EXHIBIT 9

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	27073
Sponsor	ModernaTX, Inc.
Submission Date	November 30, 2020
Receipt Date	November 30, 2020
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
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Review Completion Date	December 18, 2020
Established Name/Other names used during development	Moderna COVID-19 Vaccine/mRNA-1273
Dosage Forms/Strengths and Route of Administration	A 0.5 mL Suspension for intramuscular injection
ntended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
ntended Population	Individuals 18 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA for a COVID-19 vaccine after determining that certain statutory requirements are met.

On November 30, 2020, ModernaTX (the Sponsor, also referred to as Moderna) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group) and in preventing COVID-19 following the first dose, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ≥65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group, with one severe case in the vaccine group confirmed after this analysis.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns

identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and rates and types of solicited and unsolicited adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ⩾65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

Non-clinical toxicology studies with mRNA-1273, including a developmental toxicity study, did not raise specific safety concerns, and other non-clinical studies support the vaccine's immunogenicity, reduction of SARS-CoV-2 pulmonary and nasal viral load in animal challenge models, and absence of findings suggesting risk of vaccine-enhanced disease.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the

Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on December 17, 2020. Following a discussion of the data presented, the VRBPAC voted 20-1 (with 1 abstention) in favor of the determination that based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older.

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 17, 2020, meeting, the review team concludes that:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Moderna COVID-19 vaccine (mRNA-1273) may be effective to prevent such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.
- There is no adequate, approved, and available alternative to the product for preventing COVID-19 caused by SARS-CoV-2.

The review team therefore recommends issuance of an EUA for use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] 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).[2] 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).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause 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 (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.3 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (the Sponsor, also referred to as Moderna) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension (-25º to -15ºC) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,400 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, Moderna submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Safety conclusions were reported by the Sponsor to be unchanged from the interim analysis. FDA considers that the totality of available data is sufficient to support an evaluation of this product for EUA.

2.4 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking

regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6] These considerations are summarized below.

Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

3. Moderna COVID-19 Vaccine (mRNA-1273)

3.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25º to -15º C (-13º to 5ºF)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the

Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

3.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

4. FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study mRNA 1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and will not be discussed in detail. Study 20-0003 is a Phase 1 open label, dose-ranging, first-in-human study of mRNA-1273 and will also not be discussed in detail.

Table 1. 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 (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing- vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing- Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing- Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

4.2 Study mRNA-1273-P301

4.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive

intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo (n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 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. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. 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 RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled 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 expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

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 RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- 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; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE=1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

Subjects who had no documented COVID-19 were censored at the last study assessment date. Subjects who discontinued the study, die due to cause unrelated to COVID-19, or were

confirmed to have COVID-19 prior to 14 days after the second dose were censored at the date of discontinuation, death, or documented COVID-19. The documented COVID-19 date was defined as the later date of: 1) the earliest systemic and/or respiratory symptoms reported, and 2) date of positive RT-PCR test, where the two dates must be within 14 days of each other.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided α =0.025, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive 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 (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

