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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AR	adverse reaction
bAb	binding antibody
BOD	burden of disease
BOI	burden of infection
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMQ	Custom MedDRA Query
CMV	cytomegalovirus
CNS	central nervous system
CoV	coronavirus
COVID-19	coronavirus disease 2019
CSR	clinical study report
DART	developmental and reproductive toxicity
DSMB	Data and Safety Monitoring Board
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FRNT-mNG	focus-reduction neutralization test against mNeonGreen live virus
GM	geometric mean
GMT	geometric mean titer
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
ID_{50}	50% inhibitory dilution
ID_{80}	80% inhibitory dilution
IgG	immunoglobulin G
IM	intramuscular
IP	investigational product
LNP	lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MERS-CoV	Middle East respiratory syndrome coronavirus
MN	microneutralization
mRNA	messenger RNA
MSD	MesoScale Discovery
nAb	neutralizing antibody
NHP	nonhuman primate
mITT	modified intent-to-treat
PBMC	peripheral blood mononuclear cell
PDV	participant decision visit
PIV3	parainfluenza virus type 3
polyA	polyadenylated
PP	per-protocol
PRNT	plaque-reduction neutralization test
PsVNA	pseudotyped lentivirus reporter single-round-of-infection neutralization assay
RBD	receptor binding domain
RMP	risk management plan
RT-PCR	reverse transcriptase polymerase chain reaction
S-2P	spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SMC	safety monitoring committee
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event
Th1	T-helper 1
Th2	T-helper 2
UTR	untranslated region
VAERD	vaccine associated enhanced respiratory disease
VE	vaccine efficacy
VOC	variant of concern

Abbreviation	Definition
VOI	variant of interest
WHO	World Health Organization

2.5.1 PRODUCT DEVELOPMENT RATIONALE

2.5.1.1 Pharmacologic Class of Agent

2.5.1.1.1 mRNA Platform

ModernaTX, Inc. (Sponsor) has developed a rapid-response proprietary vaccine platform based on a messenger RNA (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). The precision and standardization of the mRNA vaccine platform enables rapid development and efficient manufacturing scale-up of safe and effective 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. Investigational mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV): NCT03382405, human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3): NCT03392389, Zika virus: NCT04917861, and influenza virus: NCT03076385 and NCT03345043.

A schematic of mRNA is provided in Figure 1. 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 (Karikó 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).

Each mRNA molecule contains noncoding, or untranslated, sequences that may carry instructions for the cell regarding how to handle the mRNA.

The 3' untranslated region (UTR) is at the end of the open reading frame and is followed by the polyadenoylated (polyA) tail, a length of adenine-rich nucleotides, which is usually 50 to 250 nucleotides in length. The polyA tail confers stability to the RNA molecule, plays a role in

the termination of transcription, and participates in the export of the mRNA molecule from the nucleus and in initiation of translation of the target protein.

Figure 1 Structure of mRNA

Abbreviations: PolyA = polyadenylated; UTR=untranslated region.

2.5.1.1.2 mRNA-1273 Mechanism of Action

The Sponsor is using its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability.

Prior to the emergence of the novel SARS-CoV-2 coronavirus, the Sponsor had developed a foundational understanding of mRNA vaccine approaches against coronavirus (CoV) based on prior experience in the development of mRNA vaccines against Middle East respiratory syndrome CoV (MERS-CoV) and severe acute respiratory syndrome coronavirus 1 (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 the Sponsor to leverage the scientific understanding and apply it to the approach used in the development of mRNA-1273. That approach utilizes the Sponsor's 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 (Corti et al 2015; Wang et al 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019).

The mRNA-1273 vaccine is delivered via intramuscular (IM) injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. Injected into the upper arm, mRNA does not persist past 1 to 3 days in tissues other than muscle (at the injection site), proximal popliteal and distal axillary lymph nodes, and spleen, in which the average half-life values ranged from 14.9 to 63.0 hours in Sprague Dawley rats (Moderna 2021a). After delivery, the mRNA utilizes the cell's translational machinery to produce the SARS-CoV-2 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 T-helper 1 (Th1)-biased CD4+ T-cell responses in humans (Jackson et al 2020).

2.5.1.2 Clinical/Pathophysiology of Condition

2.5.1.2.1 Overview of COVID-19

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV-1.

An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally (WHO 2020a). The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern on 30 Jan 2020 and declared COVID-19 a pandemic on 11 Mar 2020 (WHO 2020a; WHO 2020b). As of 26 Jul 2021, the WHO dashboard reports 4,162,304 COVID-19 deaths worldwide (WHO 2021a).

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in 3 principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by touching surfaces with virus on them (CDC 2021a). Transmission of SARS-CoV-2 from asymptomatic or presymptomatic individuals has also been documented and may account for an estimated 59% of transmission

(Johansson et al 2021). Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of 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 lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease (CDC 2021b). Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19 (CDC 2021b).

The majority of individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill (WHO 2021b). Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae (Carfi et al 2020; Halpin et al 2021). Myocardial injury has reported among patients with severe COVID-19 (Shi et al 2020). Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury (Puntmann et al 2020; Rajpal et al 2021; Sardari et al 2021; Huang et al 2020; Zhao et al 2020; Peleg et al 2020). While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

2.5.1.2.2 Unmet Medical Need

Confirmed COVID-19 mortality surpassed 2.5 million deaths worldwide and 500,000 deaths in the US in February 2021, at which time confirmed COVID-19 cases numbered over 100 million worldwide and over 25 million in the US (Dong 2021). Comparison of apparent case fatality rates from early in the pandemic (acknowledging the limitations of such data) showed that the risk of death from COVID-19 was higher among the elderly and among individuals with certain preexisting health conditions, particularly cardiovascular disease, diabetes, chronic respiratory disease, and hypertension (Ritchie et al 2021). Even for COVID-19 infection that does not result in death, healthcare resource utilization can be high. For example, in the US in early January 2021, nearly 130,000 individuals were hospitalized due to COVID-19 (392 per 1 million), of whom nearly 30,000 were in an intensive care unit (approximately 85 per 1 million) (Ritchie et al 2021).

While most individuals with COVID-19 recover and do not require hospitalization, sequelae lasting weeks or even months after recovery from acute illness have been reported, even in those with mild illness. Some survive an acute COVID-19 infection but experience permanent damage to the lungs, heart, kidneys, or brain that causes ongoing chronic illness. Even among those without permanent organ damage, symptoms including fatigue, body aches, shortness of breath, headache, and difficulties with sleep, concentration, and physical activity may persist for more than 6 months (Logue et al 2021; Havervall et al 2021).

Given the direct mortality and morbidity of COVID-19, the risks of lasting health and quality-of-life decrements even after recovery from acute illness, the minimal availability of therapeutics for use within the broad patient population, and detrimental public health effects of nonpharmaceutical pandemic mitigation measures (which include deferred preventive care, compromised management of chronic conditions, and social isolation), there is high medical need for effective means of prevention of SARS-CoV-2 infection by vaccination (Mansfield et al 2021; Escalante et al 2021). Immunization with a safe and effective COVID-19 vaccine is a critical component to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning.

Early in the pandemic, there was an internationally recognized and urgent public health need for the development of efficacious vaccines to prevent SARS-CoV-2. The Sponsor's scalable mRNA/LNP technology platform allowed for a rapid response to the pandemic and was used to develop mRNA-1273, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2.

Since December 2020, mRNA-1273 and other COVID-19 vaccines have been available under Emergency Use Authorization (EUA) and conditional approvals worldwide. As of 30 Jun 2021, 301,035,380 doses of mRNA-1273 have been distributed worldwide for use in adults 18 years of age and older.

2.5.1.3 Therapeutic Rationale Supporting Investigation

To date, nonclinical and clinical evaluations demonstrate that mRNA-1273 is well tolerated, immunogenic, and efficacious. 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.

The Sponsor performed nonclinical studies of mRNA-1273 in mice, rats, hamsters, and nonhuman primates (NHPs) to evaluate mRNA-1273-induced immune responses, protection from high-dose virus SARS-CoV-2 challenge, and to address the theoretical concern of vaccine

associated enhanced respiratory disease (VAERD) mediated by vaccine-induced antibody responses and/or T-helper 2 (Th2)-directed T-cell responses observed with other vaccines against viral respiratory diseases.

A theoretical risk for COVID-19 VAERD has been raised based on data from animals administered certain vaccine constructs (non mRNA) against other coronaviruses (SARS-CoV and MERS-CoV) (DHHS 2020). These data showed evidence of immunopathologic lung reactions associated with Th2-like immune responses when the animals were challenged with the respective wild-type virus (Yasui et al 2008; Bolles et al 2011; Tseng et al 2012; Agrawal et al 2016). These immunopathologic lung reactions were similar to the hypersensitivity observed in infants who were administered a formalin-inactivated respiratory syncytial virus vaccine and subsequently challenged via natural exposure (Chin et al 1969). Antibody-dependent disease enhancement has also been proposed as a possible explanation for cases of more serious disease following dengue vaccination, but this dengue-associated condition has a distinct mechanism (Thomas and Yoon 2019; WHO 2019).

The potential risk for mRNA-1273 to promote VAERD was assessed in young and aged mice, hamsters, and rhesus macaques (NHPs) through the evaluation of immunogenicity endpoints (immunoglobulin [Ig] G1:IgG2a ratio, Th1/Th2 cytokine profiles, and the ratio of binding to nAb) indicative of a protective versus a disease enhancement phenotype and through monitoring of viral load, viral replication, and histopathological evaluation of lung tissues after viral challenge. These nonclinical studies demonstrated that mRNA-1273 is well tolerated in different animal species; is immunogenic (drives robust SARS-CoV-2-specific binding antibody [bAb], neutralization, and Th1-directed CD4+ T-cell and CD8+ T-cell responses); fully protects animals from challenge at dose levels as low as 1 µg/dose in mice and 30 µg/dose in NHPs; and does not lead to VAERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from Study 101 demonstrated high levels of nAbs and Th1-polarized CD4+ T-cell responses (Jackson et al 2020), consistent with the immunogenicity observed in these nonclinical studies.

In Study 301, the large Phase 3 double-blind placebo-controlled study, the potential for mRNA-1273 to cause VAERD was monitored by an independent Data and Safety Monitoring Board (DSMB). The DSMB continuously monitored case counts of COVID-19 and severe COVID-19 based on prespecified criteria for any indication of higher disease incidence and/or severity in the mRNA-1273 group compared with the placebo group that might suggest a risk of vaccine harm in the form of VAERD. The prespecified criteria for enhanced disease have not been met, and VAERD has been ruled out (Section 2.5.5.6.5).

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

2.5.1.4 Summary of the Clinical Development Program and Timing of Application

2.5.1.4.1 Completed Studies

All clinical studies with mRNA-1273 are ongoing with long-term follow-up, and none have been completed to date.

2.5.1.4.2 Ongoing Studies

This application includes data from 3 ongoing studies:

- mRNA-1273-P301 (hereafter Study 301): Study 301 is a pivotal, Phase 3 efficacy, safety, and immunogenicity study that provides the primary clinical evidence of vaccine efficacy (VE) and safety. The study was designed as a randomized, observer- and participant-blind, placebo-controlled study of the efficacy, safety, and immunogenicity of mRNA-1273 compared to placebo (Part A, Blinded Phase). More than 30,000 participants 18 years of age and older were randomized 1:1 to mRNA-1273 100 µg or placebo based on 3 strata: ≥ 65 years of age, 18 to < 65 years of age and at increased risk for complications of COVID-19, and 18 to < 65 years of age and not at risk. The initial mRNA-1273 100 µg dose was followed by a second 100 µg dose 28 days later. Participants will be followed for efficacy and safety until 24 months after the second dose. Vaccine efficacy was demonstrated based on the prespecified efficacy success criterion at the interim analysis (11 Nov 2020 dataset), based on a total of 95 adjudicated COVID-19 cases (Section 2.5.4.4.1.1). The subsequent primary analysis of efficacy was performed with a total of 196 adjudicated COVID-19 cases (25 Nov 2020 dataset) and was consistent with the interim analysis. mRNA-1273 was subsequently granted EUA in the US and conditional approvals worldwide.

  After EUA in the US was granted for mRNA-1273 and another mRNA COVID-19 vaccine, Part B, the open label observational phase of the study, was initiated. All participants in Part A were invited to proceed to Part B, starting with a Participant Decision Visit (PDV), at which participants were given the option to be unblinded to their

original group assignment or remain blinded. Unblinded participants who had received placebo in Part A had the choice to be vaccinated with mRNA-1273 in Part B (Study 301 Protocol).

The Study 301 design is described in Section 2.7.3.1.1.1, and the full overview is presented in the Study 301 protocol. Study flow diagrams of Part A and Part B are provided in the Study 301 protocol (Figure 1 and Figure 2). Vaccine efficacy, immunogenicity, and clinical safety summaries are provided in Section 2.7.3.2.1.1, Section 2.7.3.2.1.2, and Section 2.7.4, respectively. The Study 301 Part A CSR (primary efficacy analysis) and Study 301 CSR Addendum 1 (Part B) are located in Module 5.

- mRNA-1273-P201 (hereafter Study 201): Study 201 is a Phase 2a safety, reactogenicity, and immunogenicity study in healthy adults that provided confirmation of the 100 µg dose. The study was designed as a randomized, parallel, observer blind, placebo controlled dose confirmation study (Part A). Two dose levels, 50 µg and 100 µg, and placebo were evaluated in 2 age cohorts: Cohort 1 enrolled participants 18 to < 55 years old (300 participants), and Cohort 2 enrolled participants ≥ 55 years old (300 participants). A total of 600 participants received either mRNA-1273 or placebo according to a 1:1:1 randomization ratio; ie, within each age cohort, 100 participants each received mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo.

  An amendment to the Study 201 protocol adapted the study design to include open label interventional phases (Part B and Part C). Part B allowed unblinding of participants and offered 2 injections of mRNA-1273 in an open-label manner, 28 days apart, to all participants who received placebo in Part A. Part B also offered a single booster dose of mRNA-1273 (50 µg) to participants who received 1 or 2 doses of mRNA-1273 (50 µg or 100 µg) in Part A. Part C was prompted by the need to proactively prepare for vaccination strategies that induce broader protection, including against emerging variants of SARS-CoV-2 such as B.1.351. Part C enrolled participants from Study 301 who received 2 doses of mRNA-1273 100 µg at least 6 months prior. Part C participants received a single injection of mRNA-1273.351 (20 µg or 50 µg) or mRNA-1273.351 mixture (50 µg total – 25 µg of mRNA-1273 and 25 µg of mRNA-1273.351). Only the data generated in Part A of this study are included in this application.

  The Study 201 design is described in Section 2.7.3.1.1.2, and the full overview is provided in the Study 201 protocol. Study flow diagrams of Part A, Part B, and Part C are provided in Study 201 Protocol. Immunogenicity and safety summaries are provided in

Section 2.7.3.2.2 and Section 2.7.4, respectively. The Study 201 Primary Analysis CSR and the Study 201 CSR Addendum 1 (End of Part A) are provided in Module 5.

- 20-0003 (hereafter Study 101): Study 101 is a National Institutes of Health Phase 1 dose -finding study of safety and immunogenicity in healthy men and nonpregnant women. A total of 120 participants across 3 age cohorts (18 to 55 years; 56 to 70 years; ≥ 71 years) were enrolled to receive an IM injection (0.5 mL) of mRNA-1273 25 µg, 50 µg, 100 µg, or 250 µg on Day 1 and Day 29. Sera obtained from 41 participants who were convalescing from COVID-19 were included as a comparative control. An amendment to the Study 101 protocol included a substudy to investigate the safety, reactogenicity, and immunogenicity of a third dose of 100 µg mRNA-1273 in eligible main study participants.

  The Study 101 design is described in Section 2.7.3.1.1.3, and the full overview is provided in the Study 101 protocol. Immunogenicity and safety summaries are provided in Section 2.7.3.2.3 and Section 2.7.4, respectively. The Study 101 Day 119 CSR and the Study 101 CSR Addendum 1 (Day 209) are located in Module 5.

A summary of the 3 clinical studies included in this application is provided in Table 1. A tabular listing of clinical studies is provided in Module 5.2.

Table 1 Ongoing mRNA-1273 Clinical Studies Included in Application

Study Number (Country)	Study Population	Study Design	Dose, Schedule, and Number of Participants Exposed	Primary and Secondary Efficacy and Immunogenicity Objectives	Safety Objectives	Study Status[a]
mRNA-1273-301 (US)	Men and nonpregnant women at least 18 years of age, at appreciable risk of SARS-CoV-2 infection, with a negative history for SARS-CoV-2 infection.	Phase 3, case-driven, randomized, stratified, observer-blind, placebo-controlled (Part A) Randomization was stratified by a combination of age and risk factors for COVID-19: • 18 to < 65 years old, not at risk for severe COVID-19 • 18 to < 65 years old, at risk for severe COVID-19 • ≥ 65 years old	100 µg mRNA-1273 or placebo 2 doses, 28 days apart 100 µg=15209 placebo=15206	• Efficacy of mRNA-1273 to prevent COVID-19 (primary). • Efficacy of mRNA-1273 to prevent severe COVID-19. • Efficacy of mRNA-1273 to prevent SARS-CoV-2 infection regardless of symptomatology or severity • Vaccine efficacy against a secondary definition of COVID-19 • Vaccine efficacy to prevent death caused by COVID-19 • Efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP • Efficacy of mRNA-1273 to prevent COVID-19 in all participants, regardless of prior SARS-CoV-2 infection • Efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection. • Immunogenicity of 2 doses of mRNA-1273	Safety and reactogenicity of 2 injections of mRNA-1273 given 28 days apart	Ongoing

Study Number (Country)	Study Population	Study Design	Dose, Schedule, and Number of Participants Exposed	Primary and Secondary Efficacy and Immunogenicity Objectives	Safety Objectives	Study Status[a]
mRNA-1273-201 (US)	Men and nonpregnant women, at least 18 years of age, in good health	Phase 2, randomized, observer-blind, placebo-controlled (Part A) Age cohorts: • 18 to < 55 years old • ≥ 55 years old	50 or 100 µg mRNA-1273or placebo 2 doses, 28 days apart 50 µg=200 100 µg=200 placebo=200	• Immunogenicity of mRNA-1273 by measure of specific binding antibody levels (primary) • Immunogenicity of mRNA-1273 by measure of specific neutralizing antibody levels	Safety and reactogenicity of 2 dose levels of mRNA-1273 given 28 days apart	Ongoing
Study 101 (US)	Men and nonpregnant women at least 18 years of age, in good health	Phase 1, open-label, dose-finding study Age cohorts: • 18 to 55 years old • 56 to 70 years old • ≥ 71 years old	10 (not enrolled), 25, 50, 100, or 250 µg mRNA-1273 2 doses, 28 days apart 25 µg (n=35) 50 µg (n=35) 100 µg (n=35) 250 µg (n=15)	Immunogenicity of mRNA-1273 measured by IgG ELISA to SARS-CoV-2 spike protein	Safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273 given 28 days apart	Ongoing

Abbreviations: COVID-19 = coronavirus disease 2019; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IP = investigational product; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2.

