Vaccines and Related Biological Products Advisory Committee Meeting Presentation

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MRNA-1273

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATE: 17 DECEMBER 2020

AVAILABLE FOR PUBLIC RELEASE

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Abbreviation	Definition
AE	adverse event
AR	adverse reaction
ARDS	acute respiratory distress syndrome
bAb	binding antibody
BARDA	Biomedical Advanced Research and Development
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMV	cytomegalovirus
CoV	coronavirus
COVID-19	disease caused by the novel 2019 coronavirus
DMID	Division of Microbiology and Infectious Diseases
DSMB	data safety monitoring board
ELISA	enzyme-linked immunosorbent assay
ERD	enhanced respiratory disease
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMFR	geometric mean fold-rise
hMPV	human metapneumovirus
ICS	intracellular cytokine staining
IgG	immunoglobulin G
IP	investigational product
LL	lower limit
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
LOD	limit of detection
MAAEs	medically-attended adverse events
MERS-CoV	Middle East respiratory syndrome coronavirus
mITT	modified intent-to-treat
mRNA	messenger RNA
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
OWS	Operation Warp Speed
PIV3	parainfluenza virus type 3
PP	per-protocol
PRNT	plaque-reduction neutralization test
PsVNA	pseudotyped lentivirus reporter single-round-of-infection neutralization assay
PsVNT50	50% pseudotyped lentivirus reporter test
PT	preferred term
RT-PCR	reverse transcription polymerase chain reaction
S-2P	spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain
SAE	serious adverse event
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	2019 novel coronavirus
Th1	T-helper 1
Th2	T-helper 2
VE	vaccine efficacy
VRBPAC	Vaccine and Related Biological Products Advisory Committee
WHO	World Health Organization

1 EXECUTIVE SUMMARY

mRNA-1273 is a novel messenger ribonucleic acid (mRNA)-based vaccine encapsulated in a lipid nanoparticle (LNP) against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The vaccine includes a single mRNA sequence encoding the pre-fusion stabilized Spike (S) protein of the SARS-CoV-2 virus. The proposed mRNA-1273 vaccine regimen consists of two 100-µg intramuscular (IM) injections administered 28 days apart.

ModernaTX, Inc. is seeking Emergency Use Authorization (EUA) for mRNA-1273 based on data from preclinical and clinical studies which indicate that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks of the Moderna COVID-19 Vaccine. In the Phase 1 and 2 clinical studies, a consistent dose response was observed across age groups by several measures of humoral immunogenicity for both binding and neutralizing antibodies. The prespecified primary efficacy results from Study 301 in more than 15,181 adult recipients of mRNA-1273 and 15,170 recipients of placebo (N=30,351) demonstrated vaccine efficacy (VE) of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19. This finding is based on 196 adjudicated cases[1] that occurred at least 14 days after the second vaccination (11 cases in the mRNA-1273 arm and 185 in the placebo arm). The mRNA-1273 safety profile in Study 301 has been characterized based on a dataset including 8 weeks median exposure, demonstrating a positive benefit-risk profile that supports broad public use.

This briefing document provides Phase 3 efficacy and safety data from 2 different cut-offs:

- The initial interim analysis for efficacy (“Interim Dataset”), based on 95 adjudicated cases (data snapshot on November 11, 2020 with a cutoff date for efficacy of November 7, 2020). Interim analyses were prespecified as early stopping criteria for efficacy.
- Primary Dataset based on the prespecified primary efficacy analysis from 196 adjudicated cases (data snapshot on November 25, 2020 with a cutoff date for efficacy of November 21, 2020) [1]. This dataset was provided to further support the EUA request and align with recommendations from the 22 October 2020 Vaccine and Related Biological Products Advisory Committee (VRBPAC) for 2-month median exposure following the second injection of mRNA-1273 for both safety and efficacy analyses. Any additional, supplemental safety data will be presented at the 17 December 2020 VRBPAC meeting. The Food and Drug Administration (FDA) has not yet had the opportunity to verify the data and analyses from these additional 2 weeks of data.

[1] Primary prespecified efficacy analysis to occur at ≥ 151 adjudicated cases of confirmed symptomatic COVID-19 infections.

Both datasets are provided in the main document. Furthermore, both datasets are consistent and support the efficacy and safety of mRNA-1273.

ModernaTX, Inc. (the Sponsor) has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The mRNA platform is based on knowledge of the established biology of cellular protein biosynthesis. mRNA is the 'blueprint' that cells use to synthesize the proteins needed for their physiology. Cells are able to uptake mRNA delivered in an LNP, translate the mRNA into its associated protein, and then express that protein viral antigen(s) on the cell surface to elicit an immune response. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is only expressed transiently before undergoing degradation by the cell's natural mRNA degradation process. Several mRNA vaccines are in development and are being used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389), Zika (NCT04064905), and influenza virus (NCT03076385 and NCT03345043). The manufacturing process, which has been under development for 10 years, is cell-free and does not use vectors or animal products, preservatives or adjuvants.

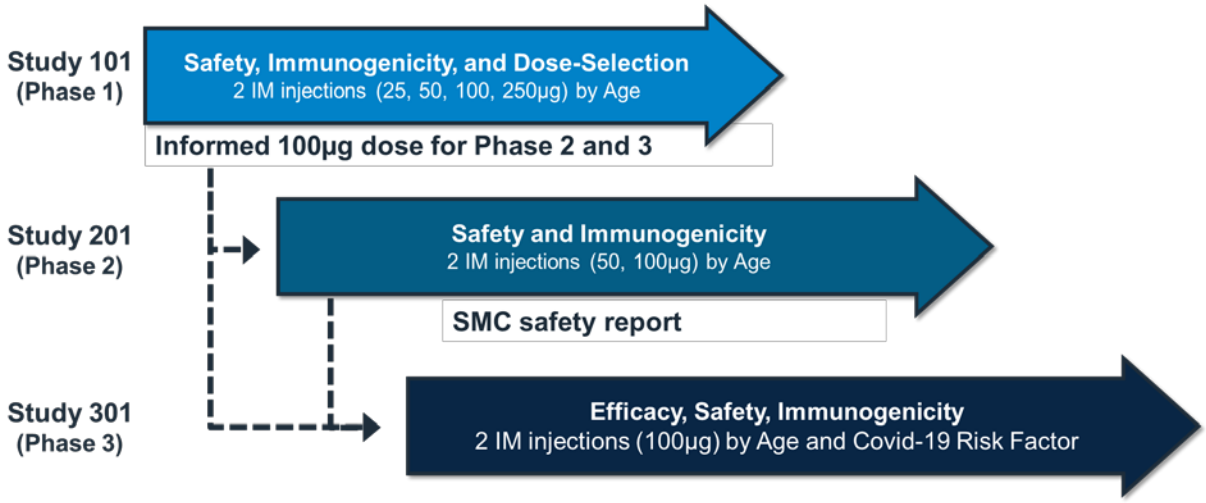
Recognizing the broad potential of mRNA science, the mRNA technology platform was designed to function so that it could rapidly pivot to address this pandemic. Moderna was able to leverage the learnings of numerous vaccines in development, along with early pre-clinical work with other coronaviruses to select the appropriate antigen design to rapidly respond to the public need. mRNA-1273 encodes the full length SARS-CoV-2 spike protein stabilized in a prefusion conformation with 2 proline mutations.

A suite of pre-clinical studies was executed to demonstrate the that mRNA-1273 is immunogenic, fully protects animals from challenge at optimal dose levels, and does not drive enhanced respiratory disease (ERD) at protective or subprotective dose levels. These nonclinical studies supported the clinical development of mRNA-1273.

The clinical development of mRNA-1273 has been expedited to address the ongoing global public health emergency resulting from the SARS-CoV-2 pandemic (Figure 1). Since the submission of the IND, the Sponsor has collaborated with the National Institutes of Health (NIH), Biomedical Advanced Research and Development (BARDA), and Operation Warp Speed (OWS) to support a systematic evaluation of the vaccine's benefit-risk profile and regularly provided packages of nonclinical and clinical data from the ongoing clinical studies to the FDA to help assess the risk and benefit profile of mRNA-1273.

The Phase 3 protocol and Statistical Analysis Plan have been designed in accordance with both FDA general guidance on COVID-19 vaccine development and product-specific guidance. The studies were also conducted with oversight by an independent DSMB and adjudication committee.

Figure 1: Overview of the mRNA-1273 Development Program



Abbreviations: SMC = Safety Monitoring Committee

The program began with the open-label, ongoing Phase 1 dose-ranging study, Study 101, to evaluate the safety and immunogenicity of 4 dose levels of mRNA-1273 across 3 age strata. The findings from Study 101 generated the recommendation for the 100-µg dose used in the Phase 2 and Phase 3 studies. Study 201, an ongoing randomized, placebo-controlled, Phase 2 safety and immunogenicity study, provided additional safety data to support the initiation of the large-scale Phase 3 study, Study 301. Study 301 is the ongoing pivotal, randomized, placebo-controlled study to evaluate efficacy, safety, and immunogenicity of mRNA-1273 in more than 30,000 participants.

Study 301

In the pivotal Phase 3 study, Study 301, 30,351 participants were randomized 1:1 to receive mRNA-1273 100 µg(N=15,181) or placebo (N=15,170). Participants in Study 301 had to be 18 years of age at the time of consent and at high risk of SARS-CoV-2 infection because their location or circumstances put them at increased risk of exposure to SARS-CoV-2. Participants were excluded if they were pregnant or breastfeeding, pediatric, immunocompromised, or had a known history of SARS-CoV-2. A full list of enrollment inclusion and exclusion criteria is provided in Appendix 11.2. To examine the efficacy of mRNA-1273 in high-risk populations, randomization was stratified based on age (< 65 and ≥ 65 years) and risk of severe COVID-19 based on the presence of comorbid conditions (ie, chronic lung disease or moderate to severe asthma, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV).

Study participants received the first injection of investigational product (IP) on Day 1 and the second injection on Day 29. Solicited local and systemic events were collected for 7 days immediately following injection, unsolicited adverse events (AEs) of any category were collected for 28 days following each vaccination, and medically-attended adverse

events (MAAEs), serious adverse events (SAEs), and cases of COVID-19 will be collected until study conclusion.

The prespecified primary efficacy endpoint of Study 301 was symptomatic COVID-19 infection, confirmed by an adjudication committee, which occurred at least 14 days after the second injection. Key prespecified secondary endpoints included cases of severe COVID-19, cases of asymptomatic COVID-19, and cases of COVID-19 occurring at least14 days after the first injection. Definitions of these endpoints are provided in Section 6.1.3.

An independent data and safety monitoring board (DSMB) was used to review the data on an ongoing basis to make recommendations to the Sponsor to either stop, pause, or continue study enrollment (details are provided in Section 7.1). In addition, a blinded adjudication committee was assembled to review potential cases to determine if the criteria for the primary and secondary endpoints were met (details are provided in Section 6.1.2).

The baseline demographics in Study 301 were representative of the United States population, and included the enrollment of individuals from diverse racial and ethnic groups as well as adults ≥ 65 years of age (details provided in Section 6.2.2). Approximately 25% of participants were ≥ 65 years of age, and approximately 10% were Black or African American, 5% were Asian, and 21% were of Hispanic or Latino ethnicity.

Efficacy Findings

Study 301 met its primary efficacy objective. mRNA-1273 demonstrated VE of 94.1% against symptomatic COVID-19 confirmed by an adjudication committee in the Per-Protocol (PP) Population ($p < 0.0001$) (Table 1). A total of 196 cases of confirmed COVID-19 occurred in the study of which 11 were in the mRNA-1273 group and 185 were in the placebo group. The lower limit (LL) of the 95% confidence interval (CI) was 89.3%, exceeding the prespecified lower limit of > 30% for the primary hypothesis.

Table 1: Primary Efficacy Endpoint Analysis in Study 301 (Per-Protocol Set)

	Nov 25 Dataset[a]	
	mRNA-1273 (N=14134)	Placebo (N=14073)
Number of participants with COVID-19, n (%)	11 (< 0.1)	185 (1.3)
Vaccine efficacy based on hazard ratio (95% CI)	94.1% (89.3%, 96.8%)	
p-value	< 0.0001	

[a] Primary efficacy analysis

Secondary efficacy endpoint results are shown in Table 2. Importantly, mRNA-1273 was effective in preventing cases of severe confirmed COVID-19. There were no cases of severe COVID-19 in the mRNA-1273 group and 30 cases of severe COVID-19 in the

placebo group at the time of the primary analysis[2]. This finding also supports that there is no increased risk of enhanced disease with mRNA-1273. There was one death due to COVID-19 in the placebo group and none in the mRNA-1273 group. mRNA-1273 was also effective in preventing cases of COVID-19 using a secondary (less stringent) definition of COVID-19 as defined in Section 6.1.3.

Table 2: Secondary Efficacy Endpoint Analysis Results in Study 301

	Nov 25 Dataset[a]	
	mRNA-1273 (N=14134)	Placebo (N=14073)
Cases of severe COVID-19 based on adjudication committee assessments starting 14 days after the second injection (secondary endpoint), n	0	30
Vaccine efficacy based on hazard ratio (95% CI)	100.0% (NE, 100.0%)	
Cases with a secondary (less restrictive) definition of COVID-19 starting 14 Days after the second injection (secondary endpoint), n	11	221
Vaccine efficacy based on hazard ratio (95% CI)[a]	95.1% (91.1%, 97.3%)	
Cases of COVID-19 related deaths based on adjudication committee assessments starting 14 days after the second injection (secondary endpoint), n	0	1
Vaccine efficacy based on hazard ratio (95% CI)	100.0% (NE, 100.0%)	
Cases of COVID-19 starting 14 days after the first injection (secondary endpoint), n	11	225
Vaccine efficacy based on hazard ratio (95% CI)	95.2% (91.2%, 97.4%)	
Cases of COVID-19 based on adjudication committee assessments starting 14 days after the second injection regardless of prior SARS-CoV-2 infection (secondary endpoint), n/N	12/15181	187/15170
Vaccine efficacy based on hazard ratio (95% CI)	93.6% (88.6%, 96.5%)	

[a] Primary efficacy analysis

Safety Findings

The safety data supporting mRNA-1273 are based on a median follow-up period for both efficacy and safety of 8 weeks after the second injection. Reported AEs align with events commonly seen with injected vaccinations.

More solicited local adverse reactions (ARs) (injection site pain, erythema, and swelling, and ipsilateral lymphadenopathy) were reported by participants in the mRNA-1273 group than placebo, with a higher occurrence after the second injection (Table 3 and Table 4). While the majority of these ARs were grade 1 (mild) or grade 2 (moderate), there was a higher occurrence of grade 3 (severe) reactions in the mRNA-1273 group

[2] As of the primary efficacy analysis there were no severe cases in the mRNA-1273 group. For one participant experiencing severe symptoms, the investigator has not yet received medical records from the hospital, and a positive RT-PCR result for SARS-COV-2 infection has not yet been confirmed. Therefore, this case has not yet been evaluated by the Adjudication Committee.

and after the second injection. The majority of local solicited ARs occurred within the first one to 2 days after injection and generally persisted for a median of 1 to 2 days.

Table 3: Summary of Solicited Local Adverse Reactions in Study 301 (Nov 25 Dataset)

	Nov 25 Dataset[a]			
	First Injection		Second Injection	
Category Grade	mRNA-1273 (N=15164) n (%)	Placebo (N=15151) n (%)	mRNA-1273 (N=14673) n (%)	Placebo (N=14562) n (%)
Any Solicited Local Adverse Reactions	12765 (84.2)	2997 (19.8)	13006 (88.6)	2735 (18.8)
Grade 3	529 (3.5)	78 (0.5)	1020 (7.0)	72 (0.5)
Grade 4	0	0	0	0

[a] 8-week median follow-up
Notes: Solicited adverse reactions include reports within 7 days of injection.
CTCAE grade definitions provided in Appendix 11.1.

Table 4: Summary of Solicited Local Adverse Reactions in Study 301 (Nov 11 Dataset)

	Nov 11 Dataset[a]			
	First Injection		Second Injection	
Category Grade	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)
Any Solicited Local Adverse Reactions	12765 (84.2)	2998 (19.8)	12381 (88.8)	2607 (18.8)
Grade 3	529 (3.5)	78 (0.5)	978 (7.0)	70 (0.5)
Grade 4	0	0	0	0

[a] EUA submission (7-week median follow-up)
Notes: Solicited adverse reactions include reports within 7 days of injection.
CTCAE grade definitions provided in Appendix 11.1.

Similar to local reactions, there were more solicited systemic ARs (fatigue, headache, myalgia, arthralgia, chills, fever, and nausea/vomiting) reported by participants in the mRNA-1273 group than placebo and more events reported after the second injection (Table 5 and Table 6**).** The majority of solicited systemic ARs were grade 1 (mild) or grade 2 (moderate). There was a higher occurrence of grade 3 (severe) and grade 4 (life threatening) events in the mRNA-1273 group. The majority of solicited systemic ARs occurred within the first 1 to 2 days after injection and generally resolved within a median of 2 days.

