continue to leverage the ongoing Phase 3 Study mRNA-1273-P301 clinical study infrastructure to provide rates and detailed clinical follow-up information for adverse events.

In addition to the ongoing Phase 3 study, Moderna will continue to characterize the safety profile of mRNA-1273 in the EUA and post-marketing periods through routine and enhanced pharmacovigilance. Moderna has a safety surveillance system in place to organize the collection and data entry in the company safety data base and evaluation of any adverse events including vaccine administration errors reported to Moderna. All AE/SAE cases will undergo follow-up for any medical records or additional information required from the reporter. In addition to adverse events, individuals calling Moderna may report inadvertent exposure to the vaccine during pregnancy which will prompt follow up queries for outcomes.

This effort will be complemented through the implementation of a pregnancy observational study. Moderna will transmit adverse events of special interest identified by the US CDC in an expedited manner to VAERS. Moderna will also engage in safety signal detection activities using qualitative as well as quantitative methods (e.g., Moderna's Global Safety Database, VAERS data mining, international spontaneous reporting systems as applicable subject to marketing authorizations). Signal detection for designated medical events (DME) consisting of medical conditions that are inherently serious, and often medicine-related, will be undertaken as well. If any significant AESI, AEFI, DME or new suspected adverse reaction are reported in vaccinees, Moderna will undertake further evaluation. Moderna will also provide periodic safety reporting as specified by the agency at the time of authorization. Moderna will perform signal management in the company global safety data base and by screening global literature.

Additional enhanced pharmacovigilance capabilities will also be used for signal validation and assessment. Tokenized real-world data enabling privacy sparing linkage and de-duplication at the patient level from approximately 130,000,000 individuals covered by commercial insurance and Medicare managed care plans within the United States will be accessible to Moderna on a continuous basis (e.g., Aetion and HealthVerity). This data will enable Moderna to calculate background disease and event rates, examine rates of adverse events in cohorts with clinical characteristics similar to those identified in passive surveillance clusters, and to conduct inferential analyses. This population complements but does not duplicate the populations under observation in the CDC's Vaccine Safety DataLink and the FDA's CMS programs. During safety signal assessment, the Sponsor will have the capacity to complete inferential epidemiologic analyses in a rapid manner, which is important for a mass vaccination campaign. The analytic and data resources the Sponsor will have in place upon EUA will decrease the time between safety signal identification and assessment leading to risk minimization, if applicable. An additional active pharmacovigilance activity will use this data to conduct an early post-authorization general safety study assessing adverse events of special interest. It will be initiated at the time of authorization and will conduct inferential analyses when product uptake reaches appropriate levels.

Moderna is planning to establish an observational pregnancy cohort study, (e.g., with pregnancy cohort established by a contract research organization or an academically affiliated organization such as the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) Mother to Baby cohort). Unlike a traditional passive pregnancy registry, this approach will enable the calculation of incidence rates for adverse pregnancy and birth outcomes. It will also enable the identification of key confounders and non-medically attended outcomes (e.g., spontaneous abortions) that are incompletely recorded in real world data sources.

Vaccine-associated disease enhancement remains a theoretical concern rather than an identified clinical entity, and as such it does not have a validated case definition. A safety signal for vaccine-associated ERD has not been detected in the Phase 3 clinical study to date. As previously described, safety follow-up for the clinical study will continue. This will serve as a primary means of signal detection for ERD, and it will also be augmented by routine pharmacovigilance. If such a signal were identified, it could be initially assessed using the analytic and data capacity the Sponsor will have in place upon EUA.

The CDC is sponsoring enhanced VAERS reporting efforts (e.g. V-SAFE) as well as sequential surveillance efforts using electronic healthcare data in the Vaccine Safety Datalink. CDC will also continue the Clinical Immunization Safety Assessment project (see summaries below). The FDA will conduct sequential surveillance using Centers for Medicare and Medicaid Services data.

Vaccine Safety Datalink (VSD)

Real-time sequential safety monitoring (Rapid Cycle Analysis [RCA]) will be conducted to detect AEs that occur in near real-time. VSD data are refreshed and sequential analyses are conducted weekly to identify statistical safety signals. To complement RCA, which monitors pre-specified AEs of interest, tree-temporal scan data mining will be conducted to monitor a wide range of unsuspected but potential AEs following immunization. The tree-temporal scan statistical algorithm will scan a set of possible risk windows and comparison windows in order to detect associations between vaccination and health outcomes. To evaluate any signals identified through this data mining method, additional analyses and medical record review will be conducted. VSD will also plan to monitor COVID-19 vaccine safety in pregnant women by monitoring vaccine coverage, pregnancy outcomes (e.g., spontaneous abortion, still birth), and acute AEs in near-real time. Longer term outcomes such as diseases in the newborn period, infant mortality, and growth and development will be studied as well. More information on VSD is available at: <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd>

Clinical Immunization Safety Assessment Project

During the national COVID-19 vaccination program, CISA will be available for U.S. healthcare providers and health departments who need consultation on immunization decision-making and assessments of complex vaccine safety events involving individual patients. CISA experts will review individual cases of adverse events after COVID-19 vaccine using structured processes designed to best suit the needs of the inquirers and their patient(s). The most complex cases will receive a ‘grand rounds’ style review and an evaluation using the CISA causality algorithm. On-call service to address urgent clinical vaccine safety questions from healthcare providers and health departments and rapid consultation on emerging vaccine safety issues will also be available to evaluate the safety of COVID-19 vaccines. In addition, CISA clinical research studies may be conducted to address clinical vaccine safety questions in targeted or special populations. More information on CISA is available at: <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa>

Vaccine Safety Assessment for Essential Workers (V-SAFE)

CDC will also implement a text messaging and web-based monitoring system called Vaccine Safety Assessment for Essential Workers (V-SAFE) designed as an active surveillance system to capture safety data among healthcare workers and other essential workers. Vaccine recipients’ contact information captured in registration systems will be leveraged to conduct health checks

via text message or email through 6 weeks following each vaccine dose. VAERS staff will follow up on reports of clinically important AEs to ensure a VAERS report is completed.

14. LABELING

Refer to [Module 1.14.1.3](#) for additional patient information that will be provided to recipients.

15. RECORD KEEPING, REPORTING, AND RECORD ACCESS BY FDA

Inventory management including records of the Moderna COVID-19 Vaccine distribution (including lot numbers, quantity, receiving sites, and receipt date) under this EUA will be maintained by the USG (i.e., BARDA and CDC) and McKesson, the centralized distributor of vaccine. Additionally, CDC and other entities involved in the activities of this EUA will ensure that entities administering the Moderna COVID-19 Vaccine under this EUA are informed and instructed to comply with the FDA-specified requirements and conditions of the EUA such as AE monitoring and reporting, data collection and analysis, and record keeping and records access.

16. REFERENCES

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^{vi} Anderson EJ, Rouphael NG, Widge AT, Jackson LA, et al. Safety and immunogenicity of SARSCoV2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020 Sep 29 [online ahead of print].

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