[a] Participants remain in all studies to all protocol-specified assessments of efficacy, immunogenicity, and safety through the scheduled end of study.

Source: Study 301 Part A CSR, Study 201 Primary Analysis CSR, Study 101 Day 119 CSR.

Ongoing studies included in the clinical development plan for mRNA-1273 but not included in this application are as follows:

Adolescent and pediatric studies

- mRNA-1273-P203 (hereafter Study 203): Study 203 is an ongoing Phase 2/3 safety, reactogenicity, and effectiveness study of mRNA-1273 in healthy adolescents 12 to < 18 years of age.

- mRNA-1273-P204 (hereafter Study 204): Study 204 is an ongoing Phase 2/3, 2-part, open label, dose-escalation, age de-escalation and randomized, observer-blind, placebo controlled- expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 vaccine in healthy children 6 months to < 12 years of age.

Other Moderna-sponsored studies in the post-authorization development plan

- mRNA-1273-P205 (hereafter Study 205): Study 205 is an ongoing Phase 2/3 study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants.

- mRNA-1273-P304 (hereafter Study 304): Study 304 is an ongoing Phase 3b open-label safety and immunogenicity study of mRNA-1273 in adult solid organ transplant recipients and healthy controls who are at least 18 years of age. Approximately 240 adult participants (220 who have had a kidney or liver transplant and 20 healthy adults) will receive 2 doses of 100 µg mRNA-1273 28 days apart. The solid organ transplant recipients will be offered the opportunity to receive a third dose of mRNA-1273 at Day 85.

- mRNA-1273-P901 (hereafter Study 901): Study 901 is an ongoing observational study to evaluate mRNA-1273 effectiveness in the US. Approximately 500,000 persons are expected to receive 2 doses of 100 µg mRNA-1273 under EUA, and their incidence of COVID-19 will be compared to a matched unvaccinated control group.

- mRNA-1273-P902 (hereafter Study 902): Study 902 is an ongoing prospective, observational pregnancy exposure registry intended to collect primary data from pregnant women who have received mRNA-1273 under the EUA. Approximately 600 participants from North America and several countries in Europe will be enrolled, and birth outcomes to be reported include major congenital malformations and other pregnancy, maternal, fetal, and infant outcomes.

- mRNA-1273-P903 (hereafter Study 903): Study 903 is an ongoing retrospective observational cohort study with mRNA-1273 vaccine surveillance using a self-controlled risk interval design in the US. The study population will be selected from HealthVerity's aggregated database that represents healthcare utilization for over 140 million patients. This study aims to augment ongoing active and passive safety signal detection through signal refinement and where warranted, evaluation of potential safety signals associated with the introduction of the mRNA-1273 vaccine.

- mRNA-1273-P904 (hereafter Study 904): Study 904 is an ongoing post-authorization active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine in the European Union.

2.5.1.5 Adherence to Current Standard Research Approaches in the Design, Conduct, and Analysis of Studies

The clinical development of mRNA-1273 has been expedited to address the ongoing global public health emergency resulting from the SARS-CoV-2 pandemic (and assigned by the WHO to the highest public health emergency status). The Study 301 protocol and statistical analysis plan (SAP) were designed in accordance with both Food and Drug Administration (FDA) general guidance on COVID-19 vaccine development (DHHS, 2020) and FDA product-specific guidance. Study 301 data were extensively discussed with European Medicines Agency, Health Canada, and other Agencies as part of the authorization pathway developed to expedite regulatory approval in each region. Study 301 was conducted with oversight by an independent DSMB and a clinical endpoint adjudication committee that reviewed potential cases of COVID-19. Study 201 and Study 101 were conducted with oversight by a safety monitoring committee (SMC) composed of external independent consultants with relevant expertise. These studies have also been conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonisation Good clinical Practice Guidelines.

In December 2020, COVID-19 vaccines became available under EUA in the US. Some Study 301 and Study 201 participants in the US became eligible for vaccination based on Centers for Disease Control and Prevention (CDC) recommendations and local supply chain distributions. While Study 301 and Study 201 participants were encouraged to stay blinded for as long as possible, their participation in the studies did not deny them the opportunity to receive a COVID-19 vaccine under EUA. Subsequent to EUA, Study 301 and Study 201 protocol

amendments adapted the study designs to include an open-label Part B that allowed unblinding of participants and offered mRNA-1273 in an open-label manner to all participants who had received placebo in Part A. Clinical investigators could exercise discretion as to whether individual participants should be unblinded upon request to allow them to make an informed decision regarding receipt of a COVID-19 vaccine outside of the studies. Investigator judgment considered a participant's risk status under CDC recommendations, any current local public health guidance, and their access to imminently receive a COVID-19 vaccine under an EUA.

2.5.1.5.1 Regulatory Agency Interactions

A summary of regulatory interactions pertinent to the clinical development of mRNA-1273 is provided in Appendix 2.5.8.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Biomarkers of immune responses are key components for the clinical development and licensure of preventive vaccines. Immune bridging studies using immune biomarkers will be critical for expanding population coverage for the mRNA-1273 development program in comparison to the pivotal study in which efficacy was established (Study 301).

The clinical biomarker strategy to support clinical development includes an extensive panel of assays to assess SARS-CoV-2 infection and characterize the immune response induced by mRNA-1273. A summary of the qualified and the validated analytical methods used for the assessment of clinical endpoints in the clinical studies of mRNA-1273 is provided in Table 2.

Although regulatory agencies have recently stated that an nAb assay is preferred as a representation of antibody function (for example, neutralization or pseudotyped virus neutralization as cited in the recent FDA Guideline on EUA for COVID-19 vaccines [DHHS 2021]), its variability is higher than that of appropriately developed binding assays. Concordance between the neutralizing and binding assays utilized in the mRNA-1273 program has been established to allow bridging based on the more precise binding assay for possible use in future development programs (Moderna 2021b). It should also be noted that other functional antibodies that are not neutralizing may contribute to protection; a correlate has not been established.

In Study 101, the vaccine-induced humoral and cellular immune responses were evaluated at prespecified timepoints through Day 209 (180 days after the second dose). Assessment of the humoral immune response included quantitative detection of S-2P and receptor-binding domain (RBD)-specific bAbs by enzyme-linked immunosorbent assay (ELISA) and evaluation of the neutralizing activity using a pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA), a live wild-type SARS-CoV-2 virus plaque-reduction neutralization test (PRNT) assay, and a live virus mNeonGreen-based focus-reduction neutralization test (FRNT-mNG). These experimental assays were developed using a fit-for-purpose approach for this Phase 1 study. In addition, in Study 101, convalescent sera obtained from 41 patients with confirmed COVID-19 diagnosis, 23 to 60 days after onset of symptoms, were used during assay development to generate a relative benchmark (based on antibody levels elicited by natural infection) (Jackson et al 2020 supplementary appendix; [Study 101 Day 119 CSR]).

Additionally, to address concerns about the theoretical risk of VAERD after injection with mRNA-1273 (Section 2.5.1.3), the SARS-CoV-2 spike-specific T-cell-responses were evaluated through Day 43 in peripheral blood mononuclear cells (PBMCs) isolated from participants enrolled in Study 101 using multiparametric flow cytometry analysis of cell surface and intracellular cytokine immunostaining.

Immunoassays for Study P201 were considered qualified for use in the assessment of clinical samples and were validated and considered acceptable for use in the assessment of clinical samples from Study 301.

Overall, the PsVNA was determined to be concordant with the bAb assays (ELISA and MesoScale Discovery [MSD] assays for SARS-CoV-2 IgG antibody quantification) (Module 5, Section 5.3.1.4).

Table 2 Overview of Bioassays for the Assessment of Clinical Endpoints

Assay Name	Methodology	Study Number(s)	Context of Use	Development Status (Performing Laboratory)[a]
SARS-CoV-2 RT-PCR	RT-PCR	201 and 301	Baseline serostatus and asymptomatic/ symptomatic SARS-CoV-2 infection	Commercial (LDT) Validated (Viracor)
Elecsys Anti-SARS-CoV-2 NP ECLIA	ECLIA	301	Baseline serostatus and asymptomatic/ symptomatic SARS-CoV-2 infection	Commercial (Roche Diagnostics) Validated (PPD GCL-US)
Anti-S-2P IgG ELISA	ELISA	201	Immunogenicity assessments	Qualified (PPD Vaccines Laboratories)
Anti-S-2P IgG ELISA	ELISA	201 and 301	Immunogenicity assessments	Validated (PPD Vaccines Laboratories)
Anti-NP IgG ELISA	ELISA	201	Infection assessment (quantitative)	Qualified (PPD Vaccines Laboratories)
Anti-NP IgG ELISA	ELISA	201 and 301	Infection assessment (quantitative)	Validated (PPD Vaccines Laboratories)
SARS-CoV-2 Virus Neutralization 1	Live virus MN	201	Immunogenicity assessment	Qualified (Battelle)
	Live virus MN	301	Immunogenicity assessment	Validated (Battelle)
MSD multiplex anti-S, NP, RBD	MSD multiplex	201 and 301	Immunogenicity assessment	Validated (VRC/VIP)
SARS-CoV-2 Pseudo-typed Virus Neutralization	PsV neutralization	201 and 301	Immunogenicity assessment	Validated (Duke University Medical Center)

Abbreviations: ECLIA = electrochemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; MN = microneutralization; MSD = MesoScale Discovery; NP = nucleocapsid protein; PsV = pseudotyped virus; RBD = receptor-binding domain; RT-PCR = reverse-transcriptase polymerase-chain reaction; S = spike; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Commercially available assays were validated by the laboratory performing the assay with the study samples.

2.5.3.1 Dose Selection

The results of Study 101 showed a consistent dose response across age cohorts by several measures of humoral immunogenicity for both bAbs and nAbs. These results were confirmed in Study 201 in which significant immune responses to SARS-CoV-2 were demonstrated in participants 18 years and older (Study 201 Primary Analysis CSR). Additionally, immunization of rhesus macaques with 30 or 100 µg mRNA-1273 induced robust SARS-CoV-2 bAb and neutralizing activity and protection in the upper and lower airways from wild-type SARS-CoV-2 challenge, with no pathologic changes observed in the lungs or signs of disease enhancement (Module 2.6.2 Section 2.6.2.2.8 and 2.6.2.2.9). The advancement of the 100 µg dose (administered as 2 injections, 28 days apart) to Study 301 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 cohort: 18 to 55 years); and (iii) 2 injections of 100 µg led to a lower incidence of reactogenicity than 2 injections of 250 µg (Jackson et al 2020; Anderson et al 2020).

2.5.4 OVERVIEW OF EFFICACY

Efficacy results from Study 301 support the proposed indication of mRNA-1273 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Immunogenicity results from Study 301, Study 201, and Study 101 provide additional data demonstrating vaccine response and persistence of immunity. A comprehensive summary of efficacy and immunogenicity is provided in Module 2.7.3. Results of Study 301, Study 201, and Study 101 are provided in the individual clinical study reports (CSRs) located in Module 5.

In Study 301, 3 analyses of efficacy have been performed on blinded data from Part A: the interim analysis (11 Nov 2020 dataset), the primary analysis (25 Nov 2020 dataset), and the final analysis (04 May 2021 dataset). The interim analysis was based on a pre-specified statistical criterion based on a total of 95 adjudicated COVID-19 cases. The primary analysis was performed with 196 adjudicated COVID-19 cases, exceeding the target total number of cases (151) pre-specified for the primary analysis. The interim and primary analyses were conducted in November 2020 to support the EUA in the US and conditional approvals in other regions of the world. The final efficacy analysis of Part A was based on a database lock of 04 May 2021. A tabular description of the analyses and corresponding datasets are presented in Table 3. Further details of the datasets are provided in the Study 301 Part A CSR.

Table 3 Description of Data Used to Analyze Efficacy for Study 301, Part A

Analysis Name	Efficacy Data Cutoff Date	Safety Data Cutoff Date	Dataset Date
Interim Analysis	07 Nov 2020	11 Nov 2020	11 Nov 2020
Primary Analysis	21 Nov 2020	25 Nov 2020	25 Nov 2020
Final Analysis	26 Mar 2021[a]	26 Mar 2021[a]	04 May 2021[b]

Abbreviations: PDV = participant decision visit; RT-PCR = reverse transcription polymerase chain reaction; SARS CoV 2 = severe acute respiratory syndrome coronavirus 2.

[a] Part A presents available data from the randomized, placebo-controlled, blinded phase of the study based on the database lock of 04 May 2021 and includes available participant level data up to early unblinding, study discontinuation, the Part B PDV, or data cutoff date (26 Mar 2021), whichever was earlier. The results of Elecsys and RT-PCR assays for asymptomatic SARS-CoV-2 infection (obtained at the PDV) are included in the final analysis.

[b] Dataset date for final analysis reflects extensive cleaning of dataset prior to database lock.

Unless stated otherwise, efficacy results in this overview discuss the final efficacy analysis of Part A, based on the 04 May 2021 dataset.

2.5.4.1 Participant Populations

2.5.4.1.1 Study 301

Study 301 included males and females 18 years of age and older who were at risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances (eg, occupational risk such as health care worker) put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. Additionally, study participants at increased risk of complications from COVID-19 were included, and randomization was stratified based on age and the presence or absence of risk factors for severe COVID-19 based on CDC recommendations as of March 2020. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable HIV infection.

Overall, in the Full Analysis Set (FAS), participant demographic and baseline characteristics were similar between the mRNA-1273 and placebo groups (Table 4). A slightly higher proportion of males versus females (52.6% versus 47.4%, respectively) were enrolled. The mean (range) participant age at screening was 51.4 years (18 to 95 years) with 75.2% of participants aged 18 to 64 years and 24.8% of participants aged 65 years and older. The majority of

participants were White (79.2%), followed by Black or African American (10.2%), and Asian (4.6%). A majority of participants reported as not Hispanic or Latino (78.6%). To enhance the diversity of the study population and because communities of color have been disproportionately affected by COVID-19, an effort was made to increase enrollment in communities of color during the course of the study. This effort was more successfully implemented toward the end of the enrollment period. Participants who did not report White race and/or who reported Hispanic or Latino ethnicity were categorized as communities of color and comprised 37.2% of the study population; the racial and ethnicity proportions observed in this study were generally representative of US demographics. A total of 684 participants (2.3%) had a positive baseline SARS-CoV-2 status; 347 participants (2.3%) in the mRNA-1273 group and 337 participants (2.2%) in the placebo group.

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 18 to <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 HIV infection (Table 4). The study enrolled a total of 41.5% of participants who were considered at elevated risk for severe COVID-19 (16.7% of participants were 18 to < 65 years and at risk and 24.8% participants ≥ 65 years), indicating that enrollment goals were met.

Overall, the majority of participants (82.5%) had a specified occupational risk for acquisition of SARS-CoV-2; the most common occupational risks included other (31.9%) and health care workers (25.2%) (Table 4). A total of 83.8% of participants had a location or living circumstances risk for acquisition of SARS-CoV-2.