Table 5: Summary of Solicited Systemic Adverse Reactions in Study 301 (Nov 25 Dataset)

Category Grade	Nov 25 Dataset[a]			
	First Injection		Second Injection	
	mRNA-1273 (N=15167) n (%)	Placebo (N=15155) n (%)	mRNA-1273 (N=14677) n (%)	Placebo (N=14565) n (%)
Any Solicited Systemic Adverse Reactions	8320 (54.9)	6399 (42.2)	11652 (79.4)	5323 (36.5)
Grade 3	447 (2.9)	308 (2.0)	2325 (15.8)	282 (1.9)
Grade 4	5 (< 0.1)	6 (< 0.1)	14 (< 0.1)	3 (< 0.1)

[a] 8-week median follow-up
Notes: Solicited adverse reactions include reports within 7 days of injection.
CTCAE grade definitions provided in Appendix 11.1.

Table 6: Summary of Solicited Systemic Adverse Reactions in Study 301 (Nov 11 Dataset)

Category Grade	Nov 11 Dataset[a]			
	First Injection		Second Injection	
	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)	mRNA-1273 (N=13947) n (%)	Placebo (N=13870) n (%)
Any Solicited Systemic Adverse Reactions	8321 (54.9)	6398 (42.2)	11064 (79.3)	5069 (36.5)
Grade 3	447 (2.9)	309 (2.0)	2188 (15.7)	273 (2.0)
Grade 4	5 (< 0.1)	6 (< 0.1)	12 (< 0.1)	3 (< 0.1)

[a] EUA submission (7-week median follow-up)
Note: Solicited adverse reactions include reports within 7 days of injection.
CTCAE grade definitions provided in Appendix 11.1.

The incidence of unsolicited AEs and was comparable in the mRNA-1273 and placebo groups (Table 7 and Table 8). The most commonly reported unsolicited AEs in the 28 days after injection were headache, fatigue, and diarrhea. The incidences of unsolicited severe AEs and SAEs were low and comparable in the mRNA-1273 and placebo groups. Overall, there was 1 discontinuation due to an adverse event in placebo and 3 discontinuations due to an adverse event in the mRNA-1273 group; discontinuations due to SAE included 2 in the placebo group and 3 in the mRNA-1273 group. There was no evidence of enhanced disease after vaccination.

Table 7: Summary of Unsolicited Adverse Events up to 28 Days After Vaccination in Study 301 (Nov 25 Dataset- Safety Set)

Category Grade	Nov 25 Dataset[a] mRNA-1273 (N=15185) n (%)	 Placebo (N=15166) n (%)
Unsolicited Adverse Events	3632 (23.9)	3277 (21.6)
Grade 3	234 (1.5)	202 (1.3)
Grade 4	0	0
Serious Adverse Event	93 (0.6)	89 (0.6)
Death	2 (< 0.1)	3 (< 0.1)

[a] 8-week median follow-up

Table 8: Summary of Unsolicited Adverse Events up to 28 Days After Vaccination in Study 301 (Nov 11 Dataset- Safety Set)

Category Grade	Nov 11 Dataset[a] mRNA-1273 (N=15167) n (%)	 Placebo (N=15154) n (%)
Unsolicited Systemic Adverse Events	3325 (21.9)	2949 (19.4)
Grade 3	190 (1.3)	216 (1.4)
Grade 4	0	0
Serious Adverse Event	82 (0.5)	86 (0.6)
Death	2 (< 0.1)	3 (< 0.1)

[a] EUA submission (7-week median follow-up)

Benefit-Risk Summary

In conclusion, the prespecified primary efficacy analysis for mRNA-1273 from Study 301 and the 2-month median exposure safety data support a positive benefit-risk profile. The data generated to date for mRNA-1273 provide clear and compelling evidence of efficacy against symptomatic COVID-19 disease, with a point estimate of vaccine efficacy of 94.1% and a lower limit of the 95% CI of 89.6%, exceeding the FDA guidance for a point estimate of at least 50% and a lower bound of 30%. Furthermore, 30 cases of severe COVID-19, including one death due to COVID-19, occurred in the placebo group, suggesting even higher efficacy against severe COVID-19 disease. With a median of 8 weeks of safety exposure in more than 15,000 recipients, mRNA-1273 has demonstrated an acceptable tolerability profile. While solicited symptoms were more common in the mRNA-1273 group and after the second dose, the majority were mild-to-moderate in severity and had a mean duration between 2 and 3 days. Overall, incidences of unsolicited AEs and SAEs were balanced between groups, with no safety signals identified to date. The DSMB has continued to recommend that the study continue as planned. Considering the ongoing public health impact due to SARS-CoV-2 and lack of approved preventative vaccines, the potential benefits of mRNA-1273 outweigh the risks.

2 BACKGROUND ON COVID-19

Summary

- As of 30 November 2020, there have been more than 62 million cases of COVID-19 and 1.4 million deaths due to COVID-19 worldwide.
- Older adults (≥ 65 years old) and people with certain underlying medical conditions are at higher risk for severe COVID-19.
- There is an urgent unmet public health need for vaccines to prevent the burden of disease associated with SARS-CoV-2 infection.

2.1 Overview of COVID-19

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV).

An outbreak of COVID-19 caused by the 2019 novel SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease has since spread globally (WHO 2020a). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 Mar 2020; however, widespread community transmission was already occurring in many locations. As of 30 November 2020, more than 62 million cases and 1.4 million deaths worldwide have been attributed to the COVID-19 pandemic (JHU 2020; WHO 2020a). Widespread community transmission of SARS-CoV-2 has been reported in the Americas, Europe, Africa, and Southeast Asia, and clusters of cases continue to be reported throughout Asia and Australia (WHO 2020a). During the winter, the combination of re-opening of schools and an increase in indoor activity, because of lower temperatures, is expected to further increase the number of COVID-19 cases and deaths in some parts of the world.

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (regardless of whether they are symptomatic) (Chen et al 2020; Licciardi et al 2020; Rothan and Byrareddy 2020; Shen et al 2020). Airborne transmission may be possible during certain medical procedures and in indoor, crowded, or poorly ventilated environments (WHO 2020b). Common symptoms of COVID-19 include fever and cough, and other symptoms include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of COVID-19 and severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, serious heart conditions, compromised immune system, obesity, pregnancy, sickle cell disease, and type 2 diabetes mellitus. Smokers are also at increased risk for severe COVID-19 (CDC 2020a).

2.2 Unmet Medical Need

Currently, there is no FDA approved vaccine against SARS-CoV-2. Without further advances in the use of nonpharmaceutical interventions, more than 2.5 million COVID-19 deaths are projected globally by 01 Mar 2021, with daily deaths peaking at approximately 15,000/day during this time (IHME). Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for the rapid development of novel prophylactic therapies, including vaccines, to prevent the spread of this disease.

3 MRNA-1273 PRODUCT DESCRIPTION

Summary

- The mRNA-1273 vaccine uses a platform based on a well-established mRNA biologic process that uses a cell's natural physiology to create SARS-CoV-2 spike proteins that elicit an immune response to protect against infection.
- The mRNA platform is uniquely suited for rapid vaccine design, development, and scale-up to accelerate response to urgent pandemic situations such as the COVID-19 pandemic.
- mRNA vaccines have several features which reduce safety risks:
    - Only translated into the precise protein coded for by the sequence, eliminating exposure to other antigens
    - Does not enter the cell nucleus or interact with the genome
    - Nonreplicating
    - Expressed transiently
- Nonclinical and clinical results provide high confidence in the immune response and tolerability of mRNA-1273.

3.1 mRNA Platform

Moderna has developed a rapid-response proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The precision and standardization of the mRNA platform enables rapid development and efficient manufacturing scale-up of safe and protective vaccines without reliance on systems that are specific to each pathogen. mRNA is highly precise in its translation into proteins that match viral antigens. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The estimated half-life for mRNA after injection is approximately 8 to 10 hours, before degradation by native RNases in the body, but the duration of effect also depends on the half-life of the expressed protein, which persists in the body for several days. mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3), Zika, and influenza virus.

A schematic of mRNA is provided in Figure 2. The mRNA is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present is fully replaced with N1-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs (Kariko et al 2005; Rozenski et al 1999). This nucleoside is included in the mRNA in place of the normal uridine base to minimize indiscriminate recognition of the mRNA by pathogen-associated molecular

pattern receptors (Desmet and Ishii 2012). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Fechter and Brownlee 2005; Kozak 1991).

Figure 2: Structure of mRNA

Abbreviations: PolyA, polyadenylated; UTR, untranslated region.

3.2 mRNA-1273 Mechanism of Action

Moderna is using its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle-encapsulated, mRNA-based vaccine against SARS-CoV-2. The proprietary lipid nanoparticles encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability.

Prior to the emergence of the novel SARS-CoV-2 coronavirus, Moderna had developed a foundational understanding of mRNA vaccine approaches against coronavirus based on prior experience toward the development of mRNA vaccines against MERS-CoV and SARS-CoV-1. This pre-clinical effort led to the evaluation of several mRNA vaccine designs against MERS-CoV, the most effective of which were spike protein designs. Of these, a full-length spike protein modified to introduce 2 proline residues to stabilize the spike protein into a prefusion conformation (S-2P) showed improved performance versus the wild type spike protein. These improvements included better expression of protein, stabilization of the spike protein in the prefusion conformation, and improved immunogenicity in murine studies.

This foundational work allowed us to leverage the scientific understanding we had developed and apply it to the approach that we have used in the development of mRNA-1273. That approach is utilization of our proprietary LNP technology to encapsulate synthetic mRNA that encodes for the full length SARS-CoV-2 spike protein stabilized in a prefusion conformation with 2 proline mutations. The CoV spike protein mediates attachment and entry of the virus into host cells by attachment followed by membrane fusion, making it a primary target for neutralizing antibodies (nAbs) that prevent infection (Chen et al 2017; Corti et al 2015; Johnson et al 2016; Kim et al 2019; Wang et al 2018; Wang et al 2015; Widjaja et al 2019; Yu et al 2015).

The mRNA-1273 vaccine is delivered via intramuscular injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilizes the cell's translational machinery to produce the spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.

mRNA-1273 stimulates innate immune responses, resulting in the production of proinflammatory cytokines and type 1 interferon. This process activates B-cell and T-cell responses from the adaptive immune system. mRNA-1273 directly activates B-cells, including memory B-cells, resulting in the secretion of antibodies that bind and neutralize SARS-CoV-2 viruses. mRNA-1273 also directly activates T-cells, which eliminate infected cells and support B-cell responses. mRNA-1273 also induces Th1-biased CD4 T-cell responses in humans (Jackson et al 2020).

3.3 Therapeutic Rationale Supporting Investigation

To date, nonclinical and clinical evaluations demonstrate that mRNA-1273 is well tolerated, is immunogenic, and drives a robust SARS-CoV-2 specific antibody and T-cell response. Nonclinical immunogenicity, biodistribution, and safety studies were completed by the Sponsor using mRNA-1273 or similar mRNA-based vaccines formulated in SM-102–containing LNPs.

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

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

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

A developmental and reproductive toxicity (DART) study to assess potential fertility and pre and postnatal development effects of mRNA-1273 in pregnant and lactating female Sprague Dawley rats was conducted at a clinically relevant 100 µg /dose. The no observed adverse effect level was 100 µg.

Overall, nonclinical animal studies demonstrated that mRNA-1273 is immunogenic, fully protects animals from challenge at optimal dose levels, and does not drive ERD at protective or subprotective dose levels.

4 OVERVIEW OF MRNA-1273 DEVELOPMENT

Summary

- Moderna has worked closely with the NIH, BARDA, and OWS on the clinical development of mRNA-1273, including the Phase 3 study protocol and Statistical Analysis Plan. Communication with the FDA has been frequent, and FDA guidance has been followed.
- mRNA-1273 is currently being evaluated in the following studies:
  - Study 301: a Phase 3, randomized, observer-blind, placebo-controlled study of the safety, efficacy, and immunogenicity of mRNA-1273 100 µg.
  - Study 201: a Phase 2a, randomized, observer-blind, and placebo-controlled study of the safety and immunogenicity of 50 µg and 100 µg mRNA-1273.
  - Study 101: a Phase 1, open-label, dose-ranging study of the safety and immunogenicity of mRNA 1273 25 µg, 50 µg, 100 µg, or 250 µg.

4.1 Regulatory Overview

The clinical development of mRNA-1273 has been expedited to address the ongoing global public health emergency resulting from the SARS-CoV-2 pandemic, but was designed in collaboration with NIH, BARDA, and OWS to support a systematic evaluation of the efficacy, immunogenicity, and safety of the candidate vaccine. Since the submission of the Investigational New Drug (IND) application, the Sponsor has regularly consulted with Center for Biologics Evaluation and Research (CBER) on the clinical development of mRNA-1273 and provided nonclinical and clinical data packages to help assess the benefit-risk profile of mRNA-1273 on an ongoing basis. The Phase 3 protocol and Statistical Analysis Plan have been designed in accordance with both FDA general guidance on COVID-19 vaccine development (DHHS 2020) and product-specific guidance. The study was conducted with oversight of an independent DSMB which was formed and chartered under the leadership of the NIH.

4.2 Clinical Development Program

The mRNA-1273 vaccine is currently being evaluated for safety and immunogenicity in a dose-ranging Phase 1 study sponsored by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), for safety and immunogenicity in a company-sponsored Phase 2a study, and for safety, efficacy, and immunogenicity in a company-sponsored Phase 3 study. Interim results of the Phase 1 study informed the dosages used in the Phase 2 and Phase 3 studies. Prior to initiating the Phase 3 study, safety and reactogenicity through 7 days post-dose 2 for the full study cohort was assessed by an independent safety monitoring committee. All three of these studies are ongoing and conducted in the US. A summary of these studies is provided in Table 9.

Table 9: Ongoing Clinical Studies of mRNA-1273

Study Number (Country)/ Status	Study Design	Age Groups (years) / Dose (Planned Participants)	Vaccine Dose and Schedule
Study 301	Phase 3, randomized, stratified, observer-blind, placebo-controlled	**Age Groups:** 18+ (n=30000) **Dose Groups:** Placebo (n=15000) mRNA-1273 100 µg (n=15000) **Stratification:** Age and, if they are < 65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 based on CDC recommendation as of Mar 2020	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart
Study 201	Phase 2a, randomized, observer-blind, and placebo-controlled	**Age Groups:** **Cohort 1**: ≥ 18 to < 55 (n=300) **Cohort 2**: ≥ 55 (n=300) **Dose Groups:** Placebo (n=200) mRNA-1273 50 µg (n=200) mRNA-1273 100 µg (n=200)	50 or 100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart
Study 101	Phase 1, open-label, dose ranging	**Age Groups:** 18 to 55 (n=75) 56 to 70 (n=40) ≥ 71 (n=40) **mRNA-1273 Dose Groups:** 10 µg (n=15)[a] 25 µg (n=35) 50 µg (n=35) 100 µg (n=35) 250 µg (n=35)[b]	10, 25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart

Abbreviations: IM = intramuscular

[a] In Study 101, Cohort 13 (10 µg, 18–55 years, n=15) was not enrolled.

[b] In Study 101, dosing at the 250 µg level was discontinued after Cohort 3 (18–55 years, n=15) and prior to enrollment in Cohorts 6 (56–70 years, n=10) and 9 (≥ 71 years, n=10).

5 PHASE 1 AND PHASE 2 STUDIES

Summary

- Immunogenicity results in Study 101 indicated that the 100-µg dose administered as 2 injections 28 days apart resulted in the induction of neutralizing antibodies (nAbs) in all participants as of 1 week after the second injection.
  - The immune response was consistent across age groups and persisted for at least 3 months after the second injection.
  - The 100-µg dose of mRNA-1273 was selected as the optimal dose for use in later stage studies.
- An evaluation of T-cell responses elicited by mRNA-1273 in Study 101 showed the induction of CD4+ T-cells predominantly of the Th-1 phenotype.
- Moderna is using multiple assays to assess immunogenicity across the Phase 1, 2, and 3 studies, with convalescent sera from patients who have recovered from SARS-CoV-2 as a positive control.
- Immunogenicity results from Study 201 confirmed the induction of binding antibodies and nAbs to the SARS-CoV-2 spike protein at both the 50 µg and 100 µg dose levels.
- Results from Study 101 showed that 2 injections of 100 µg mRNA-1273 stimulated serum binding antibodies (bAbs) to a greater degree than the 25-µg dose, induced nAb responses similar to the 250-µg dose, and led to a lower incidence of reactogenicity than the 250-µg dose. Therefore, the 100 µg dose was selected for further clinical development.

5.1 Assays Used to Assess Immunogenicity

Across the Phase 1, 2, and 3 studies, and Enzyme-Linked Immunosorbent Assay (ELISA) is being used to measure vaccine-induced binding immunoglobulin (IgG) antibodies (bAbs) to the full-length SARS-CoV-2 spike protein. Multiple assays are being used to measure the neutralizing antibody titers (nAbs) of mRNA-1273. In Study 101, nAbs were assessed by pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) (performed at the NIAID Vaccine Research Center) and by live wild-type SARS-CoV-2 virus plaque-reduction neutralization test (PRNT) assay (performed at the Vanderbilt University Medical Center). In later phases of development, nAbs have been measured by a microneutralization (MN) assay. Study 101 also evaluated the induction of CD4+ and CD8+ T-cells. This was done through an Intracellular Cytokine Staining (ICS) assay. Serostatus at baseline was assessed with Roche's Elecsys Anti-SARS-CoV-2 antibody-based electro-chemiluminescence assay (past infection) and Viracor SARS-CoV-2 RT-PCR (current infection). Asymptomatic

SARS-CoV-2 infection was defined as seroconversion to anti-SARS-CoV-2 nucleocapsid protein by the Roche Elecsys assay.