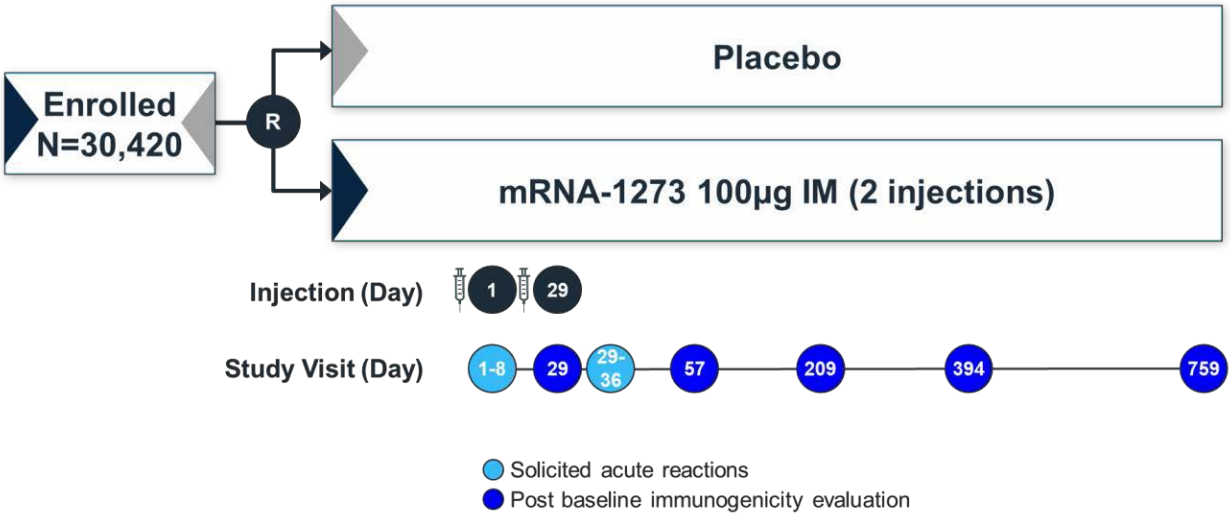
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory valuations were not assessed in Study P301 but were collected in the phase 2 Study P201.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited

adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

4.2.2 Compliance with Good Clinical Practice

As summarized in Section 5.6 (Inspections of Clinical Study Sites), Bioresearch Monitoring (BIMO) inspections were conducted at nine domestic clinical investigator sites participating in the conduct of the trial. Two of the inspections revealed deficiencies regarding the clinical investigators' conduct of the study. The deficiencies initially gave FDA cause for concern about the adequacy of the Sponsor's study monitoring. Upon further review, including consideration of additional information provided by the Sponsor, however, FDA determined that the Sponsor had a comprehensive system in place to routinely monitor compliance at all sites. FDA also determined that prior to FDA's inspections, this system was effective at independently identifying the deficiencies at the two sites, leading to implementation of corrective action plans at both sites. Following review of study-wide compliance information provided by the Sponsor that included a comprehensive and frequent monitoring plan already in place, FDA did not identify systemic concerns with trial conduct across the other study sites. The Letter of Authorization will include a condition about continued monitoring of the performance of the clinical investigators.

FDA conducted a sensitivity analysis of the primary efficacy endpoint excluding data from these sites. There was only one COVID-19 case, starting 14 days after the second dose, identified from the two sites through the November 21, 2020 efficacy data cutoff. This COVID-19 case was in a placebo recipient. The proportion of subjects enrolled at these two sites was very small relative to the overall study population, representing approximately 2.5% of the total study population. Furthermore, the sites contributed only one COVID-19 case (in the placebo group) to the primary efficacy analysis. Consequently, the study's efficacy conclusions are not materially affected by inclusion or exclusion of data from these two sites. FDA also conducted separate analyses of safety for these two sites, and in general the reported rates of solicited adverse reactions and unsolicited adverse events at these two sites were comparable to those reported in the overall safety database across study groups. Consequently, inclusion of safety data contributed by these two sites, which represent approximately 2.5% of the overall safety database (i.e., the total study population), would not materially change the conclusions of safety analyses, and their inclusion allows for the broadest possible evaluation of vaccine safety in the

trial. In light of the Sponsor's comprehensive system for identifying the deficiencies and the fact that the data from the two sites would not materially affect the safety or efficacy analyses, FDA has confidence in the data from the two sites to include the data in the overall evaluation. Therefore, FDA did not exclude the data from these two sites from either the safety or efficacy analyses presented in this review or in product labeling.