Table 4 Study 301 Baseline Demographics and Characteristics by Age Group (Full Analysis Set)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Age at screening (years)									
n	11413	11413	22826	3753	3767	7520	15166	15180	30346
Mean (SD)	45.0 (12.30)	45.1 (12.35)	45.0 (12.33)	70.7 (4.88)	70.4 (4.66)	70.6 (4.77)	51.3 (15.60)	51.4 (15.50)	51.4 (15.55)
Median	46.0	46.0	46.0	70.0	69.0	70.0	52.0	53.0	52.0
Min, Max	18, 64	18, 64	18, 64	65, 95	65, 95	65, 95	18, 95	18, 95	18, 95
Age group at screening, n (%)									
>=18 and <65 years	11413 (100)	11413 (100)	22826 (100)	0	0	0	11413 (75.3)	11413 (75.2)	22826 (75.2)
Mean (SD)	45.0 (12.30)	45.1 (12.35)	45.0 (12.33)				45.0 (12.30)	45.1 (12.35)	45.0 (12.33)
Median	46.0	46.0	46.0				46.0	46.0	46.0
Min, Max	18, 64	18, 64	18, 64				18, 64	18, 64	18, 64
>=65 years	0	0	0	3753 (100)	3767 (100)	7520 (100)	3753 (24.7)	3767 (24.8)	7520 (24.8)
Mean (SD)				70.7 (4.88)	70.4 (4.66)	70.6 (4.77)	70.7 (4.88)	70.4 (4.66)	70.6 (4.77)
Median				70.0	69.0	70.0	70.0	69.0	70.0
Min, Max				65, 95	65, 95	65, 95	65, 95	65, 95	65, 95
Age subgroup at screening, n (%)									

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
>=18 and <65 years	11413 (100)	11413 (100)	22826 (100)	0	0	0	11413 (75.3)	11413 (75.2)	22826 (75.2)
>=65 and <70 years	0	0	0	1818 (48.4)	1905 (50.6)	3723 (49.5)	1818 (12.0)	1905 (12.5)	3723 (12.3)
>=70 and <75 years	0	0	0	1194 (31.8)	1205 (32.0)	2399 (31.9)	1194 (7.9)	1205 (7.9)	2399 (7.9)
>=75 and <80 years	0	0	0	507 (13.5)	466 (12.4)	973 (12.9)	507 (3.3)	466 (3.1)	973 (3.2)
>=80 years	0	0	0	234 (6.2)	191 (5.1)	425 (5.7)	234 (1.5)	191 (1.3)	425 (1.4)
Age subgroup at screening, n (%)									
>=18 and <65 years	11413 (100)	11413 (100)	22826 (100)	0	0	0	11413 (75.3)	11413 (75.2)	22826 (75.2)
>=65 and <75 years	0	0	0	3012 (80.3)	3110 (82.6)	6122 (81.4)	3012 (19.9)	3110 (20.5)	6122 (20.2)
>=75 and <85 years	0	0	0	692 (18.4)	616 (16.4)	1308 (17.4)	692 (4.6)	616 (4.1)	1308 (4.3)
>=85 years	0	0	0	49 (1.3)	41 (1.1)	90 (1.2)	49 (0.3)	41 (0.3)	90 (0.3)
Age and health risk for severe COVID-19, n (%) [a]									
>=18 and <65 years and not at risk	8880 (77.8)	8888 (77.9)	17768 (77.8)	2 (<0.1)	0	2 (<0.1)	8882 (58.6)	8888 (58.6)	17770 (58.6)
>=18 and <65 years and at risk	2532 (22.2)	2524 (22.1)	5056 (22.2)	3 (<0.1)	6 (0.2)	9 (0.1)	2535 (16.7)	2530 (16.7)	5065 (16.7)
>=65 years	1 (<0.1)	1 (<0.1)	2 (<0.1)	3748 (99.9)	3761 (99.8)	7509 (99.9)	3749 (24.7)	3762 (24.8)	7511 (24.8)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Risk factor for severe COVID-19 at screening, n (%) [b]									
Chronic lung disease	504 (4.4)	473 (4.1)	977 (4.3)	245 (6.5)	239 (6.3)	484 (6.4)	749 (4.9)	712 (4.7)	1461 (4.8)
Significant cardiac disease	292 (2.6)	321 (2.8)	613 (2.7)	450 (12.0)	441 (11.7)	891 (11.8)	742 (4.9)	762 (5.0)	1504 (5.0)
Severe obesity	905 (7.9)	896 (7.9)	1801 (7.9)	153 (4.1)	174 (4.6)	327 (4.3)	1058 (7.0)	1070 (7.0)	2128 (7.0)
Diabetes	912 (8.0)	919 (8.1)	1831 (8.0)	545 (14.5)	541 (14.4)	1086 (14.4)	1457 (9.6)	1460 (9.6)	2917 (9.6)
Liver disease	70 (0.6)	84 (0.7)	154 (0.7)	26 (0.7)	20 (0.5)	46 (0.6)	96 (0.6)	104 (0.7)	200 (0.7)
Human immunodeficiency virus infection	75 (0.7)	77 (0.7)	152 (0.7)	16 (0.4)	17 (0.5)	33 (0.4)	91 (0.6)	94 (0.6)	185 (0.6)
At risk for severe COVID-19 at screening, n (%)									
Yes	2322 (20.3)	2320 (20.3)	4642 (20.3)	1135 (30.2)	1128 (29.9)	2263 (30.1)	3457 (22.8)	3448 (22.7)	6905 (22.8)
One risk factor for severe COVID-19	1937 (17.0)	1925 (16.9)	3862 (16.9)	878 (23.4)	866 (23.0)	1744 (23.2)	2815 (18.6)	2791 (18.4)	5606 (18.5)
Two or more risk factors for severe COVID-19	385 (3.4)	395 (3.5)	780 (3.4)	257 (6.8)	262 (7.0)	519 (6.9)	642 (4.2)	657 (4.3)	1299 (4.3)
No	9091 (79.7)	9093 (79.7)	18184 (79.7)	2618 (69.8)	2639 (70.1)	5257 (69.9)	11709 (77.2)	11732 (77.3)	23441 (77.2)
Age and risk for severe COVID-19, n (%) [c]									

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
>=18 and <65 years and not at risk	9091 (79.7)	9093 (79.7)	18184 (79.7)	0	0	0	9091 (59.9)	9093 (59.9)	18184 (59.9)
>=18 and <65 years and at risk	2322 (20.3)	2320 (20.3)	4642 (20.3)	0	0	0	2322 (15.3)	2320 (15.3)	4642 (15.3)
>=65 years and not at risk	0	0	0	2618 (69.8)	2639 (70.1)	5257 (69.9)	2618 (17.3)	2639 (17.4)	5257 (17.3)
>=65 years and at risk	0	0	0	1135 (30.2)	1128 (29.9)	2263 (30.1)	1135 (7.5)	1128 (7.4)	2263 (7.5)
Baseline RT-PCR results, n (%)									
Negative	11271 (98.8)	11268 (98.7)	22539 (98.7)	3724 (99.2)	3745 (99.4)	7469 (99.3)	14995 (98.9)	15013 (98.9)	30008 (98.9)
Positive	85 (0.7)	81 (0.7)	166 (0.7)	10 (0.3)	7 (0.2)	17 (0.2)	95 (0.6)	88 (0.6)	183 (0.6)
Missing	57 (0.5)	64 (0.6)	121 (0.5)	19 (0.5)	15 (0.4)	34 (0.5)	76 (0.5)	79 (0.5)	155 (0.5)
Baseline elecsys anti-SARS-CoV-2 results, n (%)									
Negative	11124 (97.5)	11124 (97.5)	22248 (97.5)	3720 (99.1)	3723 (98.8)	7443 (99.0)	14844 (97.9)	14847 (97.8)	29691 (97.8)
Positive	274 (2.4)	276 (2.4)	550 (2.4)	29 (0.8)	33 (0.9)	62 (0.8)	303 (2.0)	309 (2.0)	612 (2.0)
Missing	15 (0.1)	13 (0.1)	28 (0.1)	4 (0.1)	11 (0.3)	15 (0.2)	19 (0.1)	24 (0.2)	43 (0.1)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Baseline SARS-CoV-2 status, n (%) [d]									
Negative	11046 (96.8)	11037 (96.7)	22083 (96.7)	3699 (98.6)	3709 (98.5)	7408 (98.5)	14745 (97.2)	14746 (97.1)	29491 (97.2)
Positive	303 (2.7)	311 (2.7)	614 (2.7)	34 (0.9)	36 (1.0)	70 (0.9)	337 (2.2)	347 (2.3)	684 (2.3)
Missing	64 (0.6)	65 (0.6)	129 (0.6)	20 (0.5)	22 (0.6)	42 (0.6)	84 (0.6)	87 (0.6)	171 (0.6)
Sex, n (%)									
Male	5955 (52.2)	5841 (51.2)	11796 (51.7)	2102 (56.0)	2076 (55.1)	4178 (55.6)	8057 (53.1)	7917 (52.2)	15974 (52.6)
Female	5458 (47.8)	5572 (48.8)	11030 (48.3)	1651 (44.0)	1691 (44.9)	3342 (44.4)	7109 (46.9)	7263 (47.8)	14372 (47.4)
Race, n (%)									
White	8657 (75.9)	8653 (75.8)	17310 (75.8)	3344 (89.1)	3378 (89.7)	6722 (89.4)	12001 (79.1)	12031 (79.3)	24032 (79.2)
Black or African American	1316 (11.5)	1345 (11.8)	2661 (11.7)	215 (5.7)	222 (5.9)	437 (5.8)	1531 (10.1)	1567 (10.3)	3098 (10.2)
Asian	662 (5.8)	589 (5.2)	1251 (5.5)	77 (2.1)	67 (1.8)	144 (1.9)	739 (4.9)	656 (4.3)	1395 (4.6)
American Indian or Alaska Native	95 (0.8)	92 (0.8)	187 (0.8)	26 (0.7)	21 (0.6)	47 (0.6)	121 (0.8)	113 (0.7)	234 (0.8)
Native Hawaiian or other Pacific Islander	29 (0.3)	33 (0.3)	62 (0.3)	3 (<0.1)	3 (<0.1)	6 (<0.1)	32 (0.2)	36 (0.2)	68 (0.2)
Multiracial	284 (2.5)	287 (2.5)	571 (2.5)	35 (0.9)	32 (0.8)	67 (0.9)	319 (2.1)	319 (2.1)	638 (2.1)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Other	262 (2.3)	276 (2.4)	538 (2.4)	32 (0.9)	23 (0.6)	55 (0.7)	294 (1.9)	299 (2.0)	593 (2.0)
Not reported	60 (0.5)	84 (0.7)	144 (0.6)	14 (0.4)	13 (0.3)	27 (0.4)	74 (0.5)	97 (0.6)	171 (0.6)
Unknown	48 (0.4)	54 (0.5)	102 (0.4)	7 (0.2)	8 (0.2)	15 (0.2)	55 (0.4)	62 (0.4)	117 (0.4)
Ethnicity, n (%)									
Hispanic or Latino	2774 (24.3)	2767 (24.2)	5541 (24.3)	335 (8.9)	354 (9.4)	689 (9.2)	3109 (20.5)	3121 (20.6)	6230 (20.5)
Not Hispanic or Latino	8544 (74.9)	8548 (74.9)	17092 (74.9)	3377 (90.0)	3369 (89.4)	6746 (89.7)	11921 (78.6)	11917 (78.5)	23838 (78.6)
Not reported	57 (0.5)	72 (0.6)	129 (0.6)	26 (0.7)	33 (0.9)	59 (0.8)	83 (0.5)	105 (0.7)	188 (0.6)
Unknown	38 (0.3)	26 (0.2)	64 (0.3)	15 (0.4)	11 (0.3)	26 (0.3)	53 (0.3)	37 (0.2)	90 (0.3)
Race and ethnicity group, n (%) [e]									
Minority	4070 (35.7)	4075 (35.7)	8145 (35.7)	561 (14.9)	578 (15.3)	1139 (15.1)	4631 (30.5)	4653 (30.7)	9284 (30.6)
Non-minority	7330 (64.2)	7318 (64.1)	14648 (64.2)	3179 (84.7)	3183 (84.5)	6362 (84.6)	10509 (69.3)	10501 (69.2)	21010 (69.2)
Missing	13 (0.1)	20 (0.2)	33 (0.1)	13 (0.3)	6 (0.2)	19 (0.3)	26 (0.2)	26 (0.2)	52 (0.2)
Race and ethnicity group, n (%) [f]									
White	6401 (56.1)	6459 (56.6)	12860 (56.3)	3067 (81.7)	3074 (81.6)	6141 (81.7)	9468 (62.4)	9533 (62.8)	19001 (62.6)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Communities of color	4999 (43.8)	4934 (43.2)	9933 (43.5)	673 (17.9)	687 (18.2)	1360 (18.1)	5672 (37.4)	5621 (37.0)	11293 (37.2)
Missing	13 (0.1)	20 (0.2)	33 (0.1)	13 (0.3)	6 (0.2)	19 (0.3)	26 (0.2)	26 (0.2)	52 (0.2)
Weight (kg)									
n	11353	11357	22710	3730	3738	7468	15083	15095	30178
Mean (SD)	86.75 (22.352)	86.56 (22.682)	86.66 (22.518)	83.23 (19.019)	83.11 (19.334)	83.17 (19.176)	85.88 (21.629)	85.71 (21.951)	85.79 (21.790)
Median	83.64	83.64	83.64	81.60	81.20	81.40	83.00	83.00	83.00
Min, Max	30.7, 223.0	30.3, 236.4	30.3, 236.4	34.8, 184.5	37.2, 165.0	34.8, 184.5	30.7, 223.0	30.3, 236.4	30.3, 236.4
Height (cm)									
n	11352	11357	22709	3729	3739	7468	15081	15096	30177
Mean (SD)	171.16 (9.964)	170.98 (9.901)	171.07 (9.933)	170.05 (10.224)	169.97 (10.004)	170.01 (10.114)	170.88 (10.040)	170.73 (9.936)	170.81 (9.988)
Median	171.00	170.20	170.50	170.18	170.18	170.18	170.50	170.18	170.20
Min, Max	118.0, 205.7	104.1, 221.0	104.1, 221.0	124.5, 223.5	123.0, 208.3	123.0, 223.5	118.0, 223.5	104.1, 221.0	104.1, 223.5
Body mass index (kg/m^2)									
n	11352	11354	22706	3729	3738	7467	15081	15092	30173
Mean (SD)	29.53 (6.904)	29.53 (7.120)	29.53 (7.012)	28.71 (5.890)	28.67 (5.851)	28.69 (5.870)	29.32 (6.677)	29.32 (6.838)	29.32 (6.757)
Median	28.27	28.25	28.26	27.75	27.86	27.79	28.13	28.13	28.13
Min, Max	10.3, 72.7	9.8, 86.1	9.8, 86.1	12.1, 71.1	11.2, 62.9	11.2, 71.1	10.3, 72.7	9.8, 86.1	9.8, 86.1

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Body mass index subgroup, n (%)									
< 30 kg/m^2	6867 (60.2)	6859 (60.1)	13726 (60.1)	2436 (64.9)	2414 (64.1)	4850 (64.5)	9303 (61.3)	9273 (61.1)	18576 (61.2)
>=30 kg/m^2	4485 (39.3)	4495 (39.4)	8980 (39.3)	1293 (34.5)	1324 (35.1)	2617 (34.8)	5778 (38.1)	5819 (38.3)	11597 (38.2)
Missing	61 (0.5)	59 (0.5)	120 (0.5)	24 (0.6)	29 (0.8)	53 (0.7)	85 (0.6)	88 (0.6)	173 (0.6)
Occupational risk, n (%) [b]	10164 (89.1)	10120 (88.7)	20284 (88.9)	2387 (63.6)	2376 (63.1)	4763 (63.3)	12551 (82.8)	12496 (82.3)	25047 (82.5)
Healthcare workers	3339 (29.3)	3339 (29.3)	6678 (29.3)	504 (13.4)	467 (12.4)	971 (12.9)	3843 (25.3)	3806 (25.1)	7649 (25.2)
Emergency response	277 (2.4)	281 (2.5)	558 (2.4)	19 (0.5)	21 (0.6)	40 (0.5)	296 (2.0)	302 (2.0)	598 (2.0)
Retail or restaurant operations	882 (7.7)	857 (7.5)	1739 (7.6)	99 (2.6)	100 (2.7)	199 (2.6)	981 (6.5)	957 (6.3)	1938 (6.4)
Manufacturing and production operations	391 (3.4)	391 (3.4)	782 (3.4)	30 (0.8)	35 (0.9)	65 (0.9)	421 (2.8)	426 (2.8)	847 (2.8)
Warehouse shipping and fulfillment centers	163 (1.4)	181 (1.6)	344 (1.5)	12 (0.3)	9 (0.2)	21 (0.3)	175 (1.2)	190 (1.3)	365 (1.2)
Transportation and delivery services	419 (3.7)	434 (3.8)	853 (3.7)	61 (1.6)	50 (1.3)	111 (1.5)	480 (3.2)	484 (3.2)	964 (3.2)
Border protection and military personnel	63 (0.6)	65 (0.6)	128 (0.6)	6 (0.2)	3 (<0.1)	9 (0.1)	69 (0.5)	68 (0.4)	137 (0.5)
Personal care and in-home services	407 (3.6)	405 (3.5)	812 (3.6)	61 (1.6)	67 (1.8)	128 (1.7)	468 (3.1)	472 (3.1)	940 (3.1)
Hospitality and tourism workers	184 (1.6)	201 (1.8)	385 (1.7)	43 (1.1)	37 (1.0)	80 (1.1)	227 (1.5)	238 (1.6)	465 (1.5)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**
Pastoral, social or public health workers	364 (3.2)	386 (3.4)	750 (3.3)	140 (3.7)	149 (4.0)	289 (3.8)	504 (3.3)	535 (3.5)	1039 (3.4)
Educators and students	1387 (12.2)	1365 (12.0)	2752 (12.1)	170 (4.5)	186 (4.9)	356 (4.7)	1557 (10.3)	1551 (10.2)	3108 (10.2)
Other	3398 (29.8)	3415 (29.9)	6813 (29.8)	1432 (38.2)	1435 (38.1)	2867 (38.1)	4830 (31.8)	4850 (31.9)	9680 (31.9)
Location and living circumstances risk, n (%)[b]	9580 (83.9)	9599 (84.1)	19179 (84.0)	3109 (82.8)	3133 (83.2)	6242 (83.0)	12689 (83.7)	12732 (83.9)	25421 (83.8)
Resides in nursing home or assisted living facility	9 (<0.1)	24 (0.2)	33 (0.1)	20 (0.5)	11 (0.3)	31 (0.4)	29 (0.2)	35 (0.2)	64 (0.2)
Resides in multi-family dwelling	348 (3.0)	397 (3.5)	745 (3.3)	65 (1.7)	66 (1.8)	131 (1.7)	413 (2.7)	463 (3.1)	876 (2.9)
Resides in high density housing	1073 (9.4)	1038 (9.1)	2111 (9.2)	240 (6.4)	253 (6.7)	493 (6.6)	1313 (8.7)	1291 (8.5)	2604 (8.6)
Resides in low density, multi-family setting	1236 (10.8)	1248 (10.9)	2484 (10.9)	256 (6.8)	244 (6.5)	500 (6.6)	1492 (9.8)	1492 (9.8)	2984 (9.8)
Resides in a single family home	6148 (53.9)	6115 (53.6)	12263 (53.7)	2262 (60.3)	2283 (60.6)	4545 (60.4)	8410 (55.5)	8398 (55.3)	16808 (55.4)
Other	1647 (14.4)	1649 (14.4)	3296 (14.4)	529 (14.1)	548 (14.5)	1077 (14.3)	2176 (14.3)	2197 (14.5)	4373 (14.4)

Abbreviations: IRT = interactive response technology; Max = maximum; Min = minimum; RT-PCR = reverse transcription polymerase chain reaction; SD = standard deviation.

Percentages are based on the number of subjects in Full Analysis Set.

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

[b] Subjects could be under one or more categories, and are counted once at each category.

[c] Age and health risk for severe COVID-19 are derived from age and risk factors collected on case report form (CRF).