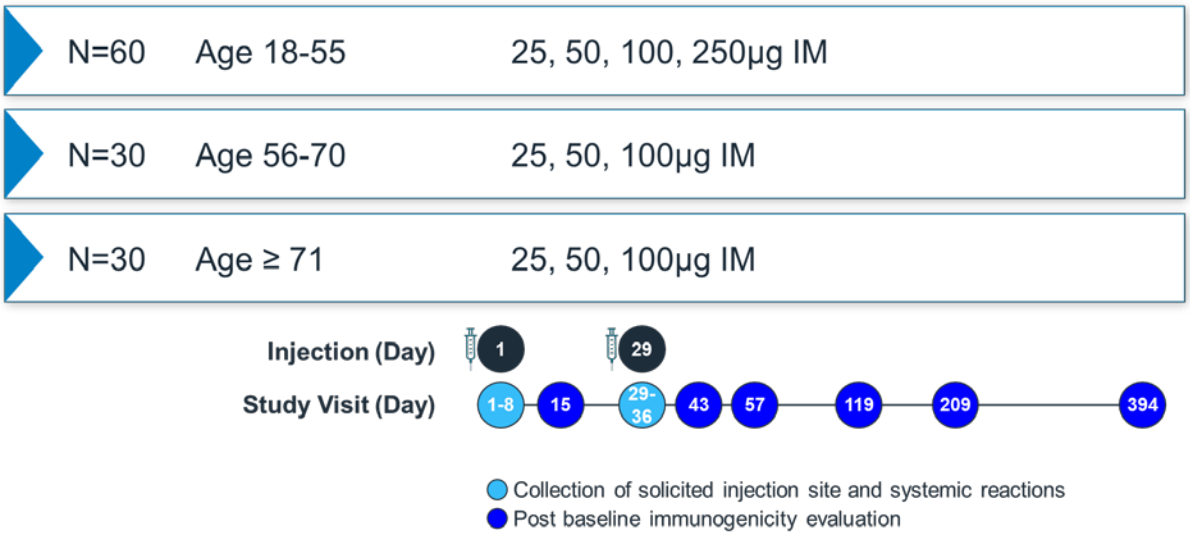
5.2 Phase 1 Dose-Finding Study (Study 101)

5.2.1 Study Design

Study 101 was a Phase 1, dose-escalation, open-label study to assess the safety and immunogenicity of mRNA-1273 in healthy adults aged 18 years and older. Study 101 was sponsored by the DMID of the NIAID.

Participants were enrolled into one of 13 cohorts based on age (Figure 3). Participants received 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273. As a control, pooled convalescent sera were obtained from 41 patients recovering from COVID-19 disease and were used as a benchmark immunogenicity comparator for antibodies induced by natural infection. Blood samples were obtained at baseline, Days 8, 15, 29 (prior to injection 2), 36, 43, and 57, as well as three, six, and 12 months after the second vaccination (Days 119, 209, and 394, respectively).

Figure 3: Study 101 Design



5.2.2 Disposition

In Study 101, 120 participants were enrolled. All participants received the first injection of mRNA-1273, and 116 (96.7%) participants received the second injection. Four (3.3%) participants discontinued IP after the first injection: 3 (2.5%) participants discontinued due to an AE (hives on lower extremities, sore throat, and maculopapular rash) and one (0.8%) participant discontinued treatment due to potential COVID-19 exposure. All 120 participants were included in at least one of the immunogenicity analyses and in the safety analyses.

5.2.3 Demographics

Data were analyzed for each age cohort separately and were not analyzed for the study population as a whole.

Age Group 18 to 55 Years of Age

The majority of participants were White (88%) and not of Hispanic or Latino ethnicity (87%). The median age was 32.1 years (range: 18 to 54), and 52% of participants were male and 48% were female.

Age Group 56 to 70 Years of Age

The majority of participants were White (90%), and all (100%) were not of Hispanic or Latino ethnicity. The median age was 65.0 years (range: 56 to 70), and 43% of participants were male and 57% were female.

Age Group ≥ 71 Years of Age

The majority of participants were White (97%) and not of Hispanic or Latino ethnicity (93%). The median age was 72.9 years (range: 71 to 83), and 57% of participants were male and 43% were female.

5.2.4 Immune Response Results

Table 10 and Table 11 show the bAb concentrations for spike IgG as measured by ELISA at all dose levels in the 18 to 55 years of age stratum and for all 3 age strata at the 100-µg dose mRNA-1273, respectively, in the Phase 1 study. Table 12 and Table 13 show the nAb titers as measured by PsVNA for the 18 to 55 years of age stratum across dose levels and for the 100-µg dose of mRNA-1273 across all 3 age strata, respectively. No formal statistical comparisons were prespecified in this study; thus, descriptive summaries are provided here.

Immunogenicity results in Study 101 indicated that the 100-µg dose of mRNA-1273 administered as 2 injections 28 days apart resulted in the induction of nAbs in all participants by 1 week after the second injection (Anderson et al 2020; Jackson et al 2020). After a single injection of 100 µg of mRNA-1273, bAbs for spike glycoprotein were detectable in all participants in all 3 age strata, with further increases observed at the second injection. The immune response was consistent across age groups and persisted 3 months after the second injection. A similar response was observed across all doses in all age cohorts, but higher responses were observed with the second injection in older adults at the 100-µg mRNA-1273 dose.

Pooled convalescent sera from patients recovered from COVID-19 were used as a clinically meaningful benchmark to assess the magnitude of the immune response to vaccination with mRNA-1273. Binding IgG antibodies against the spike protein (stabilized spike antigen, S-2P), as measured by ELISA were observed to have higher

median values at Day 43 and beyond in the mRNA-1273 groups than in the convalescent sera control group (Table 10 and Table 11).

Neutralizing activity was observed for the 100-µg mRNA-1273 dose as of Day 36; the neutralizing activity was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata (Table 12 and Table 13).

Study 101 assessments of antibody responses focused on the initial Wuhan-1 strain sequence (614D), although the 614G polymorphism in SARS-CoV-2 spike has become the globally predominant isoform. An increase in neutralizing activity was observed on the pseudovirus neutralization assay when 614G was substituted for 614D (Anderson et al 2020). These data provide evidence that the immune response to mRNA-1273 may be sufficient to neutralize the current dominant circulating strain.

An intracellular cytokine stimulation assay was used to evaluate T-cell responses elicited by the mRNA-1273 vaccine. The 25 µg, 100 µg, and 250 µg doses elicited CD4+ T-cell responses that upon stimulation by S-specific peptide pools were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. CD8+ T-cell responses to S-2P were detected at low levels after the second injection in the 100-µg dose group. This Th1-dominant profile adds to the body of nonclinical data suggesting that mRNA-1273 is unlikely to lead to enhanced disease following natural exposure to SARS-CoV-2.

The 100 µg dose of mRNA-1273 was selected as the optimal dose for use in later stage studies based on greater immunogenicity compared with the 25-ug dose. The observation that the Th1 phenotype of CD4+ T-cells was induced was clinically reassuring in terms of the risk of developing vaccine-associated ERD.

Table 10: Serum IgG ELISA Endpoint Titer Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 101 – Spike Stabilized Antigen (S-2P) – Age 18 to 55 Years

Time Point	Statistic	25 µg mRNA-1273 18–55 Years (N=15)	50 µg mRNA-1273 18–55 Years (N=15)	100 µg mRNA-1273 18–55 Years (N=15)	250 µg mRNA-1273 18–55 Years (N=15)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	15	15	15	41
	GMT	116	341	131	178	138901
	95% CI	72; 187	127; 914	65; 266	81; 392	82876; 232799
Day 29 Post-Vaccination 1 (Pre-Vaccination 2)	n	15	15	15	14	NA
	GMT	40227	118294	109209	213526	NA
	95% CI	29094; 55621	71948; 194495	79051; 150874	128832; 353896	NA
Day 43 Post-Vaccination 1 (14 Days Post-Vaccination 2)	n	13	14	14	14	NA
	GMT	379764	734025	811119	994629	NA
	95% CI	281597; 512152	588266; 915900	656336; 1002404	806189; 1227115	NA
Day 57 Post-Vaccination 1 (28 Days Post-Vaccination 2)	n	13	15	14	14	NA
	GMT	299751	562064	782719	1255376	NA
	95% CI	206070; 436020	407368; 775505	619310; 989244	969516; 1625521	NA
Day 119 Post-Vaccination 1 (90 Days Post-Vaccination 2)	n	13	ND	15	14	NA
	GMT	301540	ND	413971	604507	NA
	95% CI	217148; 418729	ND	322891; 530744	451387; 809568	NA

Abbreviations: GMT = geometric mean titer; n = number of participants with results available at time point; N = number of participants; NA = not available; ND = not determined.

Table 11: Serum IgG ELISA Endpoint Titer Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 101 – Spike Stabilized Antigen (S-2P) – All Age Groups 100 µg mRNA-1273

Time Point	Statistic	100 µg mRNA-1273 18–55 Years (N=15)	100 µg mRNA-1273 56–70 Years (N=10)	100 µg mRNA-1273 ≥ 71 Years (N=10)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	10	10	41
	GMT	131	655	953	138,901
	95% CI	65, 266	270, 1591	493, 1842	82876, 232799
Day 29 Post-Vaccination 1 (Pre-Vaccination 2)	n	15	10	10	NA
	GMT	109209	115831	203365	NA
	95% CI	79051, 150874	73288, 183069	97384, 424686	NA
Day 43 Post-Vaccination 1 (14 Days Post-Vaccination 2)	n	14	9	10	NA
	GMT	811119	1305996	8091439	NA
	95% CI	656336, 1002404	581138, 2934971	2546249, 25712881	NA
Day 57 Post-Vaccination 1 (28 Days Post-Vaccination 2)	n	14	9	10	NA
	GMT	782719	1183066	3638522	NA
	95% CI	619310, 989244	379698, 3686201	1316233, 10058130	NA
Day 119 Post-Vaccination 1 (90 Days Post-Vaccination 2)	n	15	9	10	NA
	GMT	413971	366252	195272	NA
	95% CI	322891, 530744	213031, 629675	117647, 324112	NA

Abbreviations: GMT = geometric mean titer; n = number of participants with results available at time point; N = number of participants; NA = not available.

Table 12: Pseudovirus Neutralization Assay Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 101 – ID50 – Age 18 to 55 Years

Time Point	Statistic	25 µg mRNA-1273 18–55 Years (N=15)	50 µg mRNA-1273 18–55 Years (N=15)	100 µg mRNA-1273 18–55 Years (N=15)	250 µg mRNA-1273 18–55 Years (N=15)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	15	15	15	41
	GM	10	10	10	10	106
	95% CI	ND	ND	ND	ND	60, 189
Day 29 Post-Vaccination 1 (Pre-Vaccination 2)	n	15	15	15	14	NA
	GM	12	14	18	21	NA
	95% CI	10, 14	9, 21	12, 27	13, 32	NA
Day 36 Post-Vaccination 1 (7 Days Post-Vaccination 2)	n	13	15	15	14	NA
	GM	106	294	263	378	NA
	95% CI	70, 160	178, 487	188, 368	306, 468	NA
Day 43 Post-Vaccination 1 (14 Days Post-Vaccination 2)	n	13	14	14	14	NA
	GM	112	351	360	342	NA
	95% CI	71, 177	214, 575	273, 476	267, 438	NA
Day 57 Post-Vaccination 1 (28 Days Post-Vaccination 2)	n	13	15	14	14	NA
	GM	90	234	276	277	NA
	95% CI	57, 143	153, 358	193, 393	231, 332	NA
Day 119 Post-Vaccination 1 (90 Days Post-Vaccination 2)	n	13	ND	15	14	NA
	GM	54	ND	182	185	NA
	95% CI	29, 100	ND	112, 296	128, 269	NA

Abbreviations: GM = geometric mean; ID50 = 50% inhibitory dilution; n = number of participants with results available at time point; N = number of participants; NA = not available; ND = not determined.

Table 13: Pseudovirus Neutralization Assay Geometric Mean Results With 95% Confidence Intervals by Time Point and Vaccination Group in Study 101 – ID50 – All Age Groups 100 µg mRNA-1273

Time Point	Statistic	100 µg mRNA-1273 18–55 Years (N=15)	100 µg mRNA-1273 56–70 Years (N=10)	100 µg mRNA-1273 ≥ 71 Years (N=10)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	10	10	41
	GM	10	10	10	106
	95% CI	ND	ND	ND	60, 189
Day 29 Post-Vaccination 1 (Pre-Vaccination 2)	n	15	10	10	NA
	GM	18	11	20	NA
	95% CI	12, 27	10, 12	12, 33	NA
Day 43 Post-Vaccination 1 (14 Days Post-Vaccination 2)	n	14	9	10	NA
	GM	360	404	317	NA
	95% CI	273, 476	292, 561	198, 508	NA
Day 57 Post-Vaccination 1 (28 Days Post-Vaccination 2)	n	14	9	10	NA
	GM	276	424	231	NA
	95% CI	193, 393	267, 673	150, 356	NA
Day 119 Post-Vaccination 1 (90 Days Post-Vaccination 2)	n	15	9	10	NA
	GM	182	167	109	NA
	95% CI	112, 296	88, 318	68, 175	NA

Abbreviations: GM = geometric mean; ID50 = 50% inhibitory dilution; n = number of participants with results available at time point; N = number of participants; NA = not available.

5.2.5 Dose Selection

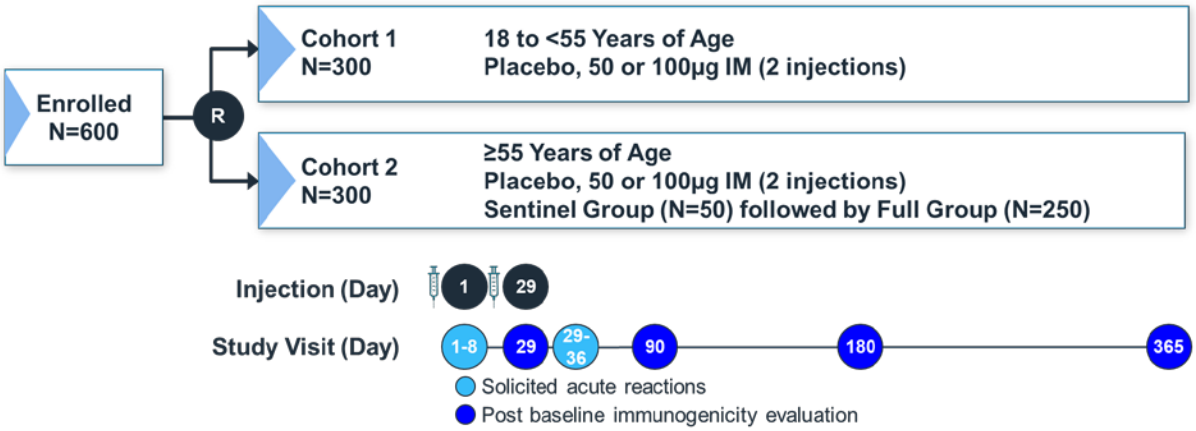
The results of Study 101 showed a consistent dose response across age groups by several measures of humoral immunogenicity for both bAbs and nAbs. The advancement of the 100 µg dose (administered as 2 injections, 28 days apart) to the Phase 2a and 3 studies was based on several observations: (i) 2 injections of 100 µg stimulated serum bAb concentrations and titers greater than 2 injections of 25 µg in the 18 to 55 years of age stratum; (ii) 2 injections of 100 µg induced nAb responses (measured by PsVNA) similar to those measured in recipients of the 250 µg dose (in the evaluated age group: 18 to 55 years); and (iii) 2 injections of 100 µg led to a lower incidence of reactogenicity than 2 injections of 250 µg (Anderson et al 2020; Jackson et al 2020). The 50-µg dose was added to the protocol for Study 101 only after the dose selection decision was made; therefore, those results were not considered in the selection of the 100µg dose.

5.3 Phase 2a Safety and Immunogenicity Study (Study 201)

5.3.1 Study Design

Study 201 is an ongoing Phase 2a, randomized, placebo-controlled, dose-confirmation study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older (Figure 4). Participants were randomized 1:1:1 to the placebo group, the mRNA-1273 50 µg group, or the mRNA-1273 100 µg group. The study was divided into 2 cohorts by age: Cohort 1 (≥ 18 to < 55 years old) and Cohort 2 (≥ 55 years old).

Figure 4: Study 201 Design



5.3.2 Disposition

As of 05 Nov 2020, 200 (100%) participants each in the mRNA-1273 50-µg group, mRNA-1273 100-µg group, and placebo group received the first injection, and 195 (97.5%) participants in the mRNA-1273 50-µg group, 198 (99.0%) participants in the mRNA-1273 100-µg group, and 194 (97.0%) participants in the placebo group received

the second injection. Of the 13 participants who did not receive the second injection, the most common reason for discontinuation was lost to follow-up (5 [0.8%] participants).