4.2.3 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

4.2.4 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study. During review of the EUA request, FDA and the Sponsor identified one additional vaccine recipient and one additional placebo recipient not accounted for in the

November 11, 2020 dataset analyses (Total Safety Set of 30,351, including 15,185 vaccine recipients and 15,166 placebo recipients). These two additional participants to not materially change the conclusions from the analyses of the November 11, 2020 safety dataset, and they are included in analyses of the November 25, 2020 dataset.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15165	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

4.2.5 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
** High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
*** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3)
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 [a] EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. [a] EUA request (interim analysis): November 11, 2020 cutoff

4.2.6 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim 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/or 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 primary efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in

the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases /N (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases / N (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 / 13934 (<0.1) 1.840	90 / 13883 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-hazard ratio (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0047 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1

[a] EUA request (interim analysis): November 7, 2020 data cutoff.

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection

**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a] =5) N[b] (%)	Placebo (N[a] =90) N[b] (%)	Total (N[a] =95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6 / 15180	92 / 15170	93.5% (85.2, 97.2)
Positive	0 / 341	1 / 334 (0.3) 17.038	100%
Negative	6 / 14312 (<0.1) 2.154	90 / 14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0 / 527	1 / 465 (0.2)	100%

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0 / 661	6 / 673 (0.9) 42.950	100%
Significant Cardiac Disease	0 / 686	3 / 678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1 / 901 (0.1) 5.524	11 / 884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0 / 1338	7 / 1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1 / 76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2 / 5269 (<0.1%)	46 / 5207 (0.9)	95.8% (82.6%,99.0%)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): November 07 2020 efficacy data cutoff.
* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and represents a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