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11413)	**mRNA-1273 (N=11413)**	**Total (N=22826)**	**Placebo (N=3753)**	**mRNA-1273 (N=3767)**	**Total (N=7520)**	**Placebo (N=15166)**	**mRNA-1273 (N=15180)**	**Total (N=30346)**

[d] Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

[e] Minority is defined as: Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders, and Non-Minority includes all the others whose race or ethnicity is not unknown, unreported or missing.

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

Source: Study 301 Part A CSR Table 14.1.3.1.2.

2.5.4.1.2 Study 201

Study 201 included healthy males and females 18 years of age and older. The study population was approximately two-thirds female (390/600 [65.0%]), mostly White (569/600 [94.8%]), and not of Hispanic or Latino ethnicity (552/600 [92.0%]), with a mean age of 50.8 years and an age range of 18 to 87 years (Section 2.7.3.2.2). No apparent differences were observed in baseline demographics across the groups.

2.5.4.1.3 Study 101

Study 101 included healthy males and females 18 years of age and older across 3 age cohorts (18 to 55 years; 56 to 70 years; ≥ 71 years).

Study 101 data were analyzed for each age cohort separately and were not analyzed for the study population as a whole. In the 18 to 55 years age cohort, approximately half of participants were female (29/60 [48%]), the majority were White (53/60 [88%]) and not of Hispanic or Latino ethnicity (52/60 [87%]), and participants had a mean (standard deviation [SD]) age of 34.0 (8.9) years and a range of 18 to 54 years (Study 101 Day 119 CSR Table 7). In the 56 to 70 years age cohort, more than half of participants were female (17/30 [57%]), the majority White (27/30 [90%]) and not of Hispanic or Latino ethnicity (30/30 [100%]), and participants had a mean (SD) age of 63.9 (4.3) years and a range of 56 to 70 years (Study 101 Day 119 CSR Table 8). In the ≥ 71 years age cohort, fewer than half of participants were female (13/30 [43%]), the majority were White (29/30 [97%]) and not of Hispanic or Latino ethnicity (28/30 [93%]), and participants had a mean (SD) age of 73.5 (2.4) years and a range of 71 to 83 years (Study 101 Day 119 CSR Table 9).

2.5.4.2 Study Design Implications

Study 301, Study 201, and Study 101 designs are described in detail in Section 2.7.3.1.1.1, Section 2.7.3.1.1.2, and Section 2.7.3.1.1.3, respectively.

Study 301 was a randomized, stratified, observer-blind, and placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 compared to placebo in adults 18 years of age and older. The design and focus were dependent on the COVID-19 pandemic and required identification of participant candidates who were at high risk of SARS-CoV-2 infection. The study enrolled participants who had no known history of SARS-CoV-2 infection but whose locations or circumstances (eg, occupational risks, such as health care worker) put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The study also enrolled

participants at risk of severe COVID-19 (eg, adults ≥ 65 years of age or adults 18 to < 65 years with certain comorbidities).

Study 201 was designed as a dose-confirming safety and immunogenicity study and Study 101 was a dose-finding safety and immunogenicity study. Study 201 and Study 101 enrolled healthy adults. While appreciably smaller in sample size, Study 201 and Study 101 support the immunogenicity and safety results of Study 301.

2.5.4.3 Statistical Methods

Efficacy was evaluated in Study 301, accompanied by immunogenicity and safety data. Study 201 and Study 101 did not evaluate clinical efficacy of mRNA-1273 but provide supportive immunogenicity and safety data. Data pooling has not been performed for this application because Study 301 was the only study that evaluated efficacy and provided the vast majority (> 95%) of the safety data supporting this application. Additionally, the populations differed across the studies in demographic, medical history, and comorbidity factors (Section 2.5.5).

2.5.4.3.1 Study 301

The statistical methodology used for analyses of efficacy, immunogenicity, and safety endpoints in Study 301 is described in detail in the Study 301 Part A CSR Section 4, as well as in the SAP (Study 301 Part A CSR Appendix 16.1.9).

As described in Section 2.5.4 and Table 3, three analyses of efficacy have been performed on data from Part A: the interim efficacy analysis (11 Nov 2020 dataset), the primary efficacy analysis (25 Nov 2020 dataset), and the final efficacy analysis of Part A (04 May 2021 dataset).

2.5.4.3.1.1 Primary and Secondary Efficacy Objectives and Endpoints

Primary efficacy objective: the VE to prevent first occurrence of COVID-19. The primary efficacy endpoint was the VE of mRNA-1273 to prevent the first adjudicated occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 was defined as symptomatic disease based on the following case definition:

- The participant must have experienced at least TWO of the following systemic symptoms: fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR

- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND

- The participant must have at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR).

Only COVID-19 cases that had been positively adjudicated by an independent, expert committee contributed to the analysis of the primary efficacy endpoint.

The sample size was driven by the total number of cases to demonstrate the VE (mRNA-1273 versus placebo) to prevent COVID-19. Sensitivity analyses were performed with COVID-19 cases counted starting at various time points.

Secondary efficacy objectives:

- the VE of mRNA-1273 to prevent severe COVID-19, defined as the first occurrence of COVID-19 starting 14 days after the second injection of investigational product (IP), (as per the primary endpoint) AND any of the following:

    - clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or the ratio of the oxygen pressure in arterial blood to the fraction of inspired oxygen < 300 mm Hg, OR

    - respiratory failure or acute respiratory distress syndrome (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation), 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 an intensive care unit or death.

- the VE of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity

- the VE of mRNA-1273 to prevent the secondary definition of COVID-19 (see Section 2.7.3.1.1.1 for secondary definition)

- the VE of mRNA-1273 to prevent death caused by COVID-19
- the VE of mRNA-1273 to prevent COVID-19 after the first injection
- the VE of mRNA-1273 to prevent COVID-19 regardless of evidence of prior SARS-CoV-2 infection
- the VE of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.

Secondary immunogenicity objective: evaluate the immunogenicity of 2 doses of mRNA-1273 given 28 days apart. The following immunogenicity assessments (assays) contributed data to this application:

- Serum bAb level against SARS-CoV-2 as measured by ELISA specific to the SARS-CoV-2 S protein (vaccine antigen), including tests for VAC65 spike IgG antibody.
- The MesoScale Discovery-electrochemiluminescence (MSD-ECL) multiplex assay measures bAb to antigens corresponding to S protein.
- Pseudovirus nAb assay for measuring nAb against SARS-CoV-2 S-pseudotyped viruses: Pseudovirus nAb 50% inhibitory dilution (ID_{50}) and 80% inhibitory dilution (ID_{80}) titers (PsVNT50 and PsVNT80).

Analyses of Study 301 exploratory efficacy endpoints are described in Study 301 Part A CSR Section 4.2.2.3.1.

2.5.4.3.2 Study 201

The analyses of Study 201 were descriptive in contrast to Study 301, which had pre-specified criteria for study success. Study 201 did not include any clinical efficacy endpoints, and immunogenicity was characterized by descriptive statistics, without formal statistical comparisons. Immunogenicity was assessed by measurement of nAb against infective SARS-CoV-2 virus by microneutralization (MN) assay and bAb against SARS-CoV-2 S-2P by ELISA.

The statistical methodology used for analyses of immunogenicity and safety in Study 201 is described in detail in the Study 201 Primary Analysis CSR Section 4, as well as in the SAP (Study 201 Primary Analysis CSR Appendix 16.1.9) and in the Study 201 CSR Addendum 1

(End of Part A) Section 4 as well as in the final SAP (Study 201 CSR Addendum 1 [End of Part A] Appendix 16.1.9).

2.5.4.3.3 Study 101

Immunogenicity in Study 101 was characterized by descriptive statistics, without formal statistical comparisons. Immunogenicity assessments included IgG ELISA to SARS-CoV-2 S protein, nAb levels against SARS-CoV-2 pseudovirus and wild-type virus, and protein-specific T-cell responses in a subset of participants.

The statistical methodology used for analyses of immunogenicity and safety in Study 101 Day 119 and Day 209 CSRs is described in detail in the Study 101 Day 119 CSR Section 4, as well as in the SAP (Study 101 Day 119 CSR Appendix 16.1.9).

2.5.4.4 Results and Subgroup Analysis

2.5.4.4.1 Study 301 Efficacy Results

A narrative of Study 301 efficacy is provided in Section 2.7.3.2.1.1 and further details are provided in the Study 301 Part A CSR.

2.5.4.4.1.1 Study 301 Primary Efficacy Endpoint

The primary efficacy endpoint was VE to prevent the first occurrence of COVID-19 starting 14 days after the second injection, based on adjudication committee assessments in the Per-protocol (PP) Set. As described in Section 2.5.4 and Table 3, VE was assessed at 3 different timepoints: an interim analysis, a primary analysis, and a final analysis.

The VE of mRNA-1273 was demonstrated at the interim analysis (11 Nov 2020 dataset) based on the pre-specified success criterion for efficacy (Section 2.7.3.2.1.1). At the interim analysis, VE was based on a total of 95 adjudicated COVID-19 cases (5 cases in the mRNA-1273 group and 90 cases in the placebo group); VE was 94.5% (95% confidence interval [CI] 86.5%, 97.8%, $p < 0.0001$) (Table 5). Since efficacy was demonstrated at the interim analysis, all subsequent efficacy analyses were considered supportive or supplementary. The primary efficacy analysis conducted on the 25 Nov 2020 dataset had a total of 196 adjudicated COVID-19 cases (11 cases in the mRNA-1273 group and 185 cases in the placebo group) and confirmed the result of the interim analysis: VE was 94.1% (95% CI 89.3%, 96.8%, $p < 0.0001$), based on the hazard ratio.

Analysis of the primary efficacy endpoint at the final Part A analysis (04 May 2021 dataset) demonstrated VE was 93.2% (95% CI: 91.0%, 94.8%, $p < 0.0001$), based on the hazard ratio, for a total of 799 adjudicated COVID-19 cases (55 cases in the mRNA-1273 group and 744 cases in the placebo group) (Table 5). The results of this analysis were consistent with results of the interim and primary analyses, confirming persistent, high efficacy over a substantially larger case database and over a median of 5.3-month blinded observation period from randomization in Part A (Section 2.7.3.2.1.1).

For the 67 days (median) from the PDV through the data cutoff date (26 Mar 2021) covered in the Study 301 CSR Addendum 1 (Part B), cases of adjudicated COVID-19 were reported and incidence rates were calculated for those participants remaining in their originally randomized groups beyond the PDV in Part B (Section 2.7.3.2.1.1). In the mRNA-1273 group, of 13,704 participants at risk, 19 (0.1%) adjudicated COVID-19 cases were detected in the PP set. In the placebo group, of 1,175 participants at risk, 3 (0.3%) adjudicated COVID-19 cases were detected. The corresponding incidence rate for the mRNA 1273 group remained low (7.961 cases per 1000 person years; 95% CI: 4.793, 12.432; Part A incidence rate was 9.599 cases per 1000 person-years [95% CI: 7.231, 12.494]). In the placebo group, of 1,175 participants at risk, 3 (0.3%) adjudicated COVID-19 cases were detected. The incidence rate for the placebo group was 77.378 cases per 1000 person years (95% CI: 15.957, 226.131), which was 10-fold higher than that for the mRNA-1273 group. These Part B data confirmed the persistence of vaccine-induced protection for a total median observation period of 7.6 months from randomization or a median of 6.5 months after the second injection across Part A and Part B up to database lock for the analysis.

Table 5 **Study 301 Primary Efficacy Endpoint Analysis Starting 14 Days After Second Injection (11 Nov 2020, 25 Nov 2020, and 04 May 2021 Datasets; Adjudicated Cases, Per-Protocol Sets)**

	11 Nov 2020 Dataset		25 Nov 2020 Dataset		04 May 2021 Dataset	
	Placebo (N=13883)	**mRNA-1273 (N=13934)**	**Placebo (N=14073)**	**mRNA-1273 (N=14134)**	**Placebo (N=14164)**	**mRNA-1273 (N=14287)**
Number of participants with COVID-19, n (%)	90 (0.6)	5 (<0.1)	185 (1.3)	11 (<0.1)	744 (5.3)	55 (0.4)
Vaccine efficacy based on hazard ratio (95% CI)[a]		0.945 (0.865, 0.978)		0.941 (0.893, 0.968)		0.932 (0.910, 0.948)
p value[b]		<0.0001		<0.0001		<0.0001
Person-years[c]	2697.5	2716.9	3273.7	3304.9	5445.2	5729.9
Incidence rate per 1,000 person-years (95% CI)[d]	33.365 (26.829, 41.011)	1.840 (0.598, 4.295)	56.510 (48.660, 65.266)	3.328 (1.662, 5.955)	136.633 (126.991, 146.814)	9.599 (7.231, 12.494)
Vaccine efficacy based on incidence rate (95% CI)[e]		0.945 (0.87, 0.98)		0.941 (0.892, 0.971)		0.930 (0.908, 0.948)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019.

[a] 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.

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

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

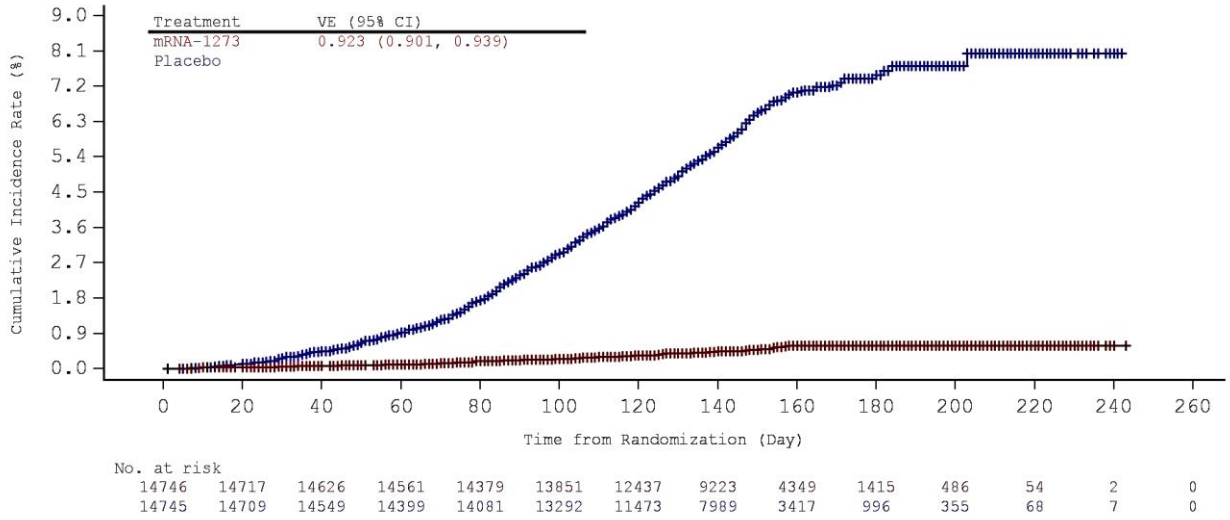
[d] Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.

[e] 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.

Source: Section 2.7.3 Table 4.

Cumulative incidence rate curves for COVID-19 based on adjudication committee assessments starting 14 days after randomization in the Modified Intent-to-Treat (mITT) Set show the divergence of incidence rates between the mRNA-1273 and placebo groups beginning at approximately 14 days after the first injection, indicating early onset of protection (Figure 2). Thereafter, for the remainder of the 5.3-month median observation period for Part A, the cumulative incidence rate for the placebo group increased steadily while it remained stable and low in the mRNA-1273 group (Section 2.7.3.2.1.1).

Figure 2 **Study 301: Cumulative Incidence Rate Curves of COVID-19* Based on Adjudication Committee Assessments Starting After Randomization (mITT Set; 04 May 2021 Database Lock)**



Abbreviations: CI = confidence interval.

* With the censoring rules for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a subject had positive RT-PCR at pre-dose 2 visit (Day 29) without eligible symptoms within 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the subject is censored at the date with positive RT-PCR or Elecsys.

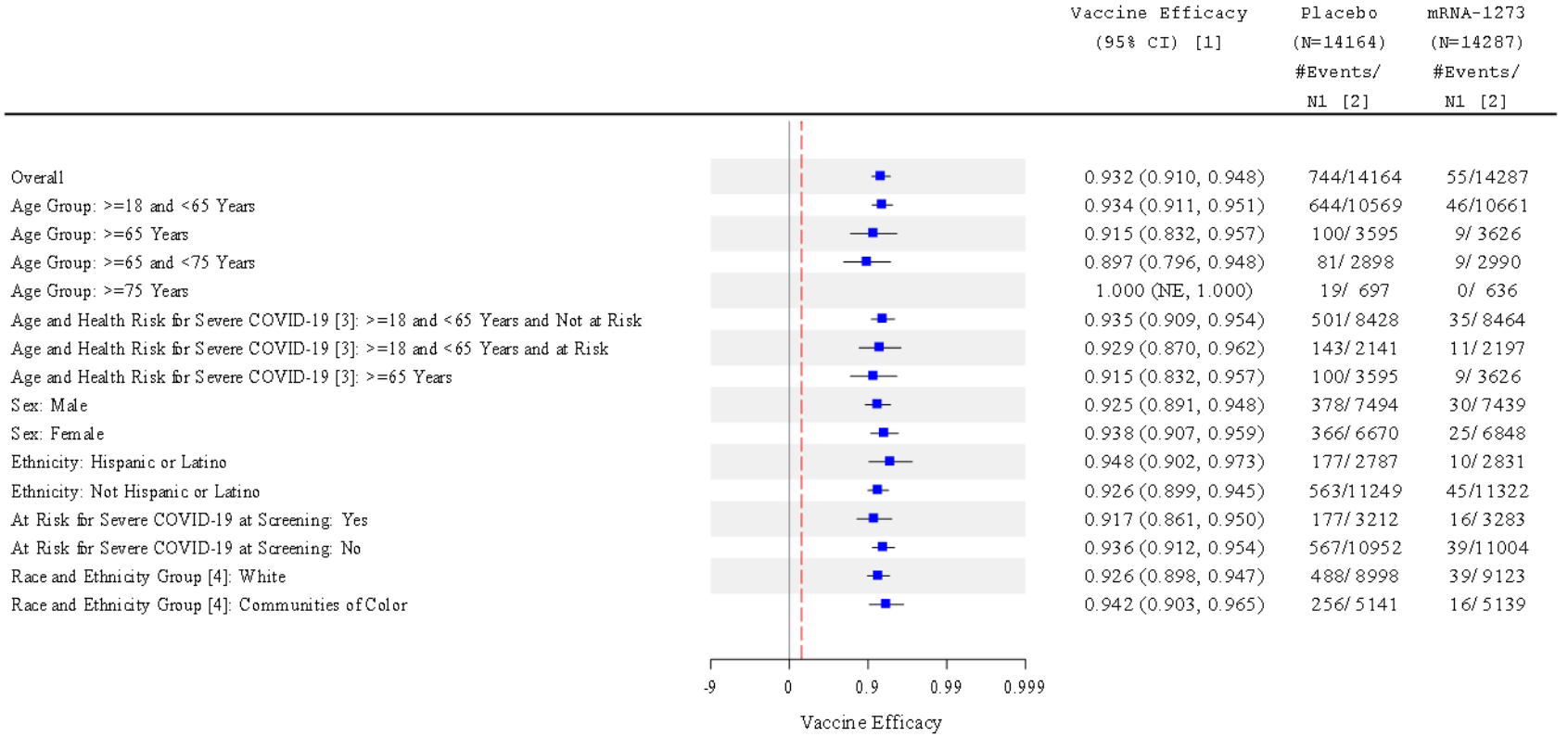
Vaccine efficacy (VE) is defined as 1 – hazard ratio (mRNA-1273 vs. placebo) and 95% CI was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

Source: Section 2.7.3 Figure 1.