5.3.3 Immune Response Results

Participants who received 2 injections of either 50 µg or 100 µg of mRNA-1273 separated by 28 days developed both bAbs and nAbs against the SARS-CoV-2 virus, with geometric mean fold rises (GMFRs) > 20-fold (bAb as measured by the ELISA assay) and > 50-fold (nAbs as measured by the MN assay), regardless of dose level (Table 14 and Table 15). These data indicate that a two-dose schedule of either 50 µg or 100 µg of mRNA-1273 results in the rapid induction of functional antibodies against SARS-CoV-2 and support the selection of the 100 µg dose for the Phase 3 clinical study.

Table 14: Summary of Binding (anti-Spike Glycoprotein) Antibody Levels in Study 201 (Per-Protocol Set for SARS-CoV-2-Specific bAb)

Timepoint Statistic	mRNA-1273 50 µg (N=185)	mRNA-1273 100 µg (N=189)	Placebo (N=186)
Baseline (Day 1)			
n[a]	185	189	186
GM level	6.08	5.88	5.95
95% CI[c]	5.65, 6.54	5.49, 6.29	5.59, 6.34
Median	6.30	5.90	6.00
Min, max	1.95, 37.70	1.95, 106.00	1.95, 16.80
Day 29			
n[b]	184	189	184
GM level	20.32	25.23	5.80
95% CI[c]	18.60, 22.21	22.78, 27.94	5.42, 6.21
Median	20.20	25.60	5.90
Min, max	4.10, 106.50	4.30, 431.60	1.95, 40.40
GM fold-rise	3.36	4.29	0.98
95% CI[c]	3.05, 3.69	3.87, 4.76	0.95, 1.01
Day 43			
n[b]	175	181	180
GM level	169.46	198.13	5.74
95% CI[c]	156.25, 183.79	182.865, 214.68	5.36, 6.14
Median	186.30	204.30	5.90
Min, max	33.80, 487.00	20.10, 487.00	1.95, 17.80
GM fold-rise	27.46	33.51	0.97
95% CI[c]	24.86, 30.33	30.37, 36.96	0.95, 1.00
Day 57			
n[b]	176	177	175
GM level	123.89	147.42	5.86
95% CI[c]	113.07, 135.75	134.47, 161.61	5.46, 6.29
Median	136.00	166.10	5.90
Min, max	21.40, 456.00	23.10, 487.00	1.95, 62.50
GM fold-rise	20.39	25.04	0.98
95% CI[c]	18.31, 22.70	22.51, 27.86	0.94, 1.03

Abbreviations: bAb = binding antibody; GM = geometric mean; IgG = immunoglobulin; max = maximum; min = minimum; LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome CoV-2; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values that are greater than the ULOQ are converted to the ULOQ.

For visit Day 29, visit window (-3/+7 days) is used to define per-protocol. If the visit (Day 29) was disrupted and could not be completed at Day 29 (-3/+7 days) as a result of the COVID-19 pandemic, the window was extended to Day 29 + 21 days.

[a] Number of participants with non-missing baseline immunogenicity information.

[b] Number of participants in the Per-Protocol Set for SARS-CoV-2-specific bAb at the corresponding visit.

[c] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.

Table 15: Summary of Neutralizing Antibody Titers in Study 201 (Per-Protocol Set for SARS-CoV-2 Specific nAb)

Timepoint / Data Category / Statistic	mRNA-1273 50 µg (N=179)	mRNA-1273 100 µg (N=186)	Placebo (N=181)
Baseline (Day 1)			
n[a]	179	186	181
GMT	20.3	20.0	20.0
95% CI[b]	19.9, 20.7	NE, NE	NE, NE
Median	20.0	20.0	20.0
Min, max	20, 120	20, 20	20, 20
Day 29			
n[c]	168	180	178
GMT	113.4	149.3	21.0
95% CI[b]	94.6, 136.0	126.5, 176.2	19.7, 22.3
Median	120.0	160.0	20.0
Min, max	20, 1280	20, 1280	20, 960
GMFR	5.59	7.46	1.05
95% CI[b]	4.65, 6.71	6.32, 8.81	0.99, 1.11
Seroconversion[d]			
n[e] (%)	131 (78.0)	160 (88.9)	3 (1.7)
95% CI[f]	70.9, 84.0	83.4, 93.1	0.3, 4.8
Day 43			
n[c]	141	150	175
GMT	1144.7	1179.4	20.4
95% CI[b]	1094.4, 1197.2	1130.5, 1230.5	19.6, 21.4
Median	1280.0	1280.0	20.0
Min, max	240, 1280	160, 1280	20, 960
GMFR	56.23	58.97	1.02
95% CI[b]	53.29, 59.34	56.52, 61.52	0.98, 1.07
Day 57			
n[c]	150	152	171
GMT	1091.0	1095.8	21.2
95% CI[b]	1035.5, 1149.5	1038.8, 1155.9	19.8, 22.6
Median	1280.0	1280.0	20.0
Min, max	240, 1280	200, 1280	20, 640
GMFR	53.65	54.79	1.06
95% CI[b]	50.54, 56.95	51.94, 57.80	0.99, 1.13
Seroconversion[d]			
n[e] (%)	150 (100)	152 (100)	3 (1.8)
95% CI[f]	97.6, 100.0	97.6, 100.0	0.4, 5.0

Abbreviations: GMT = geometric mean titer; GMFR = geometric mean fold-rise (post-baseline vs. baseline titers); LLOQ = lower limit of quantification; max = maximum; min = minimum; MN50 = 50% microneutralization; nAb = neutralizing antibody; SARS-CoV-2 = severe acute respiratory syndrome CoV-2; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values that are greater than the ULOQ are converted to the ULOQ.

For visit Day 29, visit window (-3/+7 days) was used to define per-protocol. If the visit (Day 29) was disrupted and could not be completed at Day 29 (-3/+7 days) as a result of the COVID-19 pandemic, the window was extended to Day 29 + 21 days.

Percentages are based on the number of participants in the Per-Protocol Set for SARS-CoV-2-specific nAb at the corresponding visit (n[3]).

[a] Number of participants with non-missing baseline.

[b] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.

[c] Number of participants in the Per-Protocol Set for SARS-CoV-2-specific nAb at the corresponding visit.
[d] Seroconversion at participant level is defined as a change of nAb titer from below the LLOQ to equal to LLOQ (respectively), or a 4-times or higher ratio in participants with pre-existing nAb titers.
[e] Number of participants in the corresponding category at the corresponding time point.
[f] 95% CI is calculated using the Clopper-Pearson method.

6 PHASE 3 CLINICAL EFFICACY (STUDY 301)

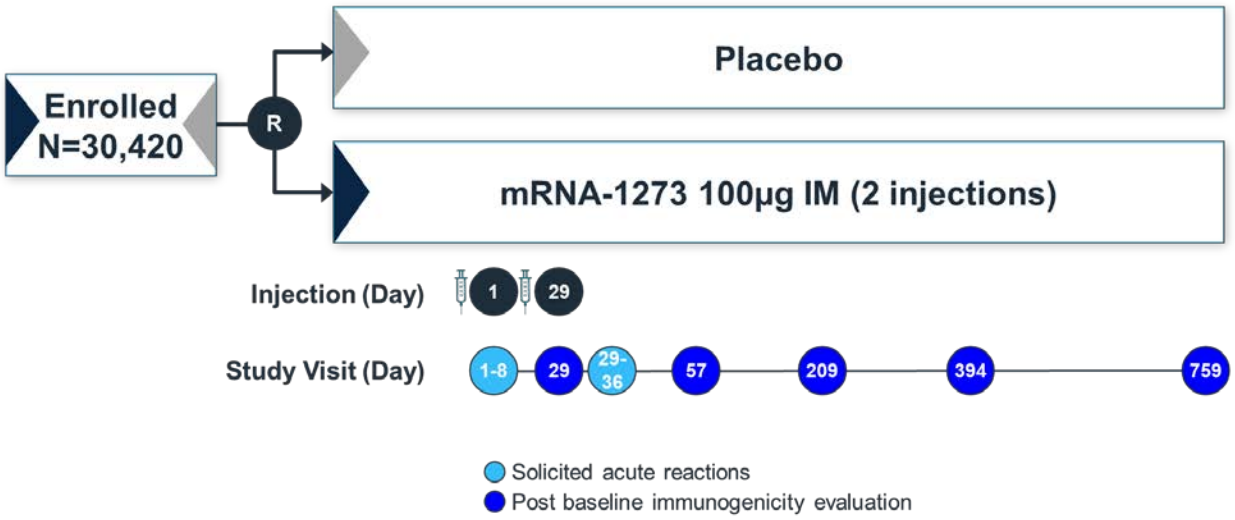
Summary

- Study 301 met its primary efficacy endpoint. There were 11 cases of positively adjudicated cases of COVID-19 in the mRNA-1273 group and 185 in the placebo group starting 14 days after the second injection for a VE of 94.1% ($p < 0.0001$).
  - The lower limit of the 95% CI for VE was 89.3%, which surpassed the prespecified lower limit of > 30%.
- mRNA-1273 was also highly effective against severe COVID-19, with no cases of severe COVID-19 occurring in the mRNA-1273 group and 30 cases in the placebo group within 14 days of the second injection at the time of the primary analysis.
- Evaluation of additional secondary efficacy analyses were consistent with the primary efficacy analyses. mRNA-1273 was effective against COVID-19 regardless of prior SARS-CoV-2 infection, using a less restrictive definition of COVID-19, and considering all cases of symptomatic COVID-19 disease starting 14 days after the first injection.
- The efficacy of mRNA-1273 was consistent across major demographic and baseline characteristic subgroups at increased risk for severe COVID-19 infections and death.

6.1 Study Design

Study 301 is an ongoing Phase 3, randomized, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 in adults aged 18 years or older (Figure 5). Participants in the study were to have no known history of SARS-CoV-2 infection, but their locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. Participants were randomized 1:1 to receive 100 µg of mRNA-1273 or saline placebo intramuscularly as a two-dose schedule given one month apart.

Figure 5: Study 301 Design



A total of 30,418 participants were randomly assigned in a 1:1 ratio to receive 2 injections of either 100 µg mRNA-1273 or placebo. Randomization was stratified based on age and the presence or absence of risk factors for severe illness for COVID-19 (based on CDC recommendation as of March 2020 (CDC 2020b)) in participants < 65 years of age. Risk was defined based on the study participants' relevant past and current medical history. It was planned that at least 25% of enrolled participants, but not to exceed 50%, were to be either ≥ 65 years of age, or ≥18 but < 65 years of age and at risk for the complications of severe COVID-19 disease at Screening. Participants were considered to be at risk for severe COVID-19 illness if they had at least 1 of the following risk factors at Screening:

- 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/m^2)
- Diabetes (Type 1, Type 2, or gestational)
- Liver disease
- Controlled human immunodeficiency virus (HIV) infection

Participants had up to 7 scheduled clinic visits, including Screening, Day 1, Day 29, Day 57 (1 month after second injection), Day 209 (6 months after second injection), Day 394 (1 year after second injection), and Day 759 (2 years after second injection).

All participants were assessed for efficacy endpoints throughout the study and provided a nasopharyngeal (NP) swab sample and blood sample against SARS-CoV-2 nucleoprotein before the first and second injection of IP to inform on their baseline viral

infection status and baseline serostatus, respectively. Only participants who were negative at their pre-dose 1 NP swab and serological sample were included in the primary analysis of efficacy. To be included as a case in the primary analysis for efficacy, cases had to be positively confirmed by the adjudication committee and had to occur at least 14 days after the second injection.

The primary efficacy endpoint was symptomatic COVID-19 disease, which was defined as the following:

- At least two of the following systemic symptoms: fever ≥ 38.0°C/100.4°F, chills, myalgia, headache, sore throat, new olfactory or taste disorder; 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
- Documentation of at least one NP swab, nasal swab, or salivary sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 virus by reverse transcriptase polymerase chain reaction (RT-PCR).

Information on severity of COVID-19 infection was obtained. To meet the protocol case definition for the secondary efficacy endpoint of severe COVID-19 disease, the participant had to meet the case definition for COVID-19 disease and one of the following criteria had to be met:

- Clinical signs of severe systemic illness, respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, SpO_2 ≤ 93% on room air at sea level or PaO_2/FiO_2 < 300 mm Hg; OR
- Respiratory failure of Acute Respiratory Distress Syndrome (ARDS) [defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)]; evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors); OR
- Significant acute renal, hepatic, or neurologic dysfunction; OR
- Admission to intensive care unit or death.

Immunogenicity data are not yet available for Study 301.

All participants were also assessed for safety endpoints, and were given an electronic diary (eDiary) to report a pre-specified list solicited local (injection site pain, erythema and swelling, and ipsilateral lymphadenopathy) and systemic (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever) ARs for 7 days after each injection of IP and to prompt an unscheduled clinic visit for clinical evaluation and NP swab sample if they experienced any symptoms of COVID-19. Participants also receive safety calls on Day 8, Day 15, Day 22, Day 36, and Day 43 to monitor for unsolicited AEs and to monitor for symptoms of COVID-19. Unsolicited symptoms, including MAAEs and SAEs, are reported by the participant, and participants were instructed to call the study center if they experienced symptoms of COVID-19 disease or

experienced any other AE they perceived as serious to ensure appropriate reporting of cases of COVID-19 and SAEs.

6.1.1 Enrollment Criteria

Key inclusion criteria include the following:

- Adults, ≥ 18 years of age at time of consent, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
- Female participants of nonchildbearing potential and female participants of childbearing potential who fulfill the following criteria:
    - Has a negative pregnancy test at Screening and on the day of the first injection (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).
    - Is not currently breastfeeding.

Key exclusion criteria include the following:

- Acutely ill or febrile (≥ 38.0ºC/100.4ºF) 72 hours prior to or at Screening.
- Pregnant or breastfeeding.
- Known history of SARS-CoV-2 infection.
- Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or current/planned simultaneous participation in another interventional study to prevent or treat COVID-19.
- Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV-positive participants on stable antiretroviral therapy are not excluded).

A full list of enrollment criteria is provided in Appendix 11.1.

6.1.2 Adjudication Committee

An adjudication committee was assembled for the purpose of reviewing potential cases to determine if the criteria for the primary and secondary endpoints had been met. The adjudication committee remained blinded to treatment assignment.

6.1.3 Endpoints

The primary efficacy endpoint was the VE of mRNA-1273 to prevent the first occurrence of COVID-19 as defined in Section 6.1, and the primary endpoint analysis included cases starting 14 days after the second injection, as adjudicated by an independent adjudication committee that was blinded to vaccine group assignment using the PP Set.

The secondary endpoints, also adjudicated by the independent adjudication committee that was blinded to assignment using the PP Set, included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 as defined in Section 6.1.
- COVID-19 regardless of symptomatology or severity, defined as the first occurrence of SARS-CoV-2 infection or COVID-19 starting 14 days after the second dose of IP.
- COVID-19 based on a secondary (less restrictive) definition starting 14 days after the second injection of IP. The secondary (less restrictive) definition of COVID-19 included having one of the following 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 AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.
- Death due to COVID-19.
- COVID-19 starting 14 days after the first injection of IP (inclusive of cases that occurred after the second injection).

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

6.1.4 Statistical Analyses

Sample Size Determination

The sample size was driven by the total number of cases that needed to be observed to reject the null hypothesis that the vaccine efficacy of mRNA-1273 to prevent symptomatic COVID-19 disease is ≤ 30%, assuming that the true vaccine efficacy is 60%. Under the assumptions of proportional hazards over time and 1:1 randomization to mRNA-1273 or placebo, a total of 151 COVID-19 cases would provide 90% power to detect a 60% reduction in the hazard rate (60% VE), rejecting the null hypothesis that VE is ≤ 30%. The study incorporated two planned interim analyses when approximately 35% and 70% of the target total number of cases had accrued using a 1-sided O'Brien-Fleming boundary for efficacy and a log-rank test statistic with a 1-sided false positive error rate of 0.025.

Sample size determination also included the following assumptions:

- A 6-month COVID-19 incidence rate of 0.75% in the placebo arm
- An annual dropout rate of 2% (loss of evaluable participants)
- 15% of participants are seropositive at baseline, are non-compliant with injection assessments, or have major protocol deviations

Approximately 30,000 participants were planned to be randomized.

Analyses Populations

Efficacy analyses were performed using the FAS and PP populations. Participants were analyzed according to the group to which they were randomized. Participant populations were defined as follows:

- FAS: All randomized participants who received at least one injection of IP.
- PP: All participants in the mITT Set who received planned injections of IP as scheduled and had no major protocol deviations, as determined and documented by Sponsor prior to database lock and unblinding, that impact critical or key study data.

Efficacy Analyses

A stratified Cox proportional hazards model was used to assess the magnitude of the treatment group difference between mRNA-1273 and placebo at a 1-sided 0.025 significance level. The VE is defined as the percent reduction in the hazard of the primary efficacy endpoint (mRNA-1273 versus placebo).