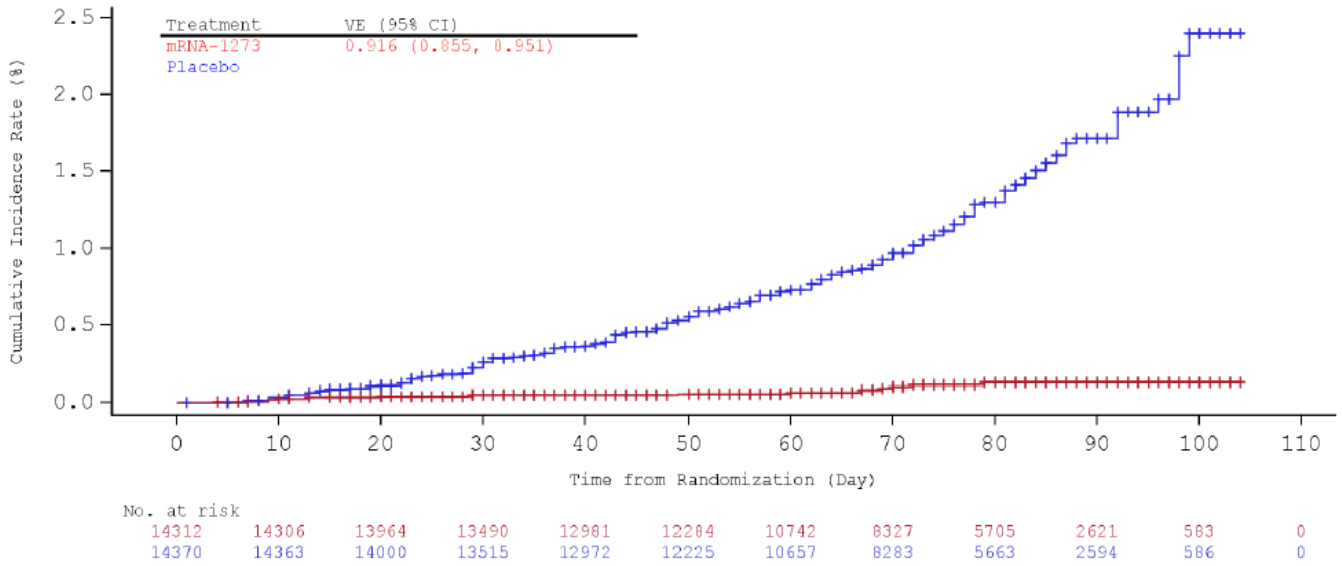
Other Secondary Efficacy Endpoints

The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Cases / N (%) Person-years of follow-up	Placebo Group N=1079 Cases / N (%) Person-years of follow-up	VE (%) (95% CI)*
After dose 1	7 / 996 (0.7) 87.5	39 / 1079 (3.6) 96.7	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5 / 996 (0.5) 38.0	11 / 1079 (1.0) 41.1	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2 / 983 (0.2) 87.2	28 / 1059 (2.6) 96.2	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-incidence rate ratio (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: Novemer 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both

participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis: EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases / N (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases / N (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 / 13934 (<0.1) 3.328	185 / 13883 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7 / 10551 (<0.1) 2.875	156 / 10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4 / 3583 (0.1); 4.595	29 / 3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1

COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.

21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).

* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

**VE and 95% CI from the stratified Cox proportional hazard model

***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%,

[1] Percentage based on number of participants in the 18 to <65 years of age group.

[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The severe COVID-19 case in a mRNA-1273 vaccine recipient described with in the discussion of the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below because it was confirmed after the analysis.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose were in the placebo group, although one severe COVID-19 occurred in the vaccine group but was not confirmed until after the analysis. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI:

89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis. The final scheduled efficacy analysis also corroborated preliminary findings of efficacy against severe COVID-19, with 30 cases in the placebo group and 0 in the vaccine group (though one severe case in the vaccine group was confirmed after the final scheduled efficacy analysis).

4.2.7 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA first independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020, followed by all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies from the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The remaining safety analyses from the November 25, 2020 cutoff date, were verified in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7

[a] There were no reports of Grade 4 injection site adverse reactions

[a] EUA request (interim analysis)-November 11, 2020

**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and axillary swelling or tenderness of the vaccination arm indicating lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary swelling or tenderness of the vaccination arm was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary swelling or tenderness was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary swelling or tenderness were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 axillary swelling or tenderness.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5%

of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary swelling or tenderness (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

The tables below present analyses of solicited local AR from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting solicited local AR are not appreciably different from those presented in the tables below.

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)
Axillary Swelling/Tenderness[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose

[a] EUA request (interim analysis)-November 11 2020

Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.

n= # of participants with specified reaction

N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

c: Axillary Swelling/Tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

Note: No grade 4 solicited local adverse reactions were reported.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Axillary Swelling/Tenderness[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.

[a] EUA request (interim analysis)-November 11 2020.

Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.

n= # of participants with specified reaction

N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

c: Axillary Swelling/Tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

Note: No grade 4 solicited local adverse reactions were reported.

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 ºF). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine

recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 ºF) was reported by <0.1% (11 participants) of vaccine recipients after dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 ºF) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

The tables below present analyses of solicited systemic AR from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting solicited systemic AR are not appreciably different from those presented in the tables below.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (61.3)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ⩾39 0 – ⩽40.0°C or ⩾102.1 – ⩽104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

The tables below present analyses of unsolicited AEs from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting unsolicited AEs are not appreciably different from those presented in the tables below.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): Novemer 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and

1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after

vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths in both the vaccine and placebo groups represent events and rates that occur in the general population of individuals of these ages and do not suggest a causal relationship to the vaccine.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo group than the vaccine group, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA 1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal

developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has independently verified all new deaths (including those reported through December 3, 2020) and other SAEs, and the rates and types of solicited and unsolicited AEs from the November 25, 2020 dataset. No new safety concerns have been identified. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, lymphadenopathy-related events were reported in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group, reflecting a similar imbalance in solicited axillary swelling or tenderness indicating lymphadenopathy (reported by 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively). There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher

than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

4.3 Study DMID Protocol 20-0003

Study Design

DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 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 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA 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 are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100-µg group compared to the 250-µg group, led to the selection of the 100 µg dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