The efficacy of mRNA-1273 for the primary efficacy endpoint was consistent across major demographic and baseline characteristic subgroups (

Figure 3). Results were consistent across subgroups stratified by age groups, age and health risk, sex, race and ethnicity, and the presence of risk factor for severe COVID-19 at screening.

Figure 3 **Study 301 Forest Plot of Subgroup Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19* Based on Adjudication Committee Assessments Starting 14 Days After Second Injection (Per-protocol Set; 04 May 2021 Database Lock)**



Abbreviations: CI = confidence interval; N1 = population in each subgroup; NE = not evaluable; RT-PCR = reverse transcriptase polymerase chain reaction.

Note: The dotted red reference line indicates vaccine efficacy of 0.3, the acceptable lower bound for the 95% CI of the primary endpoint for the interim efficacy analysis.

* With the censoring rules for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a subject had positive RT-PCR at pre-dose 2 visit (Day 29) without eligible symptoms within 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the subject is censored at the date with positive RT-PCR or Elecsys.

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

[2] Based on the number of subjects in each subgroup.

[3] Age and health risk for severe COVID-19 are derived from age and risk factor collected on case report form (CRF).

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

Source: Section 2.7.3 Figure 2.

2.5.4.4.1.2 Study 301 Secondary Efficacy Endpoints

Secondary efficacy endpoint results described in this section are based on data from the final efficacy analysis of Part A (04 May 2021 dataset), unless otherwise indicated.

Vaccine efficacy was consistent across the secondary endpoints, characterized by high VE point estimates and tight 95% CIs (Table 6). As individual endpoints, VE calculated for each secondary endpoint surpassed FDA guidance for licensure (that is, a lower bound ≤30% but >0%, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint) (DHHS, 2020).

At the time of the final analysis, there were 108 adjudicated cases of severe COVID-19, with 106 cases in the placebo group and 2 cases in the mRNA-1273 group (Table 6). The VE of mRNA-1273 to prevent adjudicated severe COVID-19 cases starting 14 days after the second injection was 98.2% (95% CI 92.8%, 99.6%). Subgroup analyses of VE to prevent adjudicated severe COVID-19 showed consistent VE point estimates in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection (Section 2.7.3.2.1.1).

Asymptomatic SARS-CoV-2 infection was reported for 712 participants at the final analysis; 498 cases in the placebo group and 214 cases in the mRNA-1273 group. The VE to prevent asymptomatic SARS-CoV-2 infection starting 14 days after second injection based on hazard ratio was 63.0% (95% CI 56.6%, 68.5%) (Table 6). The VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0% (95% CI 79.5%, 84.2%). This analysis confirms that vaccination with mRNA-1273 protects against asymptomatic infection. Furthermore, VE for asymptomatic infection (63.0%) even exceeds regulatory guidance which suggested 50% efficacy with a lower bound CI of at least 30% for COVID-19 vaccines in development during the pandemic (DHHS, 2020).

The VE for other secondary efficacy endpoints had consistent, high VE with point estimates ranging from 92.8% to 100% based on hazard ratios (Table 6).

A narrative of secondary efficacy endpoint results is provided in Section 2.7.3.2.1.1.

Table 6 Study 301 Summary of Primary and Secondary Efficacy Endpoint Analysis Results (Final Analysis, Per-protocol Set)

	Placebo (N=14164)	mRNA-1273 (N=14287)
COVID-19* based on adjudication committee assessments starting 14 days after second injection		
Number of events	744	55
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.932 (0.910, 0.948)
p-value [b]		<.0001
COVID-19* starting 14 days after second injection		
Number of events	751	55
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.932 (0.911, 0.949)
Severe COVID-19* based on adjudication committee assessments starting 14 days after second injection		
Number of events	106	2
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.982 (0.928, 0.996)
Severe COVID-19* starting 14 days after second injection		
Number of events	118	3
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.976 (0.924, 0.992)
SARS-CoV-2 infection regardless of symptomatology and severity starting 14 days after second injection [c]		
Number of events	1339	280
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.820 (0.795, 0.842)
Secondary definition of COVID-19* starting 14 days after second injection		
Number of events	807	58
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.934 (0.914, 0.949)
Death caused by COVID-19 starting 14 days after second injection		
Number of events	3	0
Vaccine efficacy based on hazard ratio (95% CI) [a]		1.000 (NE, 1.000)
COVID-19* based on adjudication committee assessments starting 14 days after first injection		
Number of events	769	56
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.933 (0.911, 0.949)

	Placebo (N=14164)	mRNA-1273 (N=14287)
COVID-19* starting 14 days after first injection		
Number of events	782	58
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.931 (0.910, 0.947)
Asymptomatic SARS-CoV-2 infection starting 14 days after second injection [c]		
Number of events	498	214
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.630 (0.566, 0.685)
COVID-19* based on adjudication committee assessments starting 14 days after second injection regardless of prior SARS-CoV-2 infection, n/N [d]		
Number of events	754/15166	58/15180
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.928 (0.906, 0.945)
COVID-19* starting 14 days after second injection regardless of prior SARS-CoV-2 infection, n/N [d]		
Number of events	762/15166	58/15180
Vaccine efficacy based on hazard ratio (95% CI) [a]		0.929 (0.907, 0.946)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* With the censoring rules for efficacy analyses. COVID-19 case is based on eligible symptoms and positive RT-PCR within 14 days. If a subject had positive RT-PCR at pre-dose 2 visit (Day 29) without eligible symptoms with 14 days, or positive Elecsys at scheduled visits prior to becoming a COVID-19 case, the subject is censored at the date with positive RT-PCR or Elecsys.

[a] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor. For asymptomatic SARS-CoV-2 infection, VE and 95% CI are estimated using Fine and Gray's sub-distribution hazard model with disease cases as competing events and with the treatment group as a covariate, adjusting for stratification factor.

[b] 1-sided p-value from stratified Cox proportional hazard model to test the null hypothesis VE <= 0.3.

[c] Including participant decision visit.

[d] n and N are based on the number of subjects in the Full Analysis Set.

Source: Section 2.7.3 Table 5.

2.5.4.4.1.3 Study 301 Exploratory Efficacy Endpoints

Participants who tested positive for COVID-19 were monitored daily for the duration and severity of symptoms (Study 301 Part A CSR Section 6.3.1). Symptom scores aggregated over the convalescence period for adjudicated COVID-19 cases showed a higher mean total COVID-19 symptom score in the placebo group (60.6) than in the mRNA-1273 group (26.8).

This indicates meaningful protection by mRNA-1273 against the magnitude of symptoms over the convalescent period in participants who were adjudicated COVID-19 cases.

The mean burden of disease (BOD) score for the mRNA-1273 group was 0.0 versus 0.1 for the placebo group (Study 301 Part A CSR Section 6.3.2). The VE point estimate (95% CI) of mRNA-1273 for BOD in the PP Set was 93.2% (91.0%, 94.8%), based on 1 – the ratio of the mean BOD scores. Although this is a statistically significant difference over the entire PP Set, the result is driven by high vaccine efficacy and the numerically dominant prevalence of mild to moderate disease.

The mean burden of infection (BOI) score for the mRNA-1273 group was 0.01 versus 0.06 for the placebo group (Study 301 Part A CSR Section 6.3.3). The VE point estimate (95% CI) of mRNA-1273 for BOI in the PP Set was 91.2% (89.0%, 93.0%), based on 1 – the ratio of the mean BOI score. Although this is a statistically significant difference over the entire PP Set, the result is driven by high vaccine efficacy and the numerically dominant prevalence of mild to moderate disease that was detected (especially versus asymptomatic infection score).

Further details of Study 301 exploratory endpoints are provided in Study 301 Part A CSR Section 6.3.

2.5.4.4.1.3.1 Efficacy and Viral Genotypic Correlates of Risk

Study 301 was the only study with data applicable to an analysis of viral genotypic correlates of risk.

Of the total adjudicated COVID-19 cases started 14 days after the second injection in the PP set during the blinded phase with sequence data, 18 were attributed to variants of concern (VOC) or variants of interest (VOI) in the placebo group and 3 in the mRNA-1273 group (Section 2.7.3.2.1.1). For VOC detected at the time in which the exploratory analysis was conducted (VOC; B.1.427, B.1.429, P1), the VE point estimate (95% CI) based on the hazard ratio for 16 participants in the placebo group and 3 in the mRNA-1273 group was 82.4% (40.4%, 94.8%). For the California VOC B.1.427 and B.1.429 combined, the VE point estimate (95% CI) based on the hazard ratio for 15 participants in the placebo group and 3 in the mRNA-1273 group was 81.2% (36.1%, 94.5%). These results should be interpreted with caution given the low case numbers in both the mRNA-1273 and placebo groups.

2.5.4.4.1.4 Study 301 Immunogenicity Results

A narrative of Study 301 immunogenicity is provided in Section 2.7.3.2.1.2 and further details are provided in the Study 301 Part A CSR Section 6.5.

2.5.4.4.1.4.1 Study 301 SARS-CoV-2 Spike Protein-Specific Binding Antibodies as Measured by MesoScale Discovery Assay

In SARS-CoV-2 baseline-negative mRNA-1273-treated participants, binding antibody seroresponse rates were 99.1% at Day 29 and 99.6% at Day 57 in terms of the MSD assay (Study 301 Part A CSR Section 6.5.1.1). In Study 301, mRNA-1273 was highly immunogenic in SARS-CoV-2 baseline-negative participants, as indicated by increased geometric mean (GM) levels of anti-SARS-CoV-2 S-protein IgG antibodies on Day 29 (28 days after the first injection), which were further increased on Day 57 (28 days after the second injection) (Section 2.7.3.2.1.2.1). In SARS-CoV-2 baseline-positive participants, the GM levels on Day 29 were higher than those observed in baseline-negative mRNA-1273 participants, and were similar to those observed on Day 57 in baseline-negative treatment participants, indicating that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection.

Similar results were observed for subgroups stratified by age (≥ 18 to < 65 years and ≥ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive participants (Section 2.7.3.2.1.2.1). In baseline negative mRNA-1273 treated participants, the GM levels on Day 29 and Day 57 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years; however, seroresponse rates remained high (98.9% to 100%) across both age groups on Day 29 and Day 57. In baseline-positive mRNA-1273 treated participants, the GM levels on Day 29 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years, while Day 57 levels were similar between age groups; seroresponse rates ranged from 95.7% to 100% across both age groups on Day 29 and Day 57.

2.5.4.4.1.4.2 Study 301 SARS-CoV-2 Spike Protein-Specific Neutralizing Antibodies as Measured by Pseudotyped Virus Neutralization Assay

In Study 301, mRNA-1273 was highly immunogenic in SARS-CoV-2 baseline-negative participants, as indicated by increased ID_{50} GM titers on Day 29, which were further increased on Day 57 (Section 2.7.3.2.1.2.2). In SARS-CoV-2 baseline-positive participants, the ID_{50} GM titers on Day 29 were higher than those observed on Day 57 in baseline-negative participants, supporting the observation that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection.

Similar baseline results were observed for subgroups stratified by age (≥ 18 to < 65 years and ≥ 65 years) in both SARS-CoV-2 baseline-negative and baseline-positive participants (Section 2.7.3.2.1.2.2). In baseline-negative mRNA-1273 treated participants, the ID_{50} GM titers on Day 29 and Day 57 were lower in participants ≥ 65 years than those observed in participants ≥ 18 to < 65 years. The seroresponse rate was also lower in the older age group than in the younger age group on Day 29 (71.1% vs. 86.6%), with similar seroresponse rates observed in both age groups on Day 57 (99.4% vs. 98.6%). No notable differences were observed between age groups in SARS-CoV-2 baseline-positive participants.

2.5.4.4.2 Study 201 Immunogenicity Results

Immunogenicity in Study 201 was assessed by measurement of bAb against SARS-CoV-2 S-2P spike protein by ELISA and nAb against infective SARS-CoV-2 virus by MN assay. mRNA-1273 was found to be immunogenic in the 50 µg and 100 µg dose schedules in both the binding and neutralizing assays. A narrative of Study 201 immunogenicity results is provided in Section 2.7.3.2.2, and further details are provided in the Study 201 Primary Analysis CSR Section 8 and the Study 201 CSR Addendum 1 (End of Part A) Section 8.

2.5.4.4.2.1 Study 201 Binding Antibody Response to Vaccination

In Study 201, the time course of bAb response to vaccination was similar between participants who received 100 µg doses of mRNA-1273 and those who received 50 µg doses, with the highest GM levels occurring at Day 43 (Section 2.7.3.2.2.1). The 100 µg dose group had numerically greater responses than the 50 µg dose group on Days 29, 43, 57, and 209. In the mRNA-1273 100 µg dose group, the GM level declined from the peak at Day 43 to Day 209; the Day 209 GM level remained higher than the Day 29 GM level prior to the second injection.

Comparing bAb GM levels between age cohorts within the 100 µg dose group, the bAb GM levels were numerically higher in the younger cohort than in the older cohort at Days 29, 43, 57, and 209 (Section 2.7.3.2.2.1). Within both age cohorts, GM levels were numerically higher in the 100 µg group than in the 50 µg group, although the difference was less pronounced in the older age cohort.

2.5.4.4.2.2 Study 201 Neutralizing Antibody Response to Vaccination

In Study 201, the time course and magnitude of nAb response to vaccination was similar between participants who received 100 µg doses of mRNA-1273 and those who received 50 µg doses. Titers peaked at Day 43 and declined to Day 209 (Section 2.7.3.2.2.2). At Day 209,

geometric mean titers (GMTs) remained higher than the GMTs observed at Day 29 for both the 100 µg and 50 µg dose groups.

Within the mRNA-1273 100 µg group, the nAb GMTs were numerically higher in the younger cohort than in the older cohort at Days 29, 43, 57, and 209 (Section 2.7.3.2.2.2).

2.5.4.4.3 Study 101 Immunogenicity Results

A narrative of Study 101 immunogenicity results is provided in Section 2.7.3.2.3, and further details are provided in Study 101 Day 119 CSR and the Study 101 CSR Addendum 1 (Day 209).

In Study 101, mRNA-1273 administered in 2 doses separated by 28 days induced robust humoral and cellular immune responses compared to a panel of convalescent serum (Section 2.7.3.2.3). Dose-dependent increases in bAb titers to both full-length S-2P and RBD were observed across age groups. S-2P GMTs were generally higher for the 100 µg dose level than for either the 50 µg or 25 µg dose levels at all time points and were similar between the 100 µg and 250 µg mRNA dose levels in the age group of 18 to 55 years. Dose-dependent increases in nAb levels were detected across age groups by 3 neutralization assays (against a wild-type SARS-CoV-2 virus, a SARS-CoV-2 pseudovirus, and a high-throughput live SARS-CoV-2 reporter assay) but only after the second vaccination dose. Binding antibody responses and nAb responses among all age groups for the 100 µg dose level persisted through Day 119 at levels that declined modestly relative to Day 57 but remained similar to or higher than responses in the panel of control convalescent sera. At Day 209, bAb and nAb responses appeared to have declined from Day 119 levels but remained within the respective 95% CIs of convalescent serum panel values.

In assessments of cellular immune response at the 25 and 100 µg dose levels, mRNA-1273 elicited CD4+ T-cell responses after stimulation with S-specific peptide pools that were strongly biased toward expression of Th1 cytokines versus minimal Th2 cytokine expression; in contrast, CD8+ T-cell responses were below the lower limit of quantitation or detected at low levels (Section 2.7.3.2.3.3).

The accelerated development of mRNA-1273 during the pandemic was dependent on the availability of real-time data from the Phase 1 Study 101. The immune responses to the 25, 100, and 250 µg doses assessed by bAb against S-2P (Section 2.7.3.2.3.1) and by nAb in the PRNT against wild-type SARS-CoV-2 (Section 2.7.3.2.3.2) in adults 18 to 55 years of age (along with the reactogenicity data from these dose levels [Section 2.5.5; Jackson et al 2020; Anderson et al 2020]) were the essential data used to decide the dose of mRNA-1273 in Study 301.

2.5.4.4.4 Comparison of Immunogenicity Results Across Studies

The immunogenicity of the 100 µg dose was qualitatively consistent across all studies for each age group for all common time points for both nAb and bAb (Section 2.7.3.3.3). Study 101 provided initial evidence that the 100 µg dose was more immunogenic than the 25 µg dose, supporting the selection of the 100 µg dose for Study 301. Study 201 provided confirmation of the robust immunogenicity of the 100 µg and 50 µg doses and also confirmed the selection of the 100 µg dose that was brought forward in Study 301. The kinetics of immunogenicity of the 100 µg dose level in Study 301 confirm and add precision to the immunogenicity kinetics first identified in Study 101. Study 101 and 201 also demonstrated the persistence of nAb and bAbs through 7 months (Day 209) that was comparable to or numerically higher than GM levels at Day 29 (prior to the second injection).