Subgroup analyses of the primary efficacy endpoint were performed in the following pre-specified subgroups to assess the consistency of VE:

- Age groups: ≥ 18, < 65, and ≥ 65
- Age and health risk for severe disease: ≥ 18 and < 65 and not at risk; ≥18 and <65 years of age and at risk and ≥ 65 years of age regardless of additional risk factors
- Sex: female and male
- Race: White and Communities of Color (including participants who self-identified as being Black, Asian, and American Indian and Alaska Native as a racial group)
- Ethnicity: Hispanic or Non-Hispanic

One interim analysis (data snapshot on November 11, 2020 with a cutoff date for efficacy of November 7, 2020) and one primary analysis (data snapshot on November 25, 2020 with a cutoff date for efficacy of November 21, 2020) were performed for efficacy endpoints. There were 95 and 196 cases of COVID-19 included in each analysis, respectively. As the US experienced a surge in reported cases of COVID-19 in the month of November, cases accrued too quickly to perform the analyses as initially planned per protocol. Data in this briefing document reflect both the interim and primary analyses for efficacy performed on 95 and 196 cases, respectively, to demonstrate the consistency of these two efficacy analyses.

6.2 Participant Disposition and Demographics

6.2.1 Participant Disposition

Participant disposition is described in Table 16. More than 30,000 participants were randomized. The most common reasons for discontinuation were withdrawal of consent by participant, confirmed SARS-CoV-2 infection (ie, diagnosed COVID-19 by detection of SARS-CoV-2 in Day 1 NP swab or symptomatic COVID-19 prior to Day 29), and other, with a similar distribution between mRNA-1273 and placebo recipients.

Table 16: Participant Disposition in Study 301 (Randomization Set)

	Nov 11 Dataset[a]		**Nov 25 Dataset[b]**	
	mRNA-1273 (N=15208) n (%)	Placebo (N=15210) n (%)	mRNA-1273 (N=15210) n (%)	Placebo (N=15210) n (%)
Received first injection	15180 (99.8)	15170 (99.7)	15181 (99.8)	15170 (99.7)
Received second injection	13982 (91.9)	13916 (91.5)	14711 (96.7)	14617 (96.1)
Discontinued study vaccine/placebo	188 (1.2)	254 (1.7)	233 (1.5)	290 (1.9)
Reason for discontinuation of study vaccine/placebo				
Adverse event	24 (0.2)	28 (0.2)	29 (0.2)	25 (0.2)
Serious adverse event	5 (< 0.1)	14 (< 0.1)	9 (< 0.1)	15 (< 0.1)
Death	3 (< 0.1)*	2 (< 0.1)	2 (< 0.1)*	3 (< 0.1)
Lost to follow-up	18 (0.1)	20 (0.1)	27 (0.2)	24 (0.2)
Physician decision	15 (< 0.1)	10 (< 0.1)	15 (< 0.1)	9 (< 0.1)
Pregnancy	2 (< 0.1)	2 (< 0.1)	3 (< 0.1)	2 (< 0.1)
Protocol deviation	2 (< 0.1)	4 (< 0.1)	3 (< 0.1)	5 (< 0.1)
Withdrawal of consent by participant	48 (0.3)	91 (0.6)	56 (0.4)	97 (0.6)
Due to SARS-CoV-2[c]	35 (0.2)	49 (0.3)	45 (0.3)	69 (0.5)
Other	36 (0.2)	34 (0.2)	44 (0.3)	41 (0.3)
Completed study[d]	0	0	0	0
Discontinued from study	120 (0.8)	168 (1.1)	159 (1.0)	206 (1.4)
Reason for discontinuation of study				
Adverse event	2 (< 0.1)	0	4 (< 0.1)	1 (< 0.1)
Serious adverse event	1 (< 0.1)	0	3 (< 0.1)	2 (< 0.1)
Death	3 (< 0.1)	4 (< 0.1)	4 (< 0.1)	6 (< 0.1)
Lost to follow-up	20 (0.1)	31 (0.2)	33 (0.2)	35 (0.2)
Physician decision	17 (0.1)	2 (< 0.1)	15 (< 0.1)	3 (< 0.1)
Pregnancy	0	0	0	0
Protocol deviation	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	0
Study terminated by Sponsor	0	0	0	0
Withdrawal of consent by participant	67 (0.4)	120 (0.8)	85 (0.6)	146 (1.0)
Other	9 (< 0.1)	10 (< 0.1)	14 (< 0.1)	13 (< 0.1)

[a] EUA submission (interim efficacy analysis)
[b] Primary efficacy analysis
[c] Study participants were considered ineligible to receive injection 2 if they were diagnosed with asymptomatic SARS-CoV-2 at Day 1 or symptomatic COVID-19 prior to Day 29.
[d] Participants were considered to have completed the study if they completed the final visit at Day 759 (Month 25), 24 months after the last injection of IP.
*During data cleaning, the reason for discontinuation of 1 mRNA-1273 participant was updated from 'death' to 'SAE'.
**During data cleaning, the reason for discontinuation of 1 placebo participant was updated from 'SAE' to 'death'

6.2.2 Baseline Demographics

Table 17 presents the baseline demographic information for participants in Study 301 included in the Full Analysis Set. Study 301 was designed to evaluate the safety and efficacy of the IP in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The study planned to enroll at least 25% and up to 50% of participants most at risk for severe complications of COVID-19, including those ≥ 65 years of age or < 65 years of age with comorbid medical conditions such as diabetes mellitus (Type 1, Type 2, or gestational), significant cardiac disease, chronic pulmonary disease, severe obesity, liver disease, and controlled human immunodeficiency virus infection.

The Sponsor had the intention to enroll a representative population of communities of color that have been disproportionately affected by COVID-19.

Table 17: Baseline Demographics and Characteristics in Study 301 (Full Analysis Set)

	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15180)	Placebo (N=15170)	mRNA-1273 (N=15181)	Placebo (N=15170)
Sex, n (%)				
Male	7928 (52.2)	8067 (53.2)	7923 (52.2)	8062 (53.1)
Female	7252 (47.8)	7103 (46.8)	7258 (47.8)	7108 (46.9)
Age at Screening (years)				
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.50)	51.3 (15.60)
Median	53.0	52.0	53.0	52.0
Min, Max	18, 95	18, 95	18, 95	18, 95
Age group at Screening, n (%)				
≥ 18 and < 65 years	11412 (75.2)	11418 (75.3)	11413 (75.2)	11418 (75.3)
≥ 65 years	3768 (24.8)	3752 (24.7)	3768 (24.8)	3752 (24.7)
Age and health risk for severe COVID-19, n (%)[c]				
≥ 18 and < 65 Years and Not at Risk	8887 (58.5)	8886 (58.6)	8888 (58.5)	8886 (58.6)
≥ 18 and < 65 Years and at Risk	2530 (16.7)	2535 (16.7)	2530 (16.7)	2535 (16.7)
≥ 65 Years	3763 (24.8)	3749 (24.7)	3763 (24.8)	3749 (24.7)
Baseline SARS-CoV-2 Status, n (%)[d]				
Negative	14312 (94.3)	14370 (94.7)	14550 (95.8)	14598 (96.2)
Positive	341 (2.2)	334 (2.2)	343 (2.3)	337 (2.2)
Missing	527 (3.5)	466 (3.1)	288 (1.9)	235 (1.5)
Race, n (%)[e]				
White	12029 (79.2)	11994 (79.1)	12029 (79.2)	11995 (79.1)
Black or African American	1562 (10.3)	1528 (10.1)	1563 (10.3)	1527 (10.1)
Asian	653 (4.3)	732 (4.8)	651 (4.3)	731 (4.8)
American Indian or Alaska Native	110 (0.7)	120 (0.8)	112 (0.7)	121 (0.8)
Native Hawaiian or Other Pacific Islander	34 (0.2)	32 (0.2)	35 (0.2)	32 (0.2)
Multiracial	314 (2.1)	320 (2.1)	315 (2.1)	321 (2.1)
Other	321 (2.1)	315 (2.1)	321 (2.1)	316 (2.1)
Not Reported	99 (0.7)	75 (0.5)	96 (0.6)	73 (0.5)
Unknown	58 (0.4)	54 (0.4)	59 (0.4)	54 (0.4)
Ethnicity, n (%)				
Hispanic or Latino	3120 (20.6)	3114 (20.5)	3121 (20.6)	3114 (20.5)
Not Hispanic or Latino	11917 (78.5)	11917 (78.6)	11918 (78.5)	11917 (78.6)
Not Reported	104 (0.7)	84 (0.6)	104 (0.7)	85 (0.6)
Unknown	39 (0.3)	55 (0.4)	38 (0.3)	54 (0.4)
Race and Ethnicity Group, n (%)[f]				
White	9532 (62.8)	9460 (62.4)	9529 (62.8)	9461 (62.4)

	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15180)	Placebo (N=15170)	mRNA-1273 (N=15181)	Placebo (N=15170)
Communities of Color	5622 (37.0)	5683 (37.5)	5626 (37.1)	5683 (37.5)
Missing	26 (0.2)	27 (0.2)	26 (0.2)	26 (0.2)
Body Mass Index, (kg/m^2)				
N	14944	14955	14985	15007
Mean (SD)	29.32 (6.87)	29.32 (6.71)	29.32 (6.86)	29.32 (6.69)
Median	28.12	28.12	28.12	28.13

Abbreviations: bAb = binding antibody concentration; IRT = interactive response technology; LLOQ = lower limit of quantification; LOD = limit of detection; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain reaction.

Note: Internet-based randomization was used to randomize participants to treatment groups based on the information the Investigator entered regarding the age and potential comorbid conditions.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] Based on stratification factor from IRT, participants who were < 65 years old were categorized as at risk for severe COVID-19 illness if they had at least 1 of the risk factors specified in the study protocol at Screening.

[d] Baseline SARS-CoV-2 status: Positive if there was immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test, or bAb against SARS-CoV-2 nucleocapsid above LOD or LLOQ at Day 1. Negative is defined as negative RT-PCR test and negative Roche Elecsys Anti-SARS-CoV-2 assay result at Day 1.

[e] Participants could be under one or more categories and were counted once at each category. The highest 3 occupational risk categories overall are presented in this table.

[f] White is defined as White and non-Hispanic, and communities of color includes all others whose race or ethnicity is not unknown, unreported, or missing.

6.3 Primary Endpoint Results

The primary endpoint was cases of Symptomatic Confirmed COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection.

The primary analysis showed that the VE of mRNA-1273 to prevent symptomatic COVID-19 in baseline seronegative participants was 94.1% (95% CI: 89.3%, 96.8%; p-value <0.0001) (Table 18). There were 196 COVID-19 cases starting 14 days after the second injection based on adjudication committee assessments in the PP Set.

These results confirmed the interim analysis of efficacy, which was performed on 95 cases, with 5 cases occurring in the mRNA-1273 group and 90 cases occurring in the placebo group. In the interim analysis, the VE point estimate was 94.5% (95% CI: 86.5, 97.8). Therefore, the results from the interim and the primary analyses were highly consistent with each other.

Table 18: Primary Efficacy Endpoint Analysis of Study 301 (Starting 14 Days After Second Injection; Per-Protocol Set)

	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=13934)	Placebo (N=13883)	mRNA-1273 (N=14134)	Placebo (N=14073)
Number of participants with COVID-19, n (%)	5 (< 0.1)	90 (0.6)	11 (< 0.1)	185 (1.3)
Vaccine efficacy based on hazard ratio (95% CI)[c]	94.5% (86.5%, 97.8%)		94.1% (89.3%, 96.8%)	
P value[d]	<0.0001		< 0.0001	
Person-years[e]	2716.9	2697.5	3304.9	3273.7
Incidence rate per 1,000 person-years (95% CI)[f]	1.84 (0.60, 4.30)	33.365 (26.83, 41.01)	3.33 (1.66, 5.96)	56.51 (48.66, 65.27)
Vaccine efficacy based on incidence rate (95% CI)[g]	0.945 (0.87, 0.98)		0.94 (0.89, 0.97)	

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] Vaccine efficacy is defined as 1 – hazard ratio (mRNA-1273 vs. placebo), and 95% CI was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

[d] One-sided p-value from stratified Cox proportional hazard model to test the null hypothesis VE ≤ 0.3.

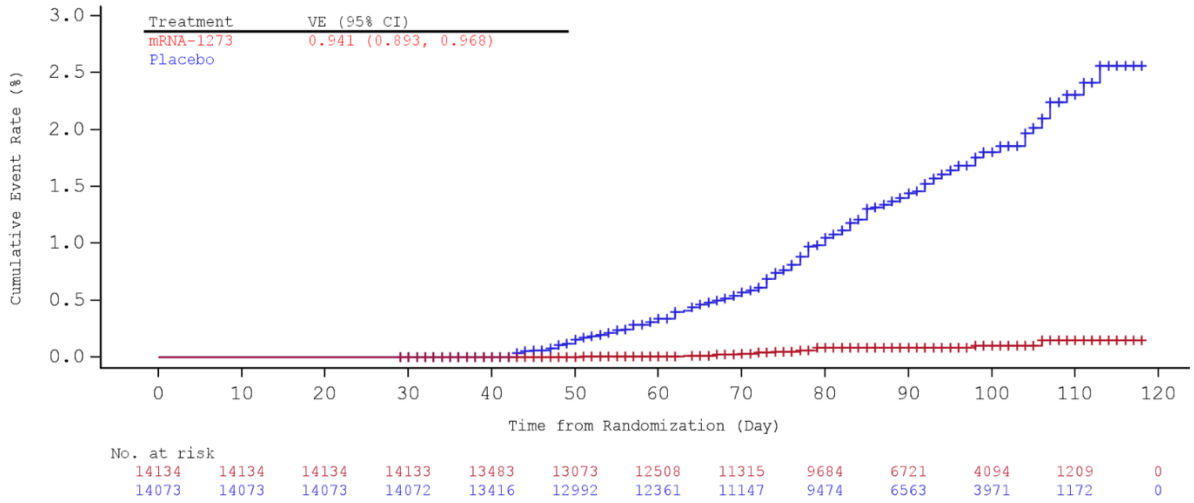
[e] Person-years is defined as the total years from randomization date to the date of COVID-19, last date of study participation, or efficacy data cutoff date, whichever is earlier.

[f] 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 was calculated using the exact method (Poisson distribution) and adjusted by person-years.

[g] Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Cumulative incidence rates of COVID-19 based on adjudication committee assessments with accrual starting 14 days after the second injection in the PP Set are presented in Figure 6.

Figure 6: Interim Dataset – Cumulative Incidence Rate of Time to First Occurrence of COVID-19 Starting 14 Days After Second Injection in Study 301 (Per-Protocol Set; Nov 25 Dataset[a])



[a] Primary efficacy analysis
Note: Vaccine efficacy is defined as 1 – hazard ratio (mRNA-1273 vs. placebo) and 95% CI was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

6.4 Secondary Endpoint Results

Table 19 reports the secondary analyses of efficacy evaluated at the interim analysis and primary analysis timepoints. The VE results for mRNA-1273 on the key secondary endpoints were similar to the VE for the primary endpoint, with point estimates of VE ranging from 93.6% to 100% based on hazard ratios.

At the time of our primary analysis, there have been 30 cases of severe COVID-19 reported in the trial, with all cases occurring in the placebo group and no cases in the mRNA-1273 group, resulting in a point estimate of efficacy against severe disease of 100%. Unfortunately, one of these cases resulted in a death due to COVID-19 in the placebo group.

Analysis of symptomatic COVID-19 disease starting 14 days after the second injection (primary endpoint) based on the PP Set (VE = 94.1%), and secondary analysis of COVID-19 starting 14 days after the first injection (inclusive of cases that occurred after the second injection) based on the PP Set (VE = 95.2%) yielded consistent results. Including participants in the analysis who had evidence of prior SARS-CoV-2 infection also yielded consistent results (VE=93.6%). However, there was only one COVID-19 case in participants with baseline positive SARS-CoV-2 status (in the placebo group), thus, the results need to be interpreted with caution. In addition, the relatively small proportion of baseline seropositive participants severely limits the interpretation.

Table 19: Summary of Key Secondary Efficacy Endpoint Analysis Results in Study 301

Set	Endpoint	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
		mRNA-1273 (N = 13934)	Placebo (N=13883)	mRNA-1273 (N=14134)	Placebo (N=14073)
PP	Cases of severe COVID-19 based on adjudication committee assessments starting 14 days after the second injection (secondary endpoint), n	0	11	0	30
	Vaccine efficacy based on hazard ratio (95% CI)[c]	100.0% (NE, 100.0%)		100.0% (NE, 100.0%)	
PP	Cases with a secondary (less restrictive) definition of COVID-19 starting 14 Days after the second injection (secondary endpoint), n	6**	121	11**	221
	Vaccine efficacy based on hazard ratio (95% CI)[c]	95.1% (88.9%, 97.8%)		95.1% (91.1%, 97.3%)	
PP	Cases of COVID-19 related deaths based on adjudication committee assessments starting 14 days after the second injection (secondary endpoint), n	0	0	0	1
	Vaccine efficacy based on hazard ratio (95% CI)[c]			100.0% (NE, 100.0%)	
PP	Cases of COVID-19 starting 14 days after the first injection (secondary endpoint), n	6**	128	11**	225
	Vaccine efficacy based on hazard ratio (95% CI)[c]	95.4% (89.5%, 98.0%)		95.2% (91.2%, 97.4%)	
FAS	Cases of COVID-19 based on adjudication committee assessments starting 14 days after the second injection regardless of prior SARS-CoV-2 infection (secondary endpoint), n/N[d]	6*/15180	92/15170	12*/15181	187/15170
	Vaccine efficacy based on hazard ratio (95% CI)[c]	93.5% (85.2%, 97.2%)		93.6% (88.6%, 96.5%)	

Abbreviations: n = number of events; N = number of participants; NE = not evaluable.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] Vaccine efficacy defined as 1 – hazard ratio (mRNA-1273 vs. placebo), and 95% CI was estimated using a Cox proportional hazard model stratified by randomization strata with Efron's method of tie handling, and with the treatment group as a covariate.