4.4 Study mRNA-1273-P201

Study Design

Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 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, who were randomized equally to receive either 2 doses of 50 µg of mRNA-1273, 100 µg of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

5. FDA Review of Other Information Submitted in Support of the EUA

5.1 Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

Moderna expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. Moderna is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered open-label mRNA-1273 vaccination and to remain in the trial, enabling Moderna to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Moderna has represented that a blinded crossover design is not feasible for them to implement, due to unwillingness of trial participants to engage in such a design, and that availability of vaccine allocated for clinical trials, which will expire soon and cannot be used under EUA, is an argument against a staged crossover approach according to EUA vaccine prioritization and availability for certain subgroups. Adverse events among those vaccinated within the open label crossover will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

5.2 Pharmacovigilance Activities

Moderna submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information. Division of Epidemiology recommendations are as follows:

1. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
    - Vaccine administration errors whether or not associated with an adverse event
    - Serious adverse events (irrespective of attribution to vaccination)
    - Cases of Multisystem Inflammatory Syndrome in adults
    - Cases of COVID-19 that result in hospitalization or death

2. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
    - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
    - Newly identified safety concerns in the interval
    - Actions taken since the last report because of adverse experiences (for example, changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

3. Moderna will conduct post-authorization observational studies for safety to evaluate the association between Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESI) along with deaths and hospitalizations, and severe COVID-19 disease. The study population should include individuals administered the authorized Moderna COVID-19 Vaccine under this EUA in the general US population, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Moderna will provide protocols and status update reports to the IND 19745 with agreed-upon study designs and milestone dates.
   The Sponsor has proposed the following three planned surveillance studies:
   - Pregnancy Cohort:
     The Sponsor plans to establish a pregnancy registry with an internal unvaccinated comparator cohort to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a full protocol for FDA review and approval prior to study start.
   - Active Follow-up for Safety:
     This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 26 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.
   - Real World Effectiveness Study:
     This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes; laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated subjects will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

   FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

4. Mandatory reporting by vaccination providers to VAERS for the following events:
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of Multisystem Inflammatory Syndrome in children and adults
   - Cases of COVID-19 that result in hospitalization or death

5. Active surveillance of vaccine recipients via the v-safe program. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

5.3 Non-Clinical Studies

Toxicology Studies

To support their EUA request, Moderna submitted the following toxicology studies:

(1) Repeat-dose toxicity study of five formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Sprague Dawley rats. Study #5002045 and 5002045 reviewed under MF19622. Study # 5002034 and 5002158 reviewed under IND 17725. Study #5002400 reviewed under IND19088. Study #5002033 reviewed under IND 17741.
(2) Repeat dose toxicity study of mRNA-1273 by intramuscular injection in Sprague Dawley rats. Study #2308-123 reviewed under IND 19745.
(3) Intramuscular combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats. Study#20248897 reviewed under IND 19745.

Based on nonclinical toxicity assessment, there were no significant safety issues to report. Two intramuscular injections of mRNA-1273 at doses up to 100 ug were well tolerated in rats. Intramuscular administrations of mRNA-1273 at dose of 100 ug to rats prior to mating and during gestation period did not reveal effects on female reproduction, fetal/embryonic development and postnatal development.