2.5.4.4.4.1 Immunogenicity and Correlate of Protection

While vaccination with mRNA-1273 was highly immunogenic and protective against COVID-19, there were still breakthrough cases of COVID-19 in the mRNA-1273 group and no correlate of protection was identified. There was no apparent bAb level or nAb titer through Day 57 in Study 301 that was predictive of the presence or absence of COVID-19 cases (Section 2.7.3.2.1.2.3 and Section 2.7.3.3.3.1).

2.5.5 OVERVIEW OF SAFETY

The evaluation of safety in this application is based primarily on results from Study 301, with supportive results from Study 201 and Study 101. The 3 studies differed in racial and ethnic diversity, underlying comorbidities, and risk of exposure to COVID-19 (Section 2.5.4.1). Additionally, over 95% of participant exposure occurred in Study 301 (Table 7). As such, safety data in this application are presented by study instead of through pooled analysis. In addition to safety data from the 3 ongoing clinical studies, an overview of post-authorization safety is summarized in this application (Section 2.5.5.12 and Section 2.7.4.6).

The safety and reactogenicity of mRNA-1273 are being evaluated in the same manner used for other preventative vaccines for infectious diseases. Safety assessments used in Studies 301 and 201 are as follows:

- Solicited local and systemic adverse reactions (ARs) starting within 7 days after each injection until resolution

- Unsolicited adverse events (AEs) occurring within 28 days after each injection
- Medically attended AEs (MAAEs) and serious AEs (SAEs) for the entire study duration of 2 years
- AEs leading to discontinuation from dosing and/or study participation
- Vital signs and physical examinations
- Pregnancies and pregnancy outcomes at any time during the study

Study 101 included assessments of new-onset chronic medical conditions. Studies 201 and 101 included clinical safety laboratory tests. Study 301 included monitoring for vaccine harm including enhanced disease (Section 2.7.4.1.1.1.6).

Adverse event data were also assessed for potential risks based on regulatory agency requests, clinical experience with this and other vaccines for COVID-19 and other infectious diseases, reports in the literature that provide emerging insights and theoretical concerns (ie, these were not prospectively defined, but instead have evolved over the course of the development program). Adverse event data in Studies 301 and 201 summarized these events in categories using Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or Custom MedDRA Queries (CMQs). For Study 301, the SMQs included terms associated with anaphylactic reaction, angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. The CMQs in Study 301 included autoimmune disorders and dermal filler reaction post vaccination. For Study 201, the SMQs included angioedema, arthritis, convulsions, demyelination, hypersensitivity, peripheral neuropathy, and vasculitis.

The potential for mRNA-1273 to cause VAERD was monitored in Study 301 by an independent DSMB (Section 2.5.1.3). Further information is provided in Section 2.5.5.6.5 and Section 2.7.4.1.1.1.6.

A comprehensive summary of safety is included in Module 2.7.4. Complete results of Study 301, Study 201, and Study 101 are provided in the individual CSRs located in Module 5.

2.5.5.1 Adverse Reactions Following Immunization

The reactogenicity profile of mRNA-1273 was characterized for local and systemic ARs, including differences in subgroups and after the first and second injections. The ARs identified during the clinical development program included solicited local ARs of pain, erythema (redness), swelling (hardness), and axillary swelling or tenderness. Solicited systemic ARs included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills. Solicited ARs were collected on the day of each injection and during the 7 days after each injection.

As discussed in Section 2.5.1.3, a theoretical risk for VAERD has been raised based on experience with other viral vaccines and on data from animals administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) (DHHS 2020). In order to address this theoretical risk, the potential of mRNA-1273 to promote VAERD was assessed in young and aged mice, hamsters, and rhesus macaques (NHPs) through the evaluation of immunogenicity endpoints (IgG1:IgG2a ratio, Th1/Th2 cytokine profiles, and the ratio of binding to nAb) indicative of a protective versus a disease enhancement phenotype, and through monitoring of viral load, viral replication, and histopathological evaluation of lung tissues after viral challenge (Section 2.5.1.3). In Study 301, potential for mRNA-1273 to cause VAERD was monitored by the DSMB and is discussed further in Section 2.5.5.6.5.

2.5.5.2 Animal Toxicology

Data from the comprehensive program of nonclinical studies provide support for the clinical efficacy and safety of mRNA-1273 at doses up to 100 µg administered twice IM 28 days apart in the clinical setting (Module 2.4, Nonclinical Overview).

The pivotal submission-enabling toxicology studies were conducted in a platform approach, with 5 mRNA vaccines that encode various antigens developed on the Sponsor's mRNA-based platform using SM-102-containing LNPs (2 Zika virus vaccines: mRNA-1706 and mRNA-1893; 1 hMPV and PIV3 vaccine: mRNA-1653; and 2 CMV vaccines: mRNA-1647 and mRNA-1443). The aggregate repeat-dose toxicity profile of mRNA vaccines that were developed with the Sponsor's mRNA-based platform in rats, at IM doses ranging from 8.9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks, was similar and consistent despite the fact the different mRNA constructs encode different antigens. Therefore, the Sponsor considers that the toxicity associated with mRNA vaccines formulated in similar LNPs is primarily driven by the LNP composition and, to a lesser extent, by the biologic activity of the antigens encoded by the mRNA; therefore, the aggregate Good Laboratory Practice repeat-dose rat data are considered to be representative of mRNA vaccines formulated in the same SM 102 LNPs and

support the clinical development of mRNA-1273 (Module 2.4). The development mRNA-1273 lots evaluated in the nonclinical pharmacology programs were prepared with a manufacturing process similar to the Good Manufacturing Practices mRNA-1273 Drug Product evaluated in the Phase 3 clinical study and were therefore representative of the lots of mRNA-1273 used in the clinical studies.

If a 100 µg/dose of mRNA-1273 is well tolerated in a rat with a conservative body weight estimate of 0.30 kg as compared to a human subject with a conservative body weight of 60.0 kg, there is a 200-fold safety margin for the human dose as compared to the rat dose based on body weight. The efficacy and safety profile of the mRNA-1273 vaccine in the Phase 3 clinical study is the ultimate determinant in identifying the approved dose for human subjects.

A developmental and reproductive toxicity (DART) study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. Maternal administration of mRNA-1273 (100 µg) before mating (2 doses) and during gestation (2 additional doses) did not have any adverse effects on the F_0 or F_1 generations. The mRNA-related non-adverse effects were limited to an increase in the number of fetuses with common skeletal variations of one or more rib nodules and one or more wavy ribs with no effect on viability or growth and development of pups. Strong maternal-to-fetal and maternal-to-pup transfer of antibodies was observed with mRNA-1273.

2.5.5.3 Exposure to mRNA-1273

Demographic characteristics in the Study 301 Safety Set were similar between the participants in the placebo and mRNA-1273 groups (Section 2.7.4.1.3.1.1). As discussed in Section 2.5.4.1.1, Study 301 enrolled a representative sample of participants from communities of color (Table 4). Study 301 also enrolled participants at high risk for severe COVID-19 (41.5%) (Table 4). In contrast, the Study 201 and Study 101 populations were overwhelmingly White, non-Hispanic or Latino, and were in good health (Section 2.5.4.1.2 and Section 2.5.4.1.3). Thus, Study 301 differed from Study 201 and Study 101 in racial and ethnic diversity, medical comorbidities, and risk of exposure to COVID-19.

The mRNA-1273 regimen intended for marketing is 2 doses of mRNA-1273 100 µg administered 28 days apart. The Study 301 Part A Safety Set includes data from 15,184 participants who received at least 1 dose of mRNA-1273 100 µg and 14,731 participants who received 2 doses of mRNA-1273 100 µg (Table 7). Additionally, 12,648 participants have received at least one dose of 100 µg mRNA-1273 in Part B of Study 301 (Section 2.7.4.1.2.1.1).The supportive studies, Study 201 and Study 101, provide data from a

total of 200 and 35 participants, respectively, exposed to at least 1 dose of mRNA-1273 100 µg. Table 7 displays a summary of participant exposure to mRNA-1273 by age group and vaccine dose in the 3 clinical studies.

For Study 301 participants in both groups who received both injections, the median duration of follow-up after the second injection to the data cutoff for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months (Section 2.7.4.1.2.2). This duration of follow-up is appropriate to characterize the immediate and longer-term safety profile following receipt of mRNA-1273. Participants in Study 301, Study 201, and Study 101 continue to be followed for long-term safety.

A complete summary of exposure, including exposure by age group, and study duration is provided in Section 2.7.4.1.2. A summary of post-authorization exposure is provided in Section 2.5.5.12 and Section 2.7.4.6.

Table 7 Participant Exposure to mRNA-1273 in Study 301, Study 201, and Study 101 by Age Group and Dose

	mRNA-1273 25 µg N=35		mRNA-1273 50 µg N=235		mRNA-1273 100 µg N=15419		mRNA-1273 250 µg N=15		Placebo N=15362		All mRNA-1273 N=15704	
Study	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
301[a]												
18 to <65	–	–	–	–	11415	11027	–	–	11411	10964	11415	11027
≥65	–	–	–	–	3769	3704	–	–	3751	3667	3769	3704
≥65 to <75	–	–	–	–	3112	3058	–	–	3010	2946	3112	3058
≥75 to <85	–	–	–	–	616	608	–	–	692	674	616	608
≥85	–	–	–	–	41	38	–	–	49	47	41	38
201												
18 to <55	–	–	100	97	100	99	–	–	100	94	200	196
≥55	–	–	100	98	100	99	–	–	100	100	200	197
101												
18 to 55	15	13	15	15	15	15	15	14	–	–	60	57
56 to 70	10	10	10	10	10	9	–	–	–	–	30	29
≥71	10	10	10	10	10	10	–	–	–	–	30	30

[a] The table includes exposure in Part A only of Study 301. In Part B, an additional 12,648 participants have received at least one dose of 100 µg mRNA-1273.

Source: Section 2.7.4 Table 6.

2.5.5.4 Solicited Adverse Reactions

2.5.5.4.1 Study 301 Part A

Study 301 participants recorded solicited local and systemic ARs in an eDiary on the day of each IP injection and during each of the 7 days after each IP injection (Study 301 Part A CSR Section 3.7.1.1). If any AR was ongoing on the seventh day, the eDiary solicited entries until resolution.

Observations for solicited ARs are consistent with the reactogenicity of the mRNA-1273 vaccine in Study 101 and Study 201. Incidence of local and systemic ARs was higher in the mRNA-1273 group than in the placebo group (Table 8 and Table 9). Most solicited ARs were grade 1 to grade 2 in severity.

In the mRNA-1273 group, pain was the most commonly reported local AR (Table 8 and Table 9). Grade 3 solicited local ARs in the mRNA-1273 group were more common after the second injection (7.0%) than after the first injection (3.5%); pain was the most common grade 3 solicited local AR, reported for 2.7% and 4.1% of participants after the first and second injections, respectively. No grade 4 solicited local ARs were reported.

The majority of solicited local ARs in participants who received mRNA-1273 occurred within the first 2 days after injection and generally lasted a median of 1 to 3 days (Section 2.7.4.2.1.1.2.1).

In the mRNA-1273 group, the incidence of solicited systemic ARs was higher after the second injection (79.5%) than after the first (54.8%) (Table 8 and Table 9). The most common solicited systemic ARs after the first injection of mRNA-1273 were fatigue (37.2%) and headache (32.6%), and the incidence was higher after the second injection (65.4% and 58.8%, respectively). The majority of solicited systemic ARs were grade 1 to grade 2 in severity. After the first injection, 3.0% of participants in the mRNA-1273 group reported grade 3 systemic ARs; fatigue (1.0%) and headache (1.8%) were the most common grade 3 systemic ARs. After the second injection, 15.9% of participants in the mRNA-1273 group reported grade 3 systemic ARs; fatigue (9.8%), myalgia (9.0%), headache (4.5%), and arthralgia (5.3%) were the most common grade 3 systemic ARs. Fever was the most commonly reported grade 4 solicited systemic AR, which represented a temperature > 40°C.

The majority of solicited systemic ARs in participants who received mRNA-1273 occurred within the first 2 days after injection and generally lasted a median of 1 to 3 days (Section 2.7.4.2.1.1.2.1).

Medication used for pain or fever was reported for 22.0% of participants in the mRNA-1273 group (versus 13.2% in the placebo group) after the first injection and for 53.5% of participants after the second injection (versus 10.9% in the placebo group) (Section 2.7.4.2.1.2).

Table 8 **Study 301: Summary of Participants With Solicited Adverse Reactions Starting Within 7 Days After First Injection by Grade (First Injection Solicited Safety Set)**

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Solicited adverse reactions - N1	15151	15166	30317
Any solicited adverse reactions	7285 (48.1)	13317 (87.8)	20602 (68.0)
95% CI	47.3, 48.9	87.3, 88.3	67.4, 68.5
Grade 1	5134 (33.9)	9329 (61.5)	14463 (47.7)
Grade 2	1782 (11.8)	3134 (20.7)	4916 (16.2)
Grade 3	363 (2.4)	849 (5.6)	1212 (4.0)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	369 (2.4)	854 (5.6)	1223 (4.0)
Solicited local adverse reactions - N1	15147	15162	30309
Any solicited local adverse reactions	3009 (19.9)	12765 (84.2)	15774 (52.0)
95% CI	19.2, 20.5	83.6, 84.8	51.5, 52.6
Grade 1	2842 (18.8)	10725 (70.7)	13567 (44.8)
Grade 2	89 (0.6)	1511 (10.0)	1600 (5.3)
Grade 3	78 (0.5)	529 (3.5)	607 (2.0)
Grade 4	0	0	0
Grade 3 or above	78 (0.5)	529 (3.5)	607 (2.0)
Pain - N1	15147	15162	30309
Any	2665 (17.6)	12688 (83.7)	15353 (50.7)
Grade 1	2551 (16.8)	10985 (72.5)	13536 (44.7)
Grade 2	59 (0.4)	1287 (8.5)	1346 (4.4)
Grade 3	55 (0.4)	416 (2.7)	471 (1.6)
Grade 4	0	0	0
Grade 3 or above	55 (0.4)	416 (2.7)	471 (1.6)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Erythema (redness) - N1	15147	15162	30309
Any	77 (0.5)	445 (2.9)	522 (1.7)
Grade 1	57 (0.4)	281 (1.9)	338 (1.1)
Grade 2	7 (<0.1)	122 (0.8)	129 (0.4)
Grade 3	13 (<0.1)	42 (0.3)	55 (0.2)
Grade 4	0	0	0
Grade 3 or above	13 (<0.1)	42 (0.3)	55 (0.2)
Swelling (hardness) - N1	15147	15162	30309
Any	65 (0.4)	935 (6.2)	1000 (3.3)
Grade 1	50 (0.3)	608 (4.0)	658 (2.2)
Grade 2	9 (<0.1)	245 (1.6)	254 (0.8)
Grade 3	6 (<0.1)	82 (0.5)	88 (0.3)
Grade 4	0	0	0
Grade 3 or above	6 (<0.1)	82 (0.5)	88 (0.3)
Axillary swelling or tenderness - N1	15147	15162	30309
Any	722 (4.8)	1553 (10.2)	2275 (7.5)
Grade 1	668 (4.4)	1394 (9.2)	2062 (6.8)
Grade 2	27 (0.2)	110 (0.7)	137 (0.5)
Grade 3	27 (0.2)	49 (0.3)	76 (0.3)
Grade 4	0	0	0
Grade 3 or above	27 (0.2)	49 (0.3)	76 (0.3)
Solicited systemic adverse reactions - N1	15151	15166	30317
Any solicited systemic adverse reactions	6397 (42.2)	8316 (54.8)	14713 (48.5)
95% CI	41.4, 43.0	54.0, 55.6	48.0, 49.1
Grade 1	4334 (28.6)	5358 (35.3)	9692 (32.0)
Grade 2	1746 (11.5)	2504 (16.5)	4250 (14.0)
Grade 3	311 (2.1)	449 (3.0)	760 (2.5)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	317 (2.1)	454 (3.0)	771 (2.5)
Fever - N1	15149	15163	30312
Any	44 (0.3)	112 (0.7)	156 (0.5)
Grade 1	28 (0.2)	73 (0.5)	101 (0.3)
Grade 2	8 (<0.1)	24 (0.2)	32 (0.1)
Grade 3	2 (<0.1)	11 (<0.1)	13 (<0.1)
Grade 4	6 (<0.1)	4 (<0.1)	10 (<0.1)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Grade 3 or above	8 (<0.1)	15 (<0.1)	23 (<0.1)
Headache - N1	15146	15162	30308
Any	4026 (26.6)	4950 (32.6)	8976 (29.6)
Grade 1	3297 (21.8)	3947 (26.0)	7244 (23.9)
Grade 2	532 (3.5)	730 (4.8)	1262 (4.2)
Grade 3	197 (1.3)	273 (1.8)	470 (1.6)
Grade 4	0	0	0
Grade 3 or above	197 (1.3)	273 (1.8)	470 (1.6)
Fatigue - N1	15146	15162	30308
Any	4133 (27.3)	5636 (37.2)	9769 (32.2)
Grade 1	2705 (17.9)	3585 (23.6)	6290 (20.8)
Grade 2	1323 (8.7)	1899 (12.5)	3222 (10.6)
Grade 3	105 (0.7)	151 (1.0)	256 (0.8)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	105 (0.7)	152 (1.0)	257 (0.8)
Myalgia - N1	15146	15162	30308
Any	2069 (13.7)	3442 (22.7)	5511 (18.2)
Grade 1	1560 (10.3)	2442 (16.1)	4002 (13.2)
Grade 2	462 (3.1)	909 (6.0)	1371 (4.5)
Grade 3	47 (0.3)	91 (0.6)	138 (0.5)
Grade 4	0	0	0
Grade 3 or above	47 (0.3)	91 (0.6)	138 (0.5)
Arthralgia - N1	15146	15162	30308
Any	1784 (11.8)	2510 (16.6)	4294 (14.2)
Grade 1	1333 (8.8)	1842 (12.1)	3175 (10.5)
Grade 2	413 (2.7)	607 (4.0)	1020 (3.4)
Grade 3	38 (0.3)	60 (0.4)	98 (0.3)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	38 (0.3)	61 (0.4)	99 (0.3)
Nausea/vomiting - N1	15146	15162	30308
Any	1075 (7.1)	1262 (8.3)	2337 (7.7)
Grade 1	887 (5.9)	1047 (6.9)	1934 (6.4)
Grade 2	175 (1.2)	205 (1.4)	380 (1.3)
Grade 3	13 (<0.1)	10 (<0.1)	23 (<0.1)
Grade 4	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Grade 3 or above	13 (<0.1)	10 (<0.1)	23 (<0.1)
Chills - N1	15146	15162	30308
Any	878 (5.8)	1251 (8.3)	2129 (7.0)
Grade 1	706 (4.7)	938 (6.2)	1644 (5.4)
Grade 2	158 (1.0)	289 (1.9)	447 (1.5)
Grade 3	14 (<0.1)	24 (0.2)	38 (0.1)
Grade 4	0	0	0
Grade 3 or above	14 (<0.1)	24 (0.2)	38 (0.1)

Abbreviations: CI = confidence intervals; N1 = number of exposed subjects who submitted any data for the event.