[d] FAS Set was used for COVID-19 based on adjudication committee assessments starting 14 days after the second injection regardless of prior SARS-CoV-2 infection, n and N are based on the number of participants in the FAS.

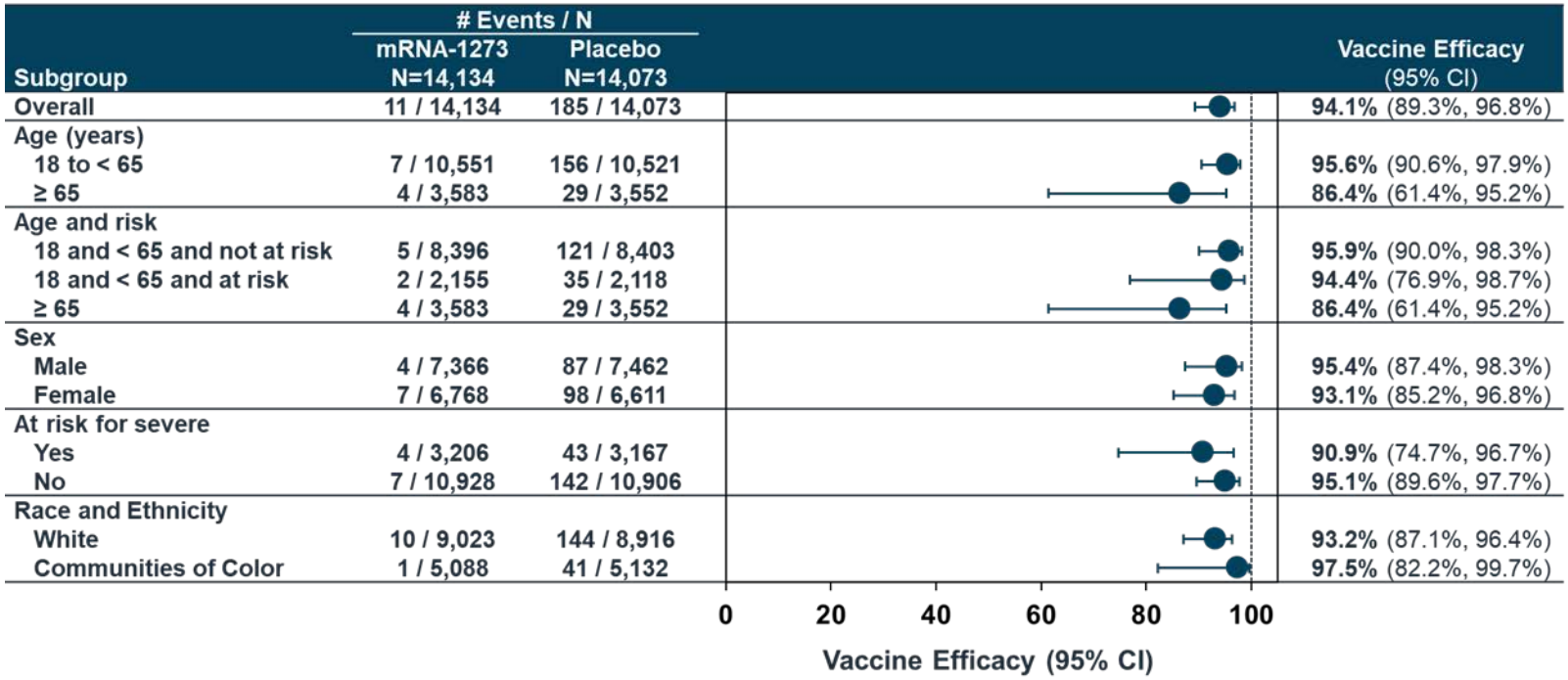
**One COVID-19 case was under mRNA-1273; the participant had positive RT-PCR at scheduled RT-PCR test on the day of the second injection and was not adjudicated for this analysis.

*One COVID-19 case was under mRNA-1273 in the FAS and was excluded from the PP Set: the participant was randomized to mRNA-1273 but only received placebo; thus, the participant was included under mRNA-1273 in FAS and excluded from PP Set.

6.5 Subgroup Analyses

The efficacy of mRNA-1273 for the primary efficacy endpoint was consistent across major demographic and baseline characteristic subgroups (Figure 7 and Figure 8). With respect to the subgroup analysis for ethnicity, limited numbers of participants in each ethnic group contributed to the primary efficacy endpoint. Therefore, the data were pooled together into a “communities of color” group for this analysis to ensure that two subpopulations in the study would be large enough for meaningful analyses.

Figure 7: Forest Plot of Subgroup Analyses of VE of mRNA-1273 to Prevent COVID 19 in Study 301 (Per-Protocol Set; Nov 25 Dataset[a])



Note: White is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.

[a] Primary efficacy analysis

Figure 8: Forest Plot of Subgroup Analyses of VE of mRNA-1273 to Prevent COVID 19 in Study 301 (Per-Protocol Set; Nov 11 Dataset[a])

Subgroup	# Events / N mRNA-1273 N=13,934	# Events / N Placebo N=13,883	Vaccine Efficacy (95% CI)
Overall	5 / 13,934	90 / 13,883	**94.5%** (86.5%, 97.8%)
Age (years)			
18 to < 65	5 / 10,407	75 / 10,384	**93.4%** (83.7%, 97.3%)
≥ 65	0 / 3,527	15 / 3,499	**100%**
Age and risk			
18 and < 65 and not at risk	4 / 8,309	57 / 8,323	**93.0%** (80.8%, 97.5%)
18 and < 65 and at risk	1 / 2,098	18 / 2,061	**94.6%** (59.4%, 99.3%)
≥ 65	0 / 3,527	15 / 3,499	**100%**
Sex			
Male	2 / 7,273	45 / 7,369	**95.5%** (81.5%, 98.9%)
Female	3 / 6,661	45 / 6,514	**93.5%** (79.2%, 98.0%)
At risk for severe			
Yes	1 / 3,116	24 / 3,075	**95.9%** (69.7%, 99.4%)
No	4 / 10,818	66 / 10,808	**94.0%** (83.5%, 97.8%)
Race and Ethnicity			
White	5 / 8,858	70 / 8,755	**93.0%** (82.6%, 97.2%)
Communities of Color	0 / 5,054	20 / 5102	**100%**

Note: White is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported or missing.

[a] EUA submission (7-week median follow-up)

7 CLINICAL SAFETY

Summary

- Based on two months of exposure in more than 15,000 participants, mRNA-1273 demonstrated an acceptable tolerability profile with no significant safety concerns.
- In Study 301, solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and systemic ARs were more common after the second injection.
- Solicited systemic ARs were more common in participants who received mRNA-1273 compared with placebo. The majority of these solicited systemic ARs were mild to moderate in severity.
- The majority of solicited local and systemic reactions also occurred within the first 1 to 2 days after administration of IP and resolved within a median of 2 to 3 days or less.
- The overall incidence of unsolicited AEs and SAEs reported up to 28 days after vaccination were similar in participants who received mRNA-1273 and placebo.

Note: Safety data were under review at the time of drafting and have been included as a follow-up draft. The November 25, 2020 Dataset including 2-months median follow-up is comparable to the Interim Dataset with November 11, 2020 cut-off, since the November 25, 2020 dataset only includes an additional 14 days of data. As the study is ongoing, data continue to accrue, and numbers in the final clinical study report may change.

Because Study 301 represents > 96% of safety data generated to date with mRNA-1273, this briefing document focuses on the safety data available from the Phase 3 study. The rates and patterns of reported solicited local and systemic symptoms from Studies 101 and 201 were comparable to the rates reported in this briefing document. For Study 301, results from both the November 11, 2020 and the November 25, 2020 data cut-offs are presented.

7.1 Protocol Safety Review Team and the Data Safety Monitoring Board

In addition to standard medical monitoring by the study investigators and Sponsors, this study implemented a Protocol Safety Review Team to monitor blinded safety data on a weekly basis. To monitor the ongoing accrual of potential safety data in an unblinded fashion during study conduct, including monitoring for the theoretical risk of enhanced disease, an independent DSMB reviews blinded and unblinded safety data on an approximate monthly basis, including the unblinded cases of COVID-19. Monitoring boundaries were established prior to study start to assess for lack of efficacy and for

evidence of enhanced disease for both COVID-19 cases of any severity and severe cases of COVID-19.

7.2 Study 301 Safety Findings

In this study, the safety and reactogenicity of mRNA-1273 100 µg compared with placebo, each administered as two injections 28 days apart, were assessed in participants 18 years of age and older at increased risk for acquiring COVID-19 based on occupation or location and living circumstances. Reactogenicity (solicited local and/or systemic ARs) was observed in the majority of participants in the mRNA-1273 group and generally increased after the second injection. The rates of local and systemic reactions were higher in the vaccine group than in the placebo group after each injection. The majority of solicited ARs in the mRNA-1273 group were grade 1 to grade 2 in severity and generally resolved within 3 days or less. The incidence rates of unsolicited AEs and severe AEs during the 28 days after injection were also generally similar in participants who received mRNA-1273 and those who received placebo.

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

7.2.1 Safety Populations

The Safety Set included randomized participants who received at least one injection of IP. The Solicited Safety Set consisted of randomized participants who received at least one injection of IP and contributed any solicited AR data. In the Safety Set and Solicited Safety Set, participants were included in the group corresponding to the IP they actually received.

7.2.2 Exposure

The median study duration from randomization for participants was similar between the mRNA-1273 group is shown in Table 20.

Table 20: Summary of Study Duration in Study 301 (Safety Set)

	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15184)	Placebo (N=15165)	mRNA-1273 (N = 15185)	Placebo (N=15166)
Number of participants, n (%)				
Received first injection	15184 (100)	15165 (100)	15185 (100)	15166 (100)
Received second injection	13985 (92.1)	13913 (91.7)	14715 (96.9)	14613 (96.4)
≥ 28 days since second injection	12136 (79.9)	11999 (79.1)	13386 (88.2)	13297 (87.7)
≥ 56 days since second injection	5131 (33.8)	5048 (33.3)	9406 (61.9)	9299 (61.3)
Study duration from randomization (days)				
Median (min, max)	78.0 (4+, 108+)	78.0+ (1+, 108+)	92.0+ (1+, 122+)	92.0+ (1+, 122+)
Study duration from first injection (days)				
Median (min, max)	78.0+ (4+, 108+)	78.0+ (1+, 108+)	92.0+ (1+, 122+)	92.0+ (1+, 122+)
Study duration from second injection (days)[c]				
Median (min, max)	49.0+ (0+, 83+)	49.0+ (0+, 83+)	63.0+ (0+, 97+)	63.0+ (0+, 97+)
Study duration from second injection in participants who received second injection (days)				
Median (min, max)	50.0+ (1, 83+)	50.0+ (1+, 83+)	63.0+ (0+, 97+)	63.0+ (0+, 97+)

Abbreviations: max = maximum; min = minimum.
Notes: + indicates ongoing participants. Percentages were based on the number of participants in the Safety Set.
[a] EUA submission (interim efficacy analysis)
[b] Primary efficacy analysis
[c] Study duration from the second injection is zero days for participants who did not receive the second injection.

7.2.3 Solicited Adverse Reactions

Solicited local and systemic ARs with an onset within 7 days after each injection (ie, the day of dosing and 6 subsequent days) were assessed. Solicited ARs were recorded daily by the study participants using eDiaries. The local solicited ARs assessed included pain, erythema, swelling, and lymphadenopathy and the general solicited ARs included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. The eDiary solicited daily participant reporting of ARs using a structured checklist. If an AR persisted beyond Day 7, the participant was prompted to continue to record until resolution. Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to grading scales (grade 0 to grade 4) modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

7.2.3.1 Solicited Local Adverse Reactions

Solicited local ARs were reported by a majority of participants in the mRNA-1273 group and were reported at a higher incidence in the mRNA-1273 group than in the placebo group after each injection (Table 21). In the mRNA-1273 group, the most common solicited local AR was pain, and the incidence was comparable after the first and second injection. The majority of solicited local ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, grade 3 solicited local ARs were more common after the second injection than after the first injection, and the most common grade 3 solicited local AR after the second injection was pain. No grade 4 solicited local ARs were reported, and only grade 3 pain was reported at a frequency > 2% after either injection.

The majority of the solicited local ARs among participants who received mRNA-1273 occurred within the first 1 to 2 days after injection and generally persisted for a median of 1 to 3 days. There was a higher incidence of solicited local ARs that persisted beyond 7 days in the mRNA-1273 group than in the placebo group after the first and second injection, with no notable difference between the first and second injection.

Several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritis. A review of these events showed that the vast majority of the unsolicited TEAEs categorized as local injection or vaccination site reactions in the second week after immunization were a subset of the solicited local AR with a duration beyond Day 7. Consultation with a dermatopathologist suggested that these were most likely dermal hypersensitivity reactions and were unlikely to represent a long term safety concern.

Table 21: Summary of Participants With Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade in Study 301 (Solicited Safety Set)

Category Grade	Nov 11 Dataset[a]				Nov 25 Dataset[b]			
	First Injection[c]		Second Injection[c]		First Injection[c]		Second Injection[c]	
	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)	mRNA-1273 (N= 13947) n (%)	Placebo (N= 13870) n (%)	mRNA-1273 (N=15168) n (%)	Placebo (N=15155) n (%)	mRNA-1273 (N=14677) n (%)	Placebo (N=14566) n (%)
Solicited local adverse reactions – N1	15163	15150	13944	13866	15164	15151	14673	14562
Any solicited local adverse reactions	12765 (84.2)	2998 (19.8)	12381 (88.8)	2607 (18.8)	12765 (84.2)	2997 (19.8)	13006 (88.6)	2735 (18.8)
Grade 1	10728 (70.8)	2839 (18.7)	8375 (60.1)	2459 (17.7)	10731 (70.8)	2837 (18.7)	8778 (59.8)	2581 (17.7)
Grade 2	1508 (9.9)	81 (0.5)	3028 (21.7)	78 (0.6)	1505 (9.9)	82 (0.5)	3208 (21.9)	82 (0.6)
Grade 3	529 (3.5)	78 (0.5)	978 (7.0)	70 (0.5)	529 (3.5)	78 (0.5)	1020 (7.0)	72 (0.5)
Grade 4	0	0	0	0	0	0	0	0
Pain – N1	15163	15150	13944	13866	15164	15151	14673	14562
Any	12690 (83.7)	2660 (17.6)	12325 (88.4)	2363 (17.0)	12690 (83.7)	2658 (17.5)	12943 (88.2)	2477 (17.0)
Grade 3	417 (2.8)	55 (0.4)	575 (4.1)	38 (0.3)	416 (2.7)	55 (0.4)	604 (4.1)	40 (0.3)
Erythema (redness) – N1	15162	15150	13944	13866	15163	15151	14673	14562
Any	431 (2.8)	65 (0.4)	1193 (8.6)	55 (0.4)	430 (2.8)	67 (0.4)	1257 (8.6)	56 (0.4)
Grade 3	42 (0.3)	13 (< 0.1)	281 (2.0)	15 (0.1)	42 (0.3)	13 (< 0.1)	287 (2.0)	15 (0.1)
Swelling (hardness) – N1	15162	15150	13944	13866	15163	15151	14673	14562
Any	934 (6.2)	52 (0.3)	1695 (12.2)	48 (0.3)	932 (6.1)	52 (0.3)	1789 (12.2)	49 (0.3)
Grade 3	82 (0.5)	6 (< 0.1)	245 (1.8)	11 (< 0.1)	82 (0.5)	6 (< 0.1)	254 (1.7)	11 (< 0.1)
Lymphadenopathy – N1[d]	15162	15150	13944	13866	15163	15151	14673	14562
Any	1553 (10.2)	722 (4.8)	1956 (14.0)	534 (3.9)	1553 (10.2)	722 (4.8)	2090 (14.2)	567 (3.9)
Grade 3	48 (0.3)	27 (0.2)	66 (0.5)	18 (0.1)	49 (0.3)	27 (0.2)	67 (0.5)	19 (0.1)

Abbreviations: Any = grade 1 or higher; eDiary = electronic diary; N1 = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Notes: Percentages were based on the number of exposed participants who submitted any data for the event (N1).
CTCAE grade definitions provided in Appendix 11.1.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] The First and Second Injection Solicited Safety Set consist of all participants in the Solicited Safety Set who received the first or second study injection and contributed any SAR data (eDiary) from the time of first or second study injection through the following 6 days.