Other Non-Clinical Studies

Several nonclinical studies in mice, hamsters, and rhesus macaques were conducted to support the safety and efficacy of the mRNA-1273 COVID-19 vaccine. mRNA-1273 was assessed for immunogenicity and for protection against SARS-CoV-2 challenge in mice, hamsters, and rhesus macaques. mRNA-1273 was highly immunogenic in all species tested with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4+ response, as well as an IFNγ+, IL-2+, CD8+ T-cell response, after a single immunization. Animals immunized intramuscularly had readily detectable S-binding IgG and SARS-CoV-2 neutralizing titers (NT50) as early as one week after a single immunization, and these titers were boosted substantially with a second immunization. Immunized mice were challenged with a mouse-adapted SARS-CoV-2, and hamsters and macaques were challenged with wild-type SARS-CoV-2. The mRNA-1273 vaccine was protective in all three species as indicated by a substantial decrease in viral RNA in bronchoalveolar lavage fluid and the nasal turbinates in the immunized animals as compared with the controls. In addition, there was no histopathologic or radiographic evidence of vaccine-elicited enhanced disease in immunized animals. Based on current hypotheses regarding the etiology of vaccine-associated enhanced respiratory disease, the data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice, hamsters, and rhesus macaques; (2) the Th1 bias in T-cell responses; and (3) the reduced viral load and lack of disease markers in vaccinated animals challenged with SARS-CoV-2.

5.4 Chemistry, Manufacturing, and Control (CMC) Information

The Moderna COVID-19 vaccine (Code number mRNA-1273) is a nucleoside-modified messenger RNA (mRNA)-based vaccine indicated for active immunization for the prevention of coronavirus disease 2019.

The manufacturing process for the drug substance (DS) consists of (b) (4) The mRNA-1273 drug product (DP) is manufactured by (b) (4) filling of final containers and labeling/packaging. To support the EUA request, process performance qualification (PPQ) data and in-process, release, and characterization data for DS and DP lots were provided for each manufacturing facility. Once authorized, the Sponsor will submit the Certificates of Analysis (CoAs) of DS and DP lots to be distributed under EUA for FDA review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent scale-related changes during vaccine development to increase production capacity. DS and DP Scale A was used for the manufacture of Phase 3 clinical-trial material (CTM), while DS and DP Scale B will be used in the manufacture of vaccine intended for emergency use. An in-depth analytical comparability assessment based on a minimum of 3 DS PPQ lots and 3 DP PPQ lots at each Scale A and Scale B was performed. The submitted data show that the DS and DP lots manufactured at Scale A and Scale B are highly comparable, and the DS lots manufactured at Scale B in different facilities are also comparable. The manufacturing process and controls have been well characterized and qualified. A more comprehensive comparability assessment encompassing additional lots is ongoing and the results will be provided to the EUA upon completion of the study.
Stability studies have been designed to support the use of vaccine under the EUA. All available stability data generated using the mRNA-1273 DS and DP lots support the emergency deployment of the Moderna COVID-19 vaccine. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Stability data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of mRNA 1273 DS and DP include tests to ensure vaccine safety, identity, purity, quality, and potency. All non-compendial analytical procedures have been adequately validated. The validation results demonstrate acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the quality control of DS and DP.

The manufacture of the Moderna COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information described in the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.

- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also performed a site visit at one facility, reviewed the inspectional histories of all applicable facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Moderna COVID-19 vaccine under an Emergency Use Authorization.

5.5 Clinical Assay Information

Two diagnostic assays were used for the assessment of the Phase 3 clinical study efficacy endpoints. The Roche Elecsys Anti-SARS-CoV-2 assay was used for the evaluation of SARS-CoV-2 serostatus of study participants before vaccination. The Viracor Eurofins Clinical Diagnostics RT-qPCR was used to determine the virus infection status of study participants before vaccination and to confirm COVID-19 cases for the evaluation of clinical-study endpoints. Both assays have received FDA emergency use authorization. Additional data were submitted to support the suitability of both assays for their intended use in the Phase 3 clinical study for mRNA 1273. The Roche Elecsys Anti-SARS-CoV-2 assay is done under contract to PPD Global Central Laboratories, and the RT-qPCR assay is done by Viracor Eurofins Clinical Diagnostics. Both contracting laboratories are CAP-accredited and CLIA certified.