Any = Grade 1 or higher.

Percentages are based on the number of exposed subjects who submitted any data for the event (N1).

95% CI is calculated using the Clopper-Pearson method.

Severity grading for solicited adverse reactions is defined in Section 2.7.4 Table 3.

Source: 2.7.4 Table 11.

Table 9 Study 301 Summary of Participants With Solicited Adverse Reactions Starting Within 7 Days After Second Injection by Grade (Second Injection Solicited Safety Set)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Solicited adverse reactions - N1	14578	14691	29269
Any solicited adverse reactions	6255 (42.9)	13556 (92.3)	19811 (67.7)
95% CI	42.1, 43.7	91.8, 92.7	67.1, 68.2
Grade 1	4346 (29.8)	4847 (33.0)	9193 (31.4)
Grade 2	1558 (10.7)	5800 (39.5)	7358 (25.1)
Grade 3	348 (2.4)	2895 (19.7)	3243 (11.1)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	351 (2.4)	2909 (19.8)	3260 (11.1)
Solicited local adverse reactions - N1	14577	14688	29265
Any solicited local adverse reactions	2757 (18.9)	13029 (88.7)	15786 (53.9)
95% CI	18.3, 19.6	88.2, 89.2	53.4, 54.5
Grade 1	2594 (17.8)	8789 (59.8)	11383 (38.9)
Grade 2	88 (0.6)	3217 (21.9)	3305 (11.3)
Grade 3	75 (0.5)	1023 (7.0)	1098 (3.8)
Grade 4	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Grade 3 or above	75 (0.5)	1023 (7.0)	1098 (3.8)
Pain - N1	14577	14688	29265
Any	2486 (17.1)	12964 (88.3)	15450 (52.8)
Grade 1	2384 (16.4)	9508 (64.7)	11892 (40.6)
Grade 2	61 (0.4)	2850 (19.4)	2911 (9.9)
Grade 3	41 (0.3)	606 (4.1)	647 (2.2)
Grade 4	0	0	0
Grade 3 or above	41 (0.3)	606 (4.1)	647 (2.2)
Erythema (redness) - N1	14577	14687	29264
Any	68 (0.5)	1274 (8.7)	1342 (4.6)
Grade 1	48 (0.3)	456 (3.1)	504 (1.7)
Grade 2	5 (<0.1)	531 (3.6)	536 (1.8)
Grade 3	15 (0.1)	287 (2.0)	302 (1.0)
Grade 4	0	0	0
Grade 3 or above	15 (0.1)	287 (2.0)	302 (1.0)
Swelling (hardness) - N1	14577	14687	29264
Any	60 (0.4)	1807 (12.3)	1867 (6.4)
Grade 1	38 (0.3)	900 (6.1)	938 (3.2)
Grade 2	10 (<0.1)	652 (4.4)	662 (2.3)
Grade 3	12 (<0.1)	255 (1.7)	267 (0.9)
Grade 4	0	0	0
Grade 3 or above	12 (<0.1)	255 (1.7)	267 (0.9)
Axillary swelling or tenderness - N1	14577	14687	29264
Any	571 (3.9)	2092 (14.2)	2663 (9.1)
Grade 1	523 (3.6)	1735 (11.8)	2258 (7.7)
Grade 2	28 (0.2)	289 (2.0)	317 (1.1)
Grade 3	20 (0.1)	68 (0.5)	88 (0.3)
Grade 4	0	0	0
Grade 3 or above	20 (0.1)	68 (0.5)	88 (0.3)
Solicited systemic adverse reactions - N1	14577	14690	29267
Any solicited systemic adverse reactions	5343 (36.7)	11678 (79.5)	17021 (58.2)
95% CI	35.9, 37.4	78.8, 80.1	57.6, 58.7
Grade 1	3519 (24.1)	3717 (25.3)	7236 (24.7)
Grade 2	1535 (10.5)	5611 (38.2)	7146 (24.4)
Grade 3	286 (2.0)	2336 (15.9)	2622 (9.0)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	289 (2.0)	2350 (16.0)	2639 (9.0)
Fever - N1	14573	14682	29255
Any	43 (0.3)	2276 (15.5)	2319 (7.9)
Grade 1	33 (0.2)	1363 (9.3)	1396 (4.8)
Grade 2	5 (<0.1)	697 (4.7)	702 (2.4)
Grade 3	2 (<0.1)	203 (1.4)	205 (0.7)
Grade 4	3 (<0.1)	13 (<0.1)	16 (<0.1)
Grade 3 or above	5 (<0.1)	216 (1.5)	221 (0.8)
Headache - N1	14575	14687	29262
Any	3427 (23.5)	8637 (58.8)	12064 (41.2)
Grade 1	2740 (18.8)	4815 (32.8)	7555 (25.8)
Grade 2	522 (3.6)	3156 (21.5)	3678 (12.6)
Grade 3	165 (1.1)	666 (4.5)	831 (2.8)
Grade 4	0	0	0
Grade 3 or above	165 (1.1)	666 (4.5)	831 (2.8)
Fatigue - N1	14575	14687	29262
Any	3418 (23.5)	9607 (65.4)	13025 (44.5)
Grade 1	2181 (15.0)	3431 (23.4)	5612 (19.2)
Grade 2	1129 (7.7)	4743 (32.3)	5872 (20.1)
Grade 3	108 (0.7)	1433 (9.8)	1541 (5.3)
Grade 4	0	0	0
Grade 3 or above	108 (0.7)	1433 (9.8)	1541 (5.3)
Myalgia - N1	14575	14687	29262
Any	1824 (12.5)	8529 (58.1)	10353 (35.4)
Grade 1	1307 (9.0)	3242 (22.1)	4549 (15.5)
Grade 2	465 (3.2)	3966 (27.0)	4431 (15.1)
Grade 3	52 (0.4)	1321 (9.0)	1373 (4.7)
Grade 4	0	0	0
Grade 3 or above	52 (0.4)	1321 (9.0)	1373 (4.7)
Arthralgia - N1	14575	14687	29262
Any	1579 (10.8)	6303 (42.9)	7882 (26.9)
Grade 1	1143 (7.8)	2809 (19.1)	3952 (13.5)
Grade 2	392 (2.7)	2719 (18.5)	3111 (10.6)
Grade 3	44 (0.3)	775 (5.3)	819 (2.8)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Grade 4	0	0	0
Grade 3 or above	44 (0.3)	775 (5.3)	819 (2.8)
Nausea/vomiting - N1	14575	14687	29262
Any	941 (6.5)	2794 (19.0)	3735 (12.8)
Grade 1	761 (5.2)	2094 (14.3)	2855 (9.8)
Grade 2	169 (1.2)	678 (4.6)	847 (2.9)
Grade 3	11 (<0.1)	21 (0.1)	32 (0.1)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	11 (<0.1)	22 (0.1)	33 (0.1)
Chills - N1	14575	14687	29262
Any	813 (5.6)	6500 (44.3)	7313 (25.0)
Grade 1	629 (4.3)	2907 (19.8)	3536 (12.1)
Grade 2	167 (1.1)	3402 (23.2)	3569 (12.2)
Grade 3	17 (0.1)	191 (1.3)	208 (0.7)
Grade 4	0	0	0
Grade 3 or above	17 (0.1)	191 (1.3)	208 (0.7)

Abbreviations: CI = confidence intervals; N1 = number of exposed subjects who submitted any data for the event.
Any = Grade 1 or higher.
Percentages are based on the number of exposed subjects who submitted any data for the event (N1).
95% CI is calculated using the Clopper-Pearson method.
Severity grading for solicited adverse reactions is in Section 2.7.4 Table 3.
Source: Section 2.7.4 Table 12.

2.5.5.4.1.1 Local Adverse Reaction With Delayed Onset Beyond 7 Days After Injection

In the Study 301 mRNA-1273 group, a local AR with delayed onset on Day 8 or later was reported for 80 participants (0.5%) after the first injection and for 10 participants (< 0.1%) after the second injection (Section 2.7.4.2.1.1.2.3). In the placebo group, 18 participants (0.1%) and 57 participants (0.4%) after the first and second injection, respectively, reported a local AR with delayed onset on Day 8 or later (Study 301 Part A CSR Table 14.3.1.21.1.4).The most common AR that was first reported on Day 8 or later was erythema, which was reported for 68 participants (0.4%) in the mRNA-1273 group after the first injection and 6 participants (< 0.1%) after the second injection.

2.5.5.4.2 Study 201

In Study 201, the incidence of solicited local and systemic ARs within 7 days after any injection was higher for participants who received mRNA-1273 (mRNA-1273 total; 356/400 [89.0%] and 315/400 [78.8%], respectively) than for those who received placebo (38/200 [19.0%] and 91/200 [45.5%], respectively) (Section 2.7.4.2.3.1.1).

The incidence of solicited local ARs after the first injection appeared to be dose dependent (131/200 participants [65.5%] in the 50 µg mRNA-1273 group and 168/200 participants [84.0%] in the 100 µg mRNA-1273 group); this was mostly driven by the dose-dependent incidence of pain (131/200 participants [65.5%] in the 50 µg group and 166/199 participants [83.4%] in the 100 µg group) (Section 2.7.4.2.3.1.1). Few participants reported local ARs other than pain. Findings were similar after the second injection, except that differences between mRNA-1273 dose levels were smaller. Grade 3 pain was reported for 1 participant each in the 50 µg and 100 µg mRNA-1273 groups (0.5%) after the first injection; all other local ARs were grade 2 or lower in severity. After the second injection, erythema was reported at grade 3 only among participants treated with 100 µg mRNA-1273 (5/198 participants [2.5%]).

The incidence of solicited systemic ARs after the first injection was similar in the 50 µg and 100 µg mRNA-1273 groups (83/200 participants [41.5%] and 89/199 participants [44.7%], respectively) and higher than in the placebo group (64/199 participants [32.2%]) (Section 2.7.4.2.3.1.1). The incidence of all solicited systemic ARs was higher in the mRNA-1273 groups after the second injection than after the first, and dose-dependent differences were observed, especially for chills, fatigue, and myalgia. The most common solicited systemic ARs in the mRNA-1273 total group were headache (101/399 participants [25.3%]) and fatigue (98/399 [24.6%]) after the first injection and fatigue (232/393 [59.0%]), headache (200/393 [50.9%]), and myalgia (185/393 [47.1%]) after the second injection. Grade 3 solicited systemic ARs were reported after the first injection for 5 participants who received mRNA-1273 at either dose and 4 participants who received placebo. After the second injection, grade 3 systemic ARs were reported for 45/393 participants (11.5%) in the mRNA-1273 total group (incidence was similar between dose levels) and 2/194 participants (1.0%) in the placebo group. Fatigue was the event most frequently reported at grade 3 (18/198 participants [9.1%] in the 100 µg mRNA-1273 group and 11/195 participants [5.6%] in the 50 µg mRNA-1273 group).

In all groups, participants most often reported solicited local and systemic ARs within the first 3 days after the first or second injection, particularly on Day 2 (Section 2.7.4.2.3.1.2). The mean duration of solicited local and systemic ARs (reported within the 7 days after any injection) was

2.9 and 3.1 days, respectively, in the mRNA-1273 total group and 2.0 and 2.4 days, respectively, in the placebo group.

Solicited ARs that were ongoing 7 days after any injection and reported as treatment-emergent AEs (TEAEs) were reported for 28/400 participants (7.0%) in the mRNA-1273 total group and 8/200 participants (4.0%) in the placebo group (Section 2.7.4.2.3.1.2). No solicited AR met SAE criteria. The persistent events with highest incidence in the mRNA-1273 total group were fatigue (14/400 participants [3.5%]), headache (11/400 [2.8%]), and arthralgia and myalgia (both 7/400 [1.8%]); most events were reported for ≤ 3 participants in any treatment group.

2.5.5.4.3 Study 101

Across all age cohorts, solicited local ARs were predominantly mild or moderate in severity, and the incidence of the solicited local ARs was similar after the first injection and after the second injection (Section 2.7.4.2.4.1). Overall, injection site pain was the most commonly reported solicited local AR; no severe injection site pain was reported in any of the age cohorts. Most solicited local ARs had an onset within 2 days after injection and lasted a median of 2 days or less.

Across all age groups, solicited systemic ARs were predominantly mild or moderate in severity (Section 2.7.4.2.4.1). Fatigue and headache were the most commonly reported solicited systemic ARs after the first injection, and fatigue, headache, myalgia, and feverishness (reported by participants as “chills”) were the most commonly reported solicited systemic ARs after the second injection. The incidence and severity of solicited systemic ARs were generally dose dependent (to a lesser extent in the 56 to 70 years age group), and incidence and severity were generally higher after the second injection than after the first, particularly at the highest (250 µg) dose and thus contributed to dose selection. Most of the solicited systemic ARs had an onset within 2 days after injection, and the median duration of solicited systemic ARs was 1 day.

2.5.5.5 Unsolicited Adverse Events

2.5.5.5.1 Summary of Unsolicited Adverse Events

2.5.5.5.1.1 Study 301 Part A

In Study 301, unsolicited TEAEs were systematically collected for up to 28 days after each IP injection; SAEs, MAAEs, and AEs leading to withdrawal were collected throughout the duration of study. Summaries of unsolicited TEAEs are provided for the 28-day post-injection follow-up

period and with follow-up for the entire duration of Part A, which is the randomized, blinded part of the study. Summaries for Part A include all data up to early unblinding, study discontinuation, the Part B PDV, or the data cutoff date (26 Mar 2021), whichever was earlier, and provide accumulated safety data through a median duration of 148 days (Section 2.7.4.1.2.2.1; Section 2.7.4.2.1.3).

During the 28-day follow-up period, the incidences of unsolicited TEAEs, severe TEAEs, and MAAEs regardless of relationship to IP were generally similar in participants who received mRNA-1273 and those who received placebo (Section 2.7.4.2.1.3.1). At least one TEAE that was assessed by the investigator to be treatment-related was reported in 13.6% and 8.2% of participants in the mRNA-1273 and placebo groups, respectively. These events were generally not severe and only rarely warranted discontinuation of treatment.

Throughout the entire Part A follow-up period, the incidence of SAEs and MAAEs regardless of causality remained balanced between the groups (Table 10).

Table 10 Study 301 Summary of Unsolicited Treatment-emergent Adverse Events in Part A (Safety Set)

	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30346) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination			
All	6513 (43.0)	6310 (41.6)	12823 (42.3)
Serious	292 (1.9)	268 (1.8)	560 (1.8)
Fatal	16 (0.1)	17 (0.1)	33 (0.1)
Medically-attended	4131 (27.2)	3468 (22.8)	7599 (25.0)
Leading to discontinuation from study vaccine	109 (0.7)	74 (0.5)	183 (0.6)
Leading to discontinuation from participation in the study	23 (0.2)	26 (0.2)	49 (0.2)
Severe	486 (3.2)	461 (3.0)	947 (3.1)
Unsolicited TEAEs related to study vaccination			
All	1288 (8.5)	2107 (13.9)	3395 (11.2)
Serious	4 (<0.1)	12 (<0.1)	16 (<0.1)
Fatal	0	0	0
Medically-attended	109 (0.7)	213 (1.4)	322 (1.1)
Leading to discontinuation from study vaccine	15 (<0.1)	20 (0.1)	35 (0.1)

	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30346) n (%)
Leading to discontinuation from participation in the study	0	1 (<0.1)	1 (<0.1)
Severe	34 (0.2)	88 (0.6)	122 (0.4)

A treatment-emergent adverse event (TEAE) 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 subjects.

Source: Study 301 Part A CSR Table 14.3.1.7.1.3.

2.5.5.5.1.2 Study 201

The incidence of unsolicited TEAEs up to the Day 57 visit was similar between the mRNA--1273 total group and the placebo group, and no dose-dependent increase was observed in the mRNA-1273 groups (Table 11). Treatment-related TEAEs were more commonly reported by participants who received mRNA-1273 (either dose) than by those who received placebo.

The incidence of MAAEs was similar in the mRNA-1273 total group and the placebo group. Few participants in any group had MAAEs considered by the investigator to be related to IP; the highest incidence was in the mRNA-1273 100 µg group.

One SAE of pneumonia, which was not considered by the investigator to be related to IP, was reported in the mRNA-1273 50 µg group.

Table 11 Study 201 Summary of Unsolicited TEAEs from Day 1 to Day 57 (Safety Set)

		mRNA-1273		
	Placebo (N=200) n (%)	50 µg (N=200) n (%)	100 µg (N=200) n (%)	Total mRNA-1273 (N=400) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination				
All	55 (27.5)	61 (30.5)	59 (29.5)	120 (30.0)
Serious	0	1 (0.5)	0	1 (0.3)
Fatal	0	0	0	0
Medically attended	19 (9.5)	24 (12.0)	18 (9.0)	42 (10.5)
Leading to discontinuation from study vaccine	1 (0.5)	1 (0.5)	0	1 (0.3)
Leading to study discontinuation	0	0	0	0
Severe	4 (2.0)	8 (4.0)	5 (2.5)	13 (3.3)
Unsolicited TEAEs related to study vaccination				

	Placebo (N=200) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	Total mRNA-1273 (N=400) n (%)
All	13 (6.5)	16 (8.0)	27 (13.5)	43 (10.8)
Serious	0	0	0	0
Fatal	0	0	0	0
Medically attended	1 (0.5)	1 (0.5)	5 (2.5)	6 (1.5)
Leading to discontinuation from study vaccine	0	0	0	0
Leading to study discontinuation	0	0	0	0
Severe	2 (1.0)	4 (2.0)	2 (1.0)	6 (1.5)

Abbreviations: TEAE = treatment-emergent adverse event.