[d] Lymphadenopathy = localized axillary swelling or tenderness ipsilateral to the vaccination arm.

7.2.3.2 Solicited Systemic Adverse Reactions

Solicited systemic ARs were reported by the majority of participants in the mRNA-1273 group and were more prevalent in the mRNA-1273 group than in the placebo group after each injection (Table 22). In the mRNA-1273 group, the incidence and severity of solicited systemic ARs appeared to increase after the second injection. In the mRNA-1273 group, the most common solicited systemic ARs after the first injection were fatigue and headache, and the frequency of reported events increased after the second injection. Frequently reported events after the second injection also included fatigue, headache, myalgia, arthralgia, and chills. The majority of solicited systemic ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, the most common grade 3 solicited systemic ARs after the second injection included fatigue, myalgia, headache, and arthralgia.

The majority of the solicited systemic ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after IP injection and generally persisted for a median of 1 to 2 days. The incidence of participants who reported solicited systemic ARs that persisted beyond 7 days was similar between the mRNA-1273 and placebo groups, with no notable difference between the first and second injection.

Table 22: Summary of Participants with Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade in Study 301 (Solicited Safety Set)

	Nov 11 Dataset[a]				Nov 25 Dataset[b]			
	First Injection[c]		Second Injection[c]		First Injection[c]		Second Injection[c]	
Category **Grade**	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)	mRNA-1273 (N=13947) n (%)	Placebo (N=13870) n (%)	mRNA-1273 (N=15168) n (%)	Placebo (N=15155) n (%)	mRNA-1273 (N=14677) n (%)	Placebo (N=14566) n (%)
Solicited systemic adverse reactions – N1	15166	15154	13947	13869	15167	15155	14677	14565
Any solicited systemic adverse reactions, n (%)	8321 (54.9)	6398 (42.2)	11064 (79.3)	5069 (36.5)	8320 (54.9)	6399 (42.2)	11652 (79.4)	5323 (36.5)
Grade 1	5370 (35.4)	4345 (28.7)	3563 (25.5)	3373 (24.3)	5372 (35.4)	4346 (28.7)	3723 (25.4)	3526 (24.2)
Grade 2	2499 (16.5)	1738 (11.5)	5301 (38.0)	1420 (10.2)	2496 (16.5)	1739 (11.5)	5590 (38.1)	1512 (10.4)
Grade 3	447 (2.9)	309 (2.0)	2188 (15.7)	273 (2.0)	447 (2.9)	308 (2.0)	2325 (15.8)	282 (1.9)
Grade 4	5 (< 0.1)	6 (< 0.1)	12 (< 0.1)	3 (< 0.1)	5 (< 0.1)	6 (< 0.1)	14 (< 0.1)	3 (< 0.1)
Fever – N1	15163	15152	13939	13864	15164	15153	14669	14559
Any	115 (0.8)	46 (0.3)	2172 (15.6)	43 (0.3)	115 (0.8)	44 (0.3)	2278 (15.5)	43 (0.3)
Grade 3	11 (< 0.1)	2 (< 0.1)	186 (1.3)	1 (< 0.1)	11 (< 0.1)	2 (< 0.1)	202 (1.4)	2 (< 0.1)
Grade 4	4 (< 0.1)	6 (< 0.1)	11 (< 0.1)	3 (< 0.1)	4 (< 0.1)	6 (< 0.1)	13 (< 0.1)	3 (< 0.1)
Headache – N1	15162	15149	13944	13866	15163	15150	14673	14562
Any	4952 (32.7)	4027 (26.6)	8165 (58.6)	3252 (23.5)	4951 (32.7)	4027 (26.6)	8602 (58.6)	3410 (23.4)
Grade 3	271 (1.8)	196 (1.3)	622 (4.5)	156 (1.1)	271 (1.8)	196 (1.3)	659 (4.5)	162 (1.1)
Fatigue – N1	15162	15149	13944	13864	15163	15150	14673	14560
Any	5635 (37.2)	4133 (27.3)	9096 (65.2)	3225 (23.3)	5635 (37.2)	4133 (27.3)	9582 (65.3)	3403 (23.4)
Grade 3	150 (1.0)	106 (0.7)	1347 (9.7)	101 (0.7)	150 (1.0)	105 (0.7)	1428 (9.7)	106 (0.7)
Grade 4	1 (< 0.1)	0	0	0	1 (< 0.1)	0	0	0
Myalgia – N1	15162	15149	13944	13865	15163	15150	14673	14560
Any	3441 (22.7)	2069 (13.7)	8036 (57.6)	1697 (12.2)	3441 (22.7)	2071 (13.7)	8508 (58.0)	1809 (12.4)
Grade 3	90 (0.6)	47 (0.3)	1233 (8.8)	49 (0.4)	90 (0.6)	47 (0.3)	1318 (9.0)	52 (0.4)
Arthralgia – N1	15162	15149	13944	13864	15163	15150	14673	14560
Any	2510 (16.6)	1783 (11.8)	5937 (42.6)	1468 (10.6)	2511 (16.6)	1783 (11.8)	6284 (42.8)	1569 (10.8)
Grade 3	60 (0.4)	37 (0.2)	725 (5.2)	43 (0.3)	60 (0.4)	37 (0.2)	770 (5.2)	44 (0.3)
Grade 4	1 (< 0.1)	0	0	0	1 (< 0.1)	0	0	0
Nausea/vomiting – N1	15162	15149	13944	13864	15163	15150	14673	14560
Any	1263 (8.3)	1074 (7.1)	2634 (18.9)	883 (6.4)	1262 (8.3)	1074 (7.1)	2785 (19.0)	934 (6.4)
Grade 3	10 (< 0.1)	12 (< 0.1)	18 (0.1)	11 (< 0.1)	10 (< 0.1)	12 (< 0.1)	20 (0.1)	11 (< 0.1)
Grade 4	0	0	1 (< 0.1)	0	0	0	1 (< 0.1)	0

Category Grade	Nov 11 Dataset[a]				Nov 25 Dataset[b]			
	First Injection[c]		Second Injection[c]		First Injection[c]		Second Injection[c]	
	mRNA-1273 (N=15167) n (%)	Placebo (N=15154) n (%)	mRNA-1273 (N=13947) n (%)	Placebo (N=13870) n (%)	mRNA-1273 (N=15168) n (%)	Placebo (N=15155) n (%)	mRNA-1273 (N=14677) n (%)	Placebo (N=14566) n (%)
Chills – N1	15162	15149	13944	13864	15163	15150	14673	14560
Any	1253 (8.3)	878 (5.8)	6100 (43.7)	755 (5.4)	1253 (8.3)	878 (5.8)	6482 (44.2)	809 (5.6)
Grade 3	24 (0.2)	14 (< 0.1)	178 (1.3)	16 (0.1)	24 (0.2)	14 (< 0.1)	191 (1.3)	17 (0.1)

Abbreviations: Any = grade 1 or higher; eDiary = electronic diary; N1 = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Notes: Percentages were based on the number of exposed participants who submitted any data for the event (N1).
CTCAE grade definitions provided in Appendix 11.1.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] The First and Second Injection Solicited Safety Set consist of all participants in the Solicited Safety Set who received the first or second study injection and contributed any SAR data (eDiary) from the time of first or second study injection through the following 6 days.

7.2.3.3 Subgroup Analyses of Solicited Adverse Reactions

Local ARs were more commonly reported by younger adults (≥ 18 to < 65 years) than older adults (≥ 65 years). Systemic reactions were also more commonly reported by younger adults (≥ 18 to < 65 years) than older adults (≥ 65 years).

7.2.4 Unsolicited Adverse Events

The reported incidences of unsolicited AEs, severe AEs, and SAEs during the 28 days after injection was generally similar among participants who received mRNA-1273 and those who received placebo (Table 23).

Table 23: Summary of Unsolicited AEs up to 28 Days After Any Vaccination in Study 301 (Safety Set)

	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15184) n (%)	Placebo (N=15165) n (%)	mRNA-1273 (N=15185) n (%)	Placebo (N=15166) n (%)
Unsolicited AEs regardless of relationship to study vaccination				
All	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Severe	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Fatal	2 (< 0.1)	3 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Leading to discontinuation from participation in the study	0	0	2 (< 0.1)	2 (< 0.1)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Medically-attended AEs	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)

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 submission (interim efficacy analysis)

[b] Primary efficacy analysis

7.2.4.1 Common Unsolicited Adverse Events

The incidence of unsolicited AEs in the 28 days after injection was generally similar between participants who received mRNA-1273 and those who received placebo (Table 24). Overall, the most commonly reported unsolicited AE in all participants in the 28 days after injection by preferred term (PT) was headache.

Table 24: Summary of Unsolicited AE Reported by at Least 1% of Participants in Any Treatment Group up to 28 Days After Any Injection in Study 301 (Safety Set)

System Organ Class Preferred Term	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15184) n (%)	Placebo (N=15165) n (%)	mRNA-1273 (N=15185) n (%)	Placebo (N=15166) n (%)
Number of participants reporting unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Number of unsolicited AEs	6157	5348	6798	6085
Nervous system disorders	624 (4.1)	552 (3.6)	684 (4.5)	622 (4.1)
Headache	435 (2.9)	409 (2.7)	466 (3.1)	458 (3.0)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	522 (3.4)	536 (3.5)	583 (3.8)
Cough	148 (1.0)	143 (0.9)	164 (1.1)	156 (1.0)
Oropharyngeal pain	137 (0.9)	184 (1.2)	147 (1.0)	203 (1.3)
Gastrointestinal disorders	426 (2.8)	387 (2.6)	478 (3.1)	440 (2.9)
Diarrhea	178 (1.2)	147 (1.0)	189 (1.2)	162 (1.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	521 (3.4)	671 (4.4)	617 (4.1)
Arthralgia	174 (1.1)	152 (1.0)	207 (1.4)	167 (1.1)
Myalgia	172 (1.1)	138 (0.9)	200 (1.3)	181 (1.2)
General disorders and administration site conditions	894 (5.9)	560 (3.7)	1006 (6.6)	622 (4.1)
Fatigue	344 (2.3)	307 (2.0)	372 (2.4)	336 (2.2)
Injection site pain	147 (1.0)	49 (0.3)	151 (1.0)	54 (0.4)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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. All AEs were coded using MedDRA Version 23.0.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

7.2.4.2 Severe Unsolicited Adverse Events

Table 25 presents the severe unsolicited adverse events reported by MedDRA PT in more than 5 participants in either the mRNA-1273 and/or the placebo group. Severe AEs were defined as AEs that prevented the participant's daily activity and required intensive therapeutic intervention. The incidence of unsolicited severe AEs in the 28 days after injection was low with comparable reported percentages noted between treatment groups. Severe unsolicited AEs reported with greater frequency in the mRNA-1273 as compared to the placebo group included categories of reactions that aligned with the solicited local and general ARs (eg, headache, myalgia, arthralgia, and injection site reactions).

Table 25: Summary of Unsolicited Severe AEs Reported by at Least 5 Participants in Any Treatment Group up to 28 Days After Any Injection in Study 301 (Safety Set)

System Organ Class Preferred Term	Nov 11 Dataset[a]		Nov 25 Dataset[b]	
	mRNA-1273 (N=15184) n (%)	Placebo (N=15165) n (%)	mRNA-1273 (N=15185) n (%)	Placebo (N=15166) n (%)
Number of participants reporting unsolicited severe AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Number of unsolicited severe AEs	275	225	291	242
Nervous system disorders	27 (0.2)	21 (0.1)	30 (0.2)	21 (0.1)
Headache	19 (0.1)	13 (< 0.1)	20 (0.1)	12 (< 0.1)
Cardiac disorders	11 (< 0.1)	13 (< 0.1)	13 (< 0.1)	13 (< 0.1)
Bradycardia	3 (< 0.1)	5 (< 0.1)	4 (< 0.1)	5 (< 0.1)
Atrial Fibrillation	4 (<0.1)	2 (<0.1)	4 (<0.1)	3 (<0.1)
Vascular disorders	28 (0.2)	39 (0.3)	30 (0.2)	43 (0.3)
Hypertension	22 (0.1)	29 (0.2)	23 (0.2)	32 (0.2)
Musculoskeletal and connective tissue disorders	24 (0.2)	18 (0.1)	23 (0.2)	24 (0.2)
Myalgia	11 (< 0.1)	0	10 (< 0.1)	2 (< 0.1)
Arthralgia	10 (< 0.1)	2 (< 0.1)	8 (< 0.1)	2 (< 0.1)
Back pain	1 (< 0.1)	5 (< 0.1)	1 (< 0.1)	7 (< 0.1)
General disorders and administration site conditions	43 (0.3)	13 (< 0.1)	49 (0.3)	13 (< 0.1)
Fatigue	12 (< 0.1)	7 (< 0.1)	12 (< 0.1)	6 (< 0.1)
Injection site erythema	11 (< 0.1)	0	11 (< 0.1)	0
Injection site pain	6 (< 0.1)	1 (< 0.1)	3 (< 0.1)	1 (< 0.1)
Investigations	22 (0.1)	13 (< 0.1)	23 (0.2)	13 (< 0.1)
Blood pressure increased	10 (< 0.1)	7 (< 0.1)	11 (< 0.1)	6 (< 0.1)
Blood pressure systolic increased	8 (< 0.1)	6 (< 0.1)	7 (< 0.1)	7 (< 0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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. All AEs were coded using MedDRA Version 23.0.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

7.2.4.3 Deaths

Thirteen deaths have been reported in the study as of December 3, 2020. A summary of participants with SAEs resulting in death is presented in Table 26.

Table 26: Participants with SAEs Resulting in Death in Study 301 through December 3, 2020

Treatment Assignment	Preferred Term	Relationship to Investigational Product
mRNA-1273	Cardio-respiratory arrest	Not related
mRNA-1273	Completed suicide	Not related
mRNA-1273	Head injury	Not related
mRNA-1273	Myocardial infarction	Not related
mRNA-1273	Multisystem organ failure	Not Related
mRNA-1273	Death NOS	Not Related
Placebo	Systemic inflammatory response syndrome Dermatitis bullous	Not related
Placebo	Myocardial infarction	Not related
Placebo	Abdominal injury (intra-abdominal perforation)	Not related
Placebo	Cardio-respiratory arrest	Not related
Placebo	COVID-19	Not Related
Placebo	Myocardial infraction	Not Related
Placebo	Death NOS	Not Related

7.2.4.4 Serious Adverse Events

The incidence of SAEs reported throughout the duration of the study was comparable between treatment groups (Table 27).

Table 27: Summary of Serious AEs Reported by Preferred Term in at Least 2 Participants in Any Treatment Group in Study 301 for the entire study duration (Safety Set) (25 Nov 2020 dataset)

System Organ Class Preferred Term	Nov 11 Dataset[a]		Nov 25 Datset[b]	
	mRNA-1273 (N=15184) n (%)	Placebo (N=15165) n (%)	mRNA-1273 (N=15185) n (%)	Placebo (N=15166) n (%)
Number of participants reporting serious AEs	113 (0.7)	120 (0.8)	147 (1.0)	153 (1.0)
Number of serious AEs	148	164	207	211
Atrial fibrillation	3 (< 0.1)	4 (< 0.1)	5 (< 0.1)	5 (< 0.1)
Myocardial infarction	5 (< 0.1)	3 (< 0.1)	5 (< 0.1)	3 (< 0.1)
Pneumonia	3 (< 0.1)	5 (< 0.1)	5 (< 0.1)	7 (< 0.1)
Pulmonary embolism	3 (< 0.1)	4 (< 0.1)	4 (< 0.1)	5 (< 0.1)
Abdominal pain upper	1 (< 0.1)	0	3 (< 0.1)	0
Cardiac failure congestive	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)	3 (< 0.1)
Cerebrovascular accident	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)	1 (< 0.1)
Cholecystitis	1 (< 0.1)	0	3 (< 0.1)	0
Dehydration	2 (< 0.1)	3 (< 0.1)	3 (< 0.1)	3 (< 0.1)
Dyspnoea	1 (< 0.1)	1 (< 0.1)	3 (< 0.1)	0
Nausea	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)	1 (< 0.1)
Nephrolithiasis	4 (< 0.1)	0	3 (< 0.1)	0
Prostate cancer	2 (< 0.1)	3 (< 0.1)	3 (< 0.1)	3 (< 0.1)
Acute respiratory failure	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Acute coronary syndrome	1 (< 0.1)	0	2 (< 0.1)	0
Acute myocardial infarction	1 (< 0.1)	3 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Appendicitis	2 (< 0.1)	3 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Arthritis	1 (< 0.1)	0	2 (< 0.1)	1 (< 0.1)
Cervical vertebral fracture	2 (< 0.1)	0	2 (< 0.1)	0
Chest pain	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Colitis	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Coronary artery disease	3 (< 0.1)	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Deep vein thrombosis	1 (< 0.1)	0	2 (< 0.1)	0
Diarrhoea	1 (< 0.1)	0	2 (< 0.1)	1 (< 0.1)
Embolic stroke	2 (< 0.1)	0	2 (< 0.1)	0
Fall	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Hiatus hernia	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Hypertension	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Respiratory Failure	0	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Road traffic accident	2 (< 0.1)	0	2 (< 0.1)	1 (< 0.1)
Seizure	2 (< 0.1)	0	2 (< 0.1)	0
Spinal stenosis	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Subdural hematoma	1 (< 0.1)	0	2 (< 0.1)	0

System Organ Class Preferred Term	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	 Placebo (N=15165) n (%)	Nov 25 Datset[b] mRNA-1273 (N=15185) n (%)	 Placebo (N=15166) n (%)
Swelling face	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Syncope	2 (< 0.1)	4 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Acute kidney injury	0	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
COVID-19	1 (< 0.1)	6 (< 0.1)	1 (< 0.1)	15 (< 0.1)
Hip fracture	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Thyroidectomy	2 (< 0.1)	0	1 (< 0.1)	0
Abdominal pain	0	2 (< 0.1)	0	2 (< 0.1)
Anaemia	0	1 (< 0.1)	0	2 (< 0.1)
Ankle fracture	0	1 (< 0.1)	0	3 (< 0.1)
Chronic obstructive pulmonary disease	0	2 (< 0.1)	0	4 (< 0.1)
Confusional state	0	2 (< 0.1)	0	2 (< 0.1)
Depression	0	2 (< 0.1)	0	3 (< 0.1)
Diverticulitis	0	1 (< 0.1)	0	2 (< 0.1)
Hypertensive emergency	0	2 (< 0.1)	0	2 (< 0.1)
Intervertebral disc protrusion	1 (< 0.1)	2 (< 0.1)	0	1 (< 0.1)
Intraductal proliferative breast lesion	0	1 (< 0.1)	0	2 (< 0.1)
Major depression	0	1 (< 0.1)	0	2 (< 0.1)
Urinary tract infection	0	3 (< 0.1)	0	4 (< 0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Notes: 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 are based on the number of safety participants. All AEs were coded using MedDRA Version 23.0.