5.6 Inspections of Clinical Study Sites

Bioresearch Monitoring (BIMO) inspections were conducted at nine domestic clinical investigator sites participating in the conduct of study protocol mRNA-1273-P301, *A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older*. Two of the inspections revealed deficiencies regarding the clinical investigators' conduct of the study. The deficiencies initially gave FDA cause for concern about the adequacy of the Sponsor's study monitoring. Upon further review, including consideration of additional information provided by the Sponsor, however, FDA determined that the Sponsor had a comprehensive system in place to routinely monitor compliance at all sites. FDA also determined that prior to FDA's inspections, this system was effective at independently identifying the deficiencies at the two sites, leading to implementation of corrective action plans at both sites. Following review of study-wide compliance information provided by the Sponsor that included a comprehensive and frequent monitoring plan already in place, FDA did not identify systemic concerns with trial conduct across the other study sites. In light of the Sponsor's comprehensive system for monitoring compliance at all sites, FDA has confidence in the data from the sites that were not inspected. The Letter of Authorization will include a condition about continued monitoring of the performance of the clinical investigators.

5.7 EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

6.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

6.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV 2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available for ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

6.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). The trial excluded participants with known or suspected history of allergic reaction to components of the mRNA-1273 vaccine but did not exclude participants with other allergies. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. However, at the time of this review, anaphylactic reactions have been reported following administration of the Pfizer/BioNTech COVID-19 vaccine, which is based on a similar mRNA/LNP platform, during vaccination campaigns in the US and UK. Two of these reports (both in the UK) were in individuals with prior history of severe/anaphylactic reactions to food or drug allergens that are not components of the vaccine. In the US, two individuals without known history of allergic reactions experienced anaphylaxis within minutes after vaccination, one resulting in hospitalization, and several apparently less severe immediate hypersensitivity reactions have also been reported. All of these events were treated with appropriate medical interventions, and none were fatal. Investigation into these events and the potential for mRNA/LNP vaccines to cause severe allergic/anaphylactic reactions is ongoing. The prescribing information and fact sheets for use of mRNA-1273 under EUA will describe the need for post-vaccination monitoring for severe immediate hypersensitivity or anaphylactic reactions and need for facilities where vaccinations are being conducted to have medical treatment immediately available to respond to such reactions. Additionally, surveillance for allergic reactions, including severe or anaphylactic reactions, following vaccination with mRNA-1273 will proceed through established mechanisms (e.g., mandatory reporting of AEs to VAERS by vaccine providers) and investigated rapidly through joint efforts by CDC and FDA.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

6.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA 1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Meeting Summary

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on December 17, 2020, to discuss Moderna's EUA request. The meeting agenda included: an overview by FDA on EUA and considerations specific to COVID-19 vaccines; a presentation on conduct of placebo-controlled studies in the event that a vaccine becomes available under EUA; presentation of data from studies of the Moderna COVID-19 Vaccine by representatives of Moderna; a public comment period; an FDA presentation of its independent review of the data submitted in support of the EUA request; and a discussion and vote by the VRBPAC.

The VRBPAC was asked to discuss the following items, with no vote:

In considering Moderna's plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in:

- Ongoing clinical trials with the Moderna COVID-19 vaccine
- Other studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine

Regarding critical data to be obtained in ongoing trials with the Moderna COVID-19 vaccine, committee members discussed the importance of collecting blood specimens obtained from breakthrough cases to evaluate T- and B- cell immunity and to identify correlates of protection, and the importance of collecting respiratory specimens obtained from breakthrough cases to evaluate effect of the vaccine on shedding of infectious virus and to provide information about potential antigenic escape mutants. Members commented that efforts should be made to obtain data on long term safety of the vaccine, waning of immunity, the vaccine's impact on virus transmission, and asymptomatic infection. In addition, they suggested that ongoing studies should collect additional data on vaccine effectiveness in subjects at increased risk for COVID-19, pregnant women and pediatric populations.