[a] EUA submission (interim efficacy analysis)

[b] Primary efficacy analysis

[c] The investigator has not yet received medical records from the hospital, and a positive RT-PCR result for SARS-COV-2 infection has not been confirmed. Therefore, this case has not yet been evaluated by the Adjudication Committee.

7.2.4.5 Enhanced Disease: COVID-19 and Severe COVID-19

The potential for the mRNA-1273 to cause enhanced disease was monitored by the DSMB, which received unblinded case counts on a continuous basis and monitored the study against prespecified boundary rules based on an imbalance in the number of severe COVID-19 cases and all COVID-19 cases starting when 1 and 9 cases had occurred from the time of first dose administration, respectively. The prespecified criteria for enhanced disease have not been met at any time from study onset through the interim analysis. There were fewer cases of severe COVID-19 or COVID-19 of any severity from time of randomization in participants who received mRNA-than in those who received placebo; thus, there was no evidence of vaccine-associated enhanced disease observed in the study.

7.2.5 Subgroup Analyses of Unsolicited Adverse Events

7.2.6 Age Group

The overall incidence of unsolicited AEs within 28 days after any IP injection regardless of relationship was comparable in younger adults (18 to < 65 years of age) and older adults (≥ 65 years of age) who received mRNA-1273. As noted in the overall population, the incidence of severe AEs was higher in the mRNA-1273 group compared with the placebo group regardless of age. There was no apparent effect of age on the relative incidence of these AEs by vaccine group.

7.2.7 Pregnancies

To be enrolled in the study, female subjects had to have a negative pregnancy test at enrollment and agree to use effective contraception until at least 3 months after the final vaccination. Details of all pregnancies in female participants are being collected from first day of dosing until study completion. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs.

Thirteen pregnancies have been reported in Study 301 – 6 in the mRNA-1273 group and 7 in the placebo group (Table 28). As of December 2, 2020, 10 of the 13 pregnancies were ongoing with no reported complications. One participant (placebo group) experienced spontaneous abortion at approximately 7 gestational weeks; this SAE was considered not related to the IP. One participant in the placebo group had an elective abortion at approximately 6 gestational weeks; this SAE was considered not related to the IP. One participant in the placebo group was lost to follow-up, and the pregnancy outcome is unknown.

Table 28: Pregnancies in Female Participants in Study 301 (Through December 2, 2020)

Treatment Group	Expected Due Date (calculated by LMP)	Previous Pregnancies	Date of First Injection	Date of Second Injection (if Applicable)	Outcome
Placebo	17 Mar 2021	3 previous pregnancies; 2 live births, and 1 abortion	3 Aug 2020	N/A	Ongoing
Placebo	1 Jun 2021	13 previous pregnancies; 11 abortions (all induced), 2 live births	26 Aug 2020	N/A	Spontaneous abortion
Placebo	7 Jun 2021	None reported	28 Aug 2020	N/A	Elective termination
Placebo	2 Jun 2021	1 live birth	24 Aug 2020	N/A	Ongoing
Placebo	26 May 2021	2 live births	4 Aug 2020	1 Sep 2020	Ongoing
Placebo	6 Jun 2021	None reported	9 Sep 2020	7 Oct 2020	Unknown (participant was lost to follow-up)
Placebo	10 Jul 2021	2 previous pregnancies, both induced abortions	24 Aug 2020	21 Sep 2020	Ongoing
mRNA-1273	18 May 2021	1 previous pregnancy	7 Aug 2020	4 Sep 2020	Ongoing
mRNA-1273	1 Apr 2021	None reported	10 Aug 2020	N/A	Ongoing
mRNA-1273	19 May 2021	None reported	14 Aug 2020	N/A	Ongoing
mRNA-1273	7 Jun 2021	2 previous pregnancies; 1 spontaneous abortion & 1 ectopic pregnancy	24 Aug 2020	N/A	Ongoing
mRNA-1273	Unknown	5 previous pregnancies; 2 live births, 2 spontaneous abortions, and 1 elective termination	13 Aug 2020	10 Sep 2020	Ongoing
mRNA-1273	2 Jul 2021	2 live births	9 Aug 2020	11 Sep 2020	Ongoing

Abbreviations: LMP = last menstrual period; N/A = not applicable.
Note: Pregnancies are only collected in the Pharmacovigilance Global Database

8 PHARMACOVIGILANCE PLAN

A pharmacovigilance plan has been drafted to summarize the important identified risks, important potential risks, and important missing information for mRNA-1273. It describes the risks associated with the clinical use of mRNA-1273 at the time of the data lock of the clinical studies for the Emergency Use Authorization (EUA) submission in the US.

At this time, Moderna has conducted a review of the non-clinical data and ongoing clinical safety data to characterize the safety specification that will form the basis of the RMP in the EUA. Should any important benefit or risk information emerge during the course of implementing the RMP, the safety specifications may be updated, and additional pharmacovigilance and risk minimization measures may be developed.

8.1 Routine Pharmacovigilance

Moderna will continue to characterize the safety profile of mRNA-1273 in the EUA and post-marketing periods. Routine pharmacovigilance will be conducted for mRNA-1273, and due to the special circumstances of the pandemic, enhancement of routine activities will be undertaken. Moderna has a safety surveillance and reporting system in place to organize the collection, data entry in the company global safety database and evaluation of any adverse events reported to Moderna. Cases will be entered into the global safety database and duplicate detection was well as queries to reporters will follow. Exposure to the vaccine during pregnancy will include follow up queries. Moderna will engage in continuous monitoring of the safety profile of mRNA-1273 including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities.

Post-authorization reporting to VAERS of any serious adverse events, COVID disease requiring hospitalization, vaccination administration errors, and Multisystem Inflammatory Syndrome (MIS) will occur through 15 day alert reports to FDA. Periodic reporting to FDA will occur quarterly or at another interval specified by the agency. All Suspected Unexpected Serious Adverse Reactions (SUSAR) from the ongoing clinical trials will be expedited to the Agency.

Additional pharmacovigilance and post-authorization safety information will be obtained through other data sources outside of the company. These include evaluations of safety information captured in safety databases managed by regulatory agencies, including the VAERS system of FDA and the Eudravigilance system of the European Medicines Agency, as well as weekly reviews of the global literature.

Table 29: mRNA-1273 Signal Data Sources and Periodicity of Assessment

Data source	Periodicity
Company global safety database	Ongoing monitoring of individual cases including AESI cases. Weekly aggregated review of AE cases for trend analyses.

	Review of disproportionate reporting.
Literature	Weekly global literature review
VAERS	Frequency of review will depend on public availability of VAERS extract. Generation of disproportionality scores using Empirical Baysian Geometrical Mean (EBGM) and its 90% credibility intervals.
Eudravigilance (and other international passive surveillance sources)	Continuous monitoring based on access to Sponsors when applicable
Health Authority websites	Ongoing review of data published on the Safety Web Portals of selected major regulatory agencies to identify required actions regarding the product, products in same class.

8.2 Active follow-up for safety

The Active Follow-up for Safety activity will use secondary, de-identified individual-level medical and pharmacy claims data that represent more than 100 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems. These data sources include Veradigm data and other HealthVerity data partners, including provider-submitted claims, adjudicated insurance claims, and pharmacy billing managers. The data are tokenized which allows linkage and de-duplication at the patient level across data sources. Of note, this population complements but does not duplicate the populations under observation in the CDC's Vaccine Safety DataLink and the FDA's CMS programs. The data will be refreshed every two weeks in a prospective fashion throughout the two-year study period. Retrospective analyses will address three core objectives: estimation of background rates, assessment of observed versus expected rates, and self-controlled risk interval analyses for prespecified adverse events that meet criteria described below. In addition, the flexibility of the Aetion evidence platform will enable the sponsor to address emerging EUA and postmarketing safety issues as they arise through additional analyses even if they were not on the original AESI list. After protocol approval by FDA, AESIs will be observed from the first mRNA-1273 vaccine dose administered among US adults through 31 December 2022. This activity was designed in response to FDA's description of the need for "active follow-up for safety" referenced in the Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020).

8.3 Pregnancy Cohort

The sponsor will establish a passive pregnancy registry system upon EUA. After protocol approval by FDA, a prospective observational study to be conducted in the US

could be initiated. The registry would enroll pregnant women and will follow them from enrollment until the end of pregnancy (live birth, stillbirth, termination of pregnancy, or spontaneous abortion); live-born infants will be followed from birth until 1 year of age. The study period will be three years from the start of the EUA.

8.4 Real World Effectiveness Study

Moderna proposes to conduct a post-authorization observational effectiveness study to complement the ongoing clinical trial. This study will be a prospective cohort study to evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing the following outcomes of interest, including laboratory confirmed and clinically diagnosed COVID-19 infection, hospitalization for COVID-19 infection, and mortality (in hospital or within 30 days after discharge). Comparison groups may include individuals of the same age who are not vaccinated with Moderna COVID-19 vaccine.

9 BENEFIT-RISK CONCLUSIONS

9.1 Benefits

The primary efficacy objective of Study 301 was met, with the vaccine efficacy of mRNA-1273 to prevent symptomatic COVID-19 disease observed to be 94.1% after more than 151 cases accrued. The vaccine was also observed to be efficacious in preventing severe COVID-19 and in preventing COVID-19 regardless of prior SARS-CoV-2 infection in key secondary analyses of efficacy. The population in Study 301 included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. In an exploratory subgroup analysis, the estimates of efficacy of mRNA-1273 against symptomatic COVID-19 disease was comparable across the demographic groups analyzed, which is particularly notable in older adults and younger adults with pre-existing medical risk factors.

The immunogenicity of mRNA-1273 was evaluated in Studies 101 and 201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal Phase 3 study. In Study 101, doses of 100 µg or higher generated the highest titers of bAb or nAb, and the 100 µg dose was observed to have a better tolerability profile than the 250 µg dose in subjects 18-55 YOA. Together, this was the basis for selecting the 100 µg dose for use in the pivotal Phase 3 study. The antibody levels after 2 injections of mRNA-1273 exceeded those in convalescent sera. Similar responses were observed among all groups for the 100-µg dose and responses were detected in all participants through Day 119. Day 119 responses declined relative to Day 57 but remained comparable to responses in convalescent serum. The immunogenicity results from the 100 µg dose group in Study 201 confirmed the robust immunogenicity results observed in the Phase 1 study.

9.2 Risks

The safety of mRNA-1273 is largely based on data from the pivotal Phase 3 study using the November 11, 2020 data snapshot (supplemental safety data from the November 25, 2020 data snapshot will be presented). Solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and systemic ARs were more common after the second injection. The majority of these reactions occurred within the first 1 to 2 days after administration of mRNA-1273 and persisted for a median of 2 to 3 days or less.

The overall incidences of unsolicited AEs reported up to 28 days after vaccination and SAEs reported throughout the entire study were similar in participants who received mRNA-1273 or placebo. A total of 13 deaths occurred in Study 301, including a single death due to COVID-19 in the placebo group, with 6 deaths occurring in the mRNA-1273 group and 7 deaths occurring in the placebo group. None were considered

related to study vaccine. Causes of death were not unexpected given the population enrolled in the study.

There were fewer cases of severe COVID-19 or COVID-19 in participants who received mRNA-1273 compared with placebo, and thus no evidence of vaccine-associated ERD has been observed. There was no difference in the incidence of solicited AEs based on SARS-CoV-2 serology at baseline.

9.3 Benefit-Risk Assessment

There is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Based on the results from the pivotal Phase 3 study, mRNA-1273 prevents COVID-19 and severe COVID-19 with an observed vaccine efficacy of 94.1% and 100%, respectively. The efficacy of mRNA-1273 to prevent COVID-19 and severe COVID-19 demonstrated in the trial at the time of our primary analysis, also mitigates concern about the risk of enhanced disease during the 28- day period following two injections of vaccine. The clinical benefit of mRNA-1273 was consistent in older and younger adults, with or without risk factors for complications of COVID-19, in males and females, and in participants who were White as compared to those from communities of color.

The results from the pivotal efficacy trial are supported by the substantial immune response observed in the Phase 1 and 2 trials that was consistent across age groups and persisted over 3 months after the second injection of mRNA-1273. mRNA-1273 produced a robust immune response both in terms of bAbs and nAbs, and induced CD4+ T-cells with a Th-1 dominant phenotype.

Based on administration of mRNA-1273 to more than 15,693 adults across all 3 clinical studies to date, there have been no emergent safety concerns and the adverse event profile has been observed to be largely characterized by mild to moderate reactogenicity of a median duration of 2-3 days. Vaccination with mRNA-1273 results in transient local injection site and systemic reactions. The incidence of unsolicited AEs and AEs leading to discontinuation of study vaccine were similar between the treatment groups. Less common but clinically-significant AEs, such as SAE and deaths, were reported at similar rates for placebo and vaccine recipients. The overall safety profile observed in the Phase 3 large-scale safety and efficacy trial was generally consistent with the safety profile observed to date in the Phase 1 and 2 studies.

Based on the data presented in this submission, mRNA-1273 administered as two 100 µg injections 28 days apart is an effective vaccine with an acceptable safety profile for the prevention of COVID-19 in adults 18 years of age and older. Considering the ongoing public health emergency due to SARS-CoV-2, the lack of approved preventative vaccines, as well as the available safety and efficacy data from the three clinical studies presented herein, the Sponsor considers that the known and potential

benefits of the product outweigh the known and potential risks for mRNA-1273 and warrant consideration for EUA under Section 564 (b)(1)(C) of the Federal Food, Drug, and Cosmetic Act.

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11 APPENDICES

11.1 Solicited Adverse Reactions and Grades

Table 30: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	None	Does not interfere with activity	Repeated use of over- the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over- the-counter (non- narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over- the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock

11.2 Study 301 Enrollment Criteria

Participants were eligible to be included in the study only if all the following criteria apply:

1. Adults, ≥ 18 years of age at time of consent, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
2. Understands and agrees to comply with the study procedures and provides written informed consent.
3. Able to comply with study procedures based on the assessment of the Investigator.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or post-menopausal (defined as amenorrhea for ≥ 12 consecutive months prior to Screening without an alternative medical cause). A follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm post-menopausal status.
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at Screening and on the day of the first injection (Day 1).
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1).
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29).
    - Is not currently breastfeeding.
6. Adequate female contraception is defined as consistent and correct use of an FDA approved contraceptive method in accordance with the product label. For example:
    - Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
    - Intrauterine device
    - Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
    - Sterilization of a female participant’s monogamous male partner prior to entry into the study
7. Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8. Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.

Participants were excluded from the study if any of the following criteria apply:

1. Is acutely ill or febrile 72 hours prior to or at Screening. Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
2. Is pregnant or breastfeeding.
3. Known history of SARS-CoV-2 infection.
4. Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or current/planned simultaneous participation in another interventional study to prevent or treat COVID-19.
5. Demonstrated inability to comply with the study procedures.
6. An immediate family member or household member of this study's personnel.
7. Known or suspected allergy or history of anaphylaxis, urticaria, or other significant AR to the vaccine or its excipients.
8. Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.
9. Has received or plans to receive a non-study vaccine within 28 days prior to or after any injection of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any injection of IP).
10. Has participated in an interventional clinical study within 28 days prior to the day of enrollment.
11. Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV-positive participants on stable antiretroviral therapy are not excluded).
12. Has received systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to Screening.
13. Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.
14. Has donated ≥ 450 mL of blood products within 28 days prior to Screening.