Committee members were asked to discuss whether the ongoing Phase 3 trial should be continued using a blinded cross-over design or an open-label design as proposed by Moderna. Some members stressed the importance of using a blinded cross-over design in order to preserve data integrity and to allow an evaluation of waning of immunity and duration of protection. Other members opined that even though a blinded cross-over design would be ideal, it would present with logistical challenges, and that high drop-out rates can be anticipated because clinical trial participants would obtain a vaccine made available under EUA before a blinded cross-over could be implemented. Therefore, open-label unblinded vaccination of placebo recipients, even though not ideal, may be a more realistic option. However, to preserve blinded placebo-controlled follow-up for as long as is practical, some committee members opined that placebo recipients should be offered the vaccine as they become eligible for vaccination according to CDC prioritization groups.

The committee suggested for the following data to be obtained in additional studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine: data on vaccine effectiveness in the elderly, immunogenicity data from dose ranging studies, in particular in immunocompromised subpopulations, effectiveness of the vaccine following one dose, and interchangeability of the two COVID-19 mRNA vaccines. Additional studies should be conducted to obtain data regarding duration of protection, to identify a correlate of protection, to further evaluate Bell's palsy as an adverse event as well as to evaluate other neurological and cardiac outcomes (both in terms of vaccine safety and effect of vaccination on prevention of these outcomes when related to COVID-19), co-administration with other vaccines, and vaccine safety and effectiveness in pregnant and pediatric subjects.

Following this discussion, the VRBPAC was asked to vote on whether, based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The results of the vote were as follows: Yes = 20, No = 0, Abstain = 1. Thus, the committee voted in favor of a determination that based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older.

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 17, 2020 meeting, the review team concludes that:

- As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, it is reasonable to believe that the Moderna COVID-19 vaccine (mRNA-1273) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2. In the final scheduled primary efficacy analysis of PCR-confirmed and adjudicated COVID-19 cases in an ongoing randomized, blinded, placebo-controlled Phase 3 clinical trial, vaccine efficacy after 14 days post dose 2 was 94.1% (95% CI 89.3%, 96.8%). Efficacy outcomes were high across demographic subgroups and in participants with medical comorbidities associated with higher risk of severe COVID-19. A secondary efficacy analysis using a more severe COVID-19 case definition included 30 adjudicated cases in the placebo group and none in the vaccine group (though one severe case in the vaccine group was confirmed after this analysis). Additional post-hoc efficacy analyses also suggested efficacy against COVID-19 in the time period between dose 1 and dose 2.

- Based on the data summarized in Sections 4 and 5 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 14 days after dose 2, reduction in the risk of confirmed COVID-19 after dose 1 and before dose 2, and reduction in the risk of confirmed severe COVID-19 any time after dose 1. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up (including further evaluation of risk of Bell's palsy and severe allergic/anaphylactic reactions following vaccination), risks associated with vaccination of specific populations such as children younger than 18 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, and available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The review team therefore recommends issuance of an EUA for use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

9. References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England).* 2020;395(10224):565-574.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e278.
5. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011).
6. FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. October 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.
7. FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.
8. National Vaccine Injury Compensation Program. Vaccine Injury Table, Revised and Effective March 21, 2017. https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.
9. International Coalition of Medicines Regulatory Authorities. Statement on continuation of vaccine trials. http://www.icmra.info/drupal/en/covid-19/statement_on_continuation_of_vaccine_trials. 2020.
10. Krause PR, Fleming TR, Longini IM, et al. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *The New England journal of medicine.* 2020.
11. Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science.* 2020:eabf5084.
12. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html.
13. Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group, the. Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States. *JAMA.* 2007;298(18):2155-2163.
14. Verhees RAF, Dondorp W, Thijs C, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: Is a trial on mortality ethically acceptable? *Vaccine.* 2018;36(21):2991-2997.
15. Flannery B, Reynolds SB, Blanton L, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014. 2017;139(5):e20164244.
16. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1845-1853.