A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.

Percentages are based on the number of safety subjects.

Source: Study 201 Primary Analysis CSR Table 14.3.1.7.2.

2.5.5.5.1.3 Study 101

The incidence of unsolicited AEs was similar across the dose groups and age groups (18 to 55 years of age [44/60 participants; 73%], 56 to 70 years of age [22/30 participants; 73%], and ≥ 71 years of age [23/30 participants; 77%]) (Section 2.7.4.2.4.2.1). Most unsolicited AEs were mild or moderate in severity. All unsolicited AEs related to mRNA-1273 were mild or moderate in severity, except for 2 severe AEs (dizziness and syncope both occurring on Day 1 after the second injection) that were reported in 1 participant in the 18 to 55 years age group (mRNA-1273 250 µg group). All AEs related to mRNA-1273 resolved.

Adverse events leading to treatment discontinuation were reported in 3 participants. Of these, 1 mild AE of urticaria (mRNA-1273 25 µg group, age group: 18 to 55 years) was considered by the investigator to be related to mRNA-1273. All MAAEs reported during the study were not related to mRNA-1273.

2.5.5.5.2 Common, Unsolicited Adverse Events

2.5.5.5.2.1 Study 301 Part A

The incidence of TEAEs was similar between the mRNA-1273 and placebo groups in the 28-day follow-up period (31.3% and 28.6%, respectively) and in the full Part A follow-up period (41.6% and 43.0%, respectively) (Section 2.7.4.2.1.3.2). The most commonly reported unsolicited TEAEs in the mRNA-1273 and placebo groups, respectively, were fatigue (5.0% vs. 4.4%) and

headache (4.9% vs. 4.5%) during the 28-day follow-up period and during the Part A period (fatigue 5.8% vs. 5.3% and headache 6.0% vs. 5.8%).

Commonly reported AEs were generally consistent with the solicited symptoms captured for the evaluation of reactogenicity. During the 28-day follow-up period, unsolicited TEAEs that were reported for ≥ 1% of participants in the mRNA-1273 group and showed higher incidence compared with that in the placebo group were lymphadenopathy (1.7% vs. 0.8%), injection site pain (1.7% vs. 0.8%), and injection site erythema (1.0% vs. 0.3%) (Section 2.7.4.2.1.3.2). Most of the lymphadenopathy events were localized and ipsilateral and regional to the injection site (Section 2.7.4.2.1.3.2.2), as anticipated given the mechanism of action of mRNA-1273 (Section 2.5.1.1.2). Most lymphadenopathy events resolved within 14 days after onset, and the reported characteristics of most events did not suggest generalized lymphadenopathy. Other TEAEs that were reported for ≥ 1% of participants in the mRNA-1273 group and did not show higher incidence compared with that in the placebo group were arthralgia, myalgia, diarrhea, cough, nausea, oropharyngeal pain, nasal congestion, and hypertension. Observations were similar with follow-up for the full duration of Part A.

Other less commonly reported unsolicited TEAEs for which a numerical imbalance was observed included herpes zoster; paresthesia, dysesthesia, hyperesthesia, hypoesthesia; cervical radiculopathy; facial paralysis; vertigo or positional vertigo; and facial bone fracture (Section 2.7.4.2.1.3.2.2). Additionally, further analysis of preferred terms associated with pericarditis and myocarditis was included as it has been identified in the post-authorization space as an important identified risk (Section 2.7.4.2.1.3.2.1). Investigation of these events did not suggest additional safety concerns with mRNA-1273 (see Section 2.7.4.2.1.3.2 for details).

The incidence of severe TEAEs was similar between the mRNA-1273 and placebo groups in the 28-day follow-up period (1.7% and 1.5%, respectively) (Section 2.7.4.2.1.3.3). Hypertension was reported as severe for 28 and 34 participants, respectively (0.2% in each group); no other event was reported as severe for > 0.1% of participants in either group. The incidence of severe TEAEs assessed by the investigator as related to IP was higher in the mRNA-1273 group compared with that in the placebo group in the 28-day follow-up period (0.5% and 0.2%, respectively). Events that were reported as severe and assessed by the investigator to be treatment-related for more participants in the mRNA-1273 group than in the placebo group, respectively, were fatigue (16 participants vs. 6 participants) and myalgia (8 participants vs. 2 participants), both of which were among the solicited systemic ARs.

2.5.5.5.2.2 Study 201

Commonly reported AEs were generally consistent with the solicited symptoms captured for the evaluation of reactogenicity. The common unsolicited TEAEs with the highest incidence (≥ 2%) in the mRNA-1273 total group or placebo group (by decreasing incidence in the mRNA-1273 total group) were headache (18/400 participants [4.5%] and 6/200 participants [3.0%], respectively), fatigue (15/400 [3.8%] and 6/200 [3.0%], respectively), arthralgia (9/400 [2.3%] and 4/200 [2.0%], respectively), myalgia (8/400 [2.0%] and 3/200 [1.5%], respectively), and COVID--19 (2/400 [0.5%] and 5/200 [2.5%], respectively) (Section 2.7.4.2.3.2.2).

Most unsolicited TEAEs reported up to the Day 57 visit in the mRNA-1273 total and placebo groups were mild or moderate in severity (Section 2.7.4.2.3.2.3). Few participants reported severe unsolicited TEAEs up to the Day 57 visit: 13/400 participants [3.3%] in the mRNA-1273 total group and 4/200 participants [2.0%] in the placebo group.

2.5.5.5.2.3 Study 101

No clinically relevant dose-dependent trends were noted in the incidence of unsolicited AEs among the dose groups or age groups (Section 2.7.4.2.4.2.2). All unsolicited AEs were nonserious.

The most commonly reported (> 2 participants overall) unsolicited AEs among participants 18 to 55 years of age were bradycardia, vomiting, vessel puncture site bruise, muscle strain, decreased appetite, and oropharyngeal pain (4/60 participants [7%] each) and injection site bruising, injection site pruritus, contusion, and skin abrasion (3/60 participants [5%] each) (Section 2.7.4.2.4.2.2).

No unsolicited AEs were reported in more than 2 participants among participants 56 to 70 years of age (Section 2.7.4.2.4.2.2).

The most commonly reported (> 2 participants overall) unsolicited AEs among participants ≥ 71 years of age were skin abrasion (6/30 participants [20%]); and injection site bruising, vessel puncture site bruise, and dizziness (3/30 participants [10%] with each AE term (Section 2.7.4.2.4.2.2).

2.5.5.6 Deaths, Serious Adverse Events, and Discontinuation From Study Vaccine

2.5.5.6.1 Deaths

2.5.5.6.1.1 Study 301 Part A

In Study 301, a total of 32 deaths were reported in Part A: 16 participants (0.1%) in each group (Section 2.7.4.2.1.4.1). None of the unsolicited TEAEs leading to death were considered by the investigator to be related to IP (Table 12). No trends were apparent in the timing of deaths relative to dosing or in the causes of death. Baseline age was ≥ 65 years for 9 of the participants in the mRNA-1273 group and 6 participants in the placebo group (Section 2.7.4.2.1.4.1). One additional participant in the mRNA-1273 group died during Part B due to a TEAE that began during Part A.

COVID-19 was reported as a TEAE leading to death for 1 participant in the mRNA-1273 group and 3 participants in the placebo group. The participant in the mRNA-1273 group was 74 years old and received mRNA-1273 dose 1 but declined to receive dose 2. On Study Day 120, 119 days after the first dose, the participant began to experience symptoms of COVID-19, tested positive for SARS-CoV-2 via RT-PCR on Day 127, and died on Day 175. Additional details are provided in Section 2.7.4.2.1.4.1.

Table 12 Study 301 Participants With Serious Adverse Events Resulting in Death (Part A; Safety Set)

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Cardiac failure congestive	145	Not related
mRNA-1273	Cardiac arrest	89	Not related
mRNA-1273	Myocardial infarction	58	Not related
mRNA-1273	Cardio-respiratory arrest	21	Not related
mRNA-1273	Hepatocellular carcinoma	107	Not related
mRNA-1273	COVID-19	175	Not related
mRNA-1273	Myocardial infarction	45	Not related
mRNA-1273	Pulmonary mass[b]	136	Not related
mRNA-1273	Cardio-respiratory arrest	155	Not related
mRNA-1273	Completed suicide	21	Not related
mRNA-1273	Death	70	Not related
mRNA-1273	Gastrointestinal haemorrhage, multiple organ dysfunction syndrome, acute respiratory failure	60	Not related

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Death	138	Not related
mRNA-1273	Death	54	Not related
mRNA-1273	Head injury	37	Not related
mRNA-1273	Death	110	Not related
mRNA-1273	Coronary artery disease, diabetic complication	71	Not related
Placebo	COVID-19	64	Not related
Placebo	Gastric perforation	13	Not related
Placebo	Pancreatic carcinoma stage IV	145	Not related
Placebo	Amyotrophic lateral sclerosis	86	Not related
Placebo	Myocardial infarction	29	Not related
Placebo	Myocardial infarction	103	Not related
Placebo	Myocardial infarction	47	Not related
Placebo	Cardio-pulmonary arrest	7	Not related
Placebo	Death	120	Not related
Placebo	Systemic inflammatory response syndrome	38	Not related
Placebo	COVID-19	143	Not related
Placebo	Completed suicide	87	Not related
Placebo	Myocardial infarction	86	Not related
Placebo	Death	64	Not related
Placebo	Seizure	97	Not related
Placebo	COVID-19	109	Not related

Abbreviations: COVID-19 = coronavirus disease 2019; IP = investigational product

[a] Relationship is based on investigator assessment.

[b] This participant's event began during Part A but the fatal outcome occurred during Part B.

Source: Section 2.7.4 Table 17.

2.5.5.6.1.2 Study 201 and Study 101

In Study 201 and Study 101, no deaths occurred at the time of the database locks for the CSRs (Section 2.7.4.2.3.3.1 and Section 2.7.4.2.4.3.1).

2.5.5.6.2 Serious Adverse Events

2.5.5.6.2.1 Study 301 Part A

In Study 301, no difference was observed between the groups in the rates of reported SAEs during Part A (1.8% in the mRNA-1273 group [401 events] and 1.9% in the placebo group [439 events]) (Table 13). COVID-19 was reported as an SAE for 2 participants (< 0.1%) in the

mRNA-1273 group and for 40 participants (0.3%) in the placebo group. No other event was reported as an SAE in ≥ 0.1% of participants in either group.

At least 1 SAE that was considered by the investigator to be related to treatment was reported for 12 participants (< 0.1%) in the mRNA-1273 group and 4 participants (< 0.1%) in the placebo group (Table 14). Swelling of the face was reported as a treatment-related SAE for 2 participants in the mRNA-1273 group and 1 participant in the placebo group (described further in Section 2.7.4.2.1.4.2); no other event was reported as treatment-related for more than 1 participant in either group or overall.

Table 13 Study 301 Participant Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Part A (Safety Set)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	292 (1.9)	268 (1.8)		560 (1.8)
Number of unsolicited adverse events	439	401		840
Infections and infestations	77 (0.5)	48 (0.3)		125 (0.4)
Pneumonia	11 (<0.1)	9 (<0.1)	0.82 (0.35, 1.92)	20 (<0.1)
Appendicitis	5 (<0.1)	4 (<0.1)		9 (<0.1)
Sepsis	3 (<0.1)	4 (<0.1)		7 (<0.1)
Cellulitis	0	3 (<0.1)		3 (<0.1)
Bronchitis	0	2 (<0.1)		2 (<0.1)
COVID-19	40 (0.3)	2 (<0.1)	0.05 (0.01, 0.19)	42 (0.1)
Peritonitis	0	2 (<0.1)		2 (<0.1)
Postoperative abscess	0	2 (<0.1)		2 (<0.1)
Urosepsis	0	2 (<0.1)		2 (<0.1)
Abscess limb	0	1 (<0.1)		1 (<0.1)
Appendicitis perforated	1 (<0.1)	1 (<0.1)		2 (<0.1)
Clostridium difficile infection	0	1 (<0.1)		1 (<0.1)
Diabetic foot infection	0	1 (<0.1)		1 (<0.1)
Diverticulitis	3 (<0.1)	1 (<0.1)		4 (<0.1)
Gastroenteritis viral	0	1 (<0.1)		1 (<0.1)
Giardiasis	0	1 (<0.1)		1 (<0.1)
Hepatitis A	0	1 (<0.1)		1 (<0.1)
Liver abscess	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Lung abscess	0	1 (<0.1)		1 (<0.1)
Pneumonia mycoplasmal	0	1 (<0.1)		1 (<0.1)
Pneumonia staphylococcal	0	1 (<0.1)		1 (<0.1)
Post procedural infection	0	1 (<0.1)		1 (<0.1)
Postoperative wound infection	0	1 (<0.1)		1 (<0.1)
Pyelonephritis acute	1 (<0.1)	1 (<0.1)		2 (<0.1)
Salpingitis	0	1 (<0.1)		1 (<0.1)
Septic shock	3 (<0.1)	1 (<0.1)		4 (<0.1)
Spinal cord abscess	0	1 (<0.1)		1 (<0.1)
Toxic shock syndrome	0	1 (<0.1)		1 (<0.1)
Upper respiratory tract infection	0	1 (<0.1)		1 (<0.1)
Urinary tract infection	5 (<0.1)	1 (<0.1)		6 (<0.1)
Viral infection	0	1 (<0.1)		1 (<0.1)
Viral pharyngitis	0	1 (<0.1)		1 (<0.1)
Wound infection	0	1 (<0.1)		1 (<0.1)
COVID-19 pneumonia	8 (<0.1)	0		8 (<0.1)
Clostridium difficile colitis	1 (<0.1)	0		1 (<0.1)
Coccidioidomycosis	1 (<0.1)	0		1 (<0.1)
Enterococcal bacteraemia	1 (<0.1)	0		1 (<0.1)
Localised infection	1 (<0.1)	0		1 (<0.1)
Meningitis aseptic	1 (<0.1)	0		1 (<0.1)
Osteomyelitis	1 (<0.1)	0		1 (<0.1)
Perirectal abscess	1 (<0.1)	0		1 (<0.1)
Pharyngitis streptococcal	1 (<0.1)	0		1 (<0.1)
Pneumonia bacterial	1 (<0.1)	0		1 (<0.1)
Pneumonia klebsiella	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Pyelonephritis	2 (<0.1)	0		2 (<0.1)
Streptococcal sepsis	1 (<0.1)	0		1 (<0.1)
Tooth abscess	1 (<0.1)	0		1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (0.2)	27 (0.2)		51 (0.2)
Prostate cancer	4 (<0.1)	5 (<0.1)		9 (<0.1)
Hepatocellular carcinoma	0	2 (<0.1)		2 (<0.1)
B-cell small lymphocytic lymphoma	0	1 (<0.1)		1 (<0.1)
Benign lung neoplasm	0	1 (<0.1)		1 (<0.1)
Cancer pain	0	1 (<0.1)		1 (<0.1)
Clear cell renal cell carcinoma	1 (<0.1)	1 (<0.1)		2 (<0.1)
Colorectal cancer	0	1 (<0.1)		1 (<0.1)
Gastric cancer	0	1 (<0.1)		1 (<0.1)
Gastrointestinal stromal tumour	0	1 (<0.1)		1 (<0.1)
Invasive lobular breast carcinoma	0	1 (<0.1)		1 (<0.1)
Liposarcoma	0	1 (<0.1)		1 (<0.1)
Malignant melanoma	0	1 (<0.1)		1 (<0.1)
Meningioma	0	1 (<0.1)		1 (<0.1)
Metastases to bone	0	1 (<0.1)		1 (<0.1)
Metastases to lung	0	1 (<0.1)		1 (<0.1)
Metastatic neoplasm	0	1 (<0.1)		1 (<0.1)
Non-Hodgkin's lymphoma	0	1 (<0.1)		1 (<0.1)
Oesophageal carcinoma	0	1 (<0.1)		1 (<0.1)
Papillary thyroid cancer	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pelvic neoplasm	0	1 (<0.1)		1 (<0.1)
Plasma cell myeloma	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Renal cell carcinoma	1 (<0.1)	1 (<0.1)		2 (<0.1)
Splenic marginal zone lymphoma	0	1 (<0.1)		1 (<0.1)
Throat cancer	0	1 (<0.1)		1 (<0.1)
Thymoma malignant	0	1 (<0.1)		1 (<0.1)
Thyroid cancer metastatic	0	1 (<0.1)		1 (<0.1)
Adenocarcinoma gastric	1 (<0.1)	0		1 (<0.1)
Breast cancer stage I	1 (<0.1)	0		1 (<0.1)
Colon cancer stage III	1 (<0.1)	0		1 (<0.1)
Endometrial cancer	3 (<0.1)	0		3 (<0.1)
Intraductal proliferative breast lesion	3 (<0.1)	0		3 (<0.1)
Invasive ductal breast carcinoma	1 (<0.1)	0		1 (<0.1)
Leiomyosarcoma metastatic	1 (<0.1)	0		1 (<0.1)
Lung adenocarcinoma	1 (<0.1)	0		1 (<0.1)
Non-small cell lung cancer	1 (<0.1)	0		1 (<0.1)
Pancreatic carcinoma stage IV	1 (<0.1)	0		1 (<0.1)
Prostate cancer metastatic	1 (<0.1)	0		1 (<0.1)
Thyroid cancer	1 (<0.1)	0		1 (<0.1)
Uterine leiomyoma	1 (<0.1)	0		1 (<0.1)
Blood and lymphatic system disorders	7 (<0.1)	3 (<0.1)		10 (<0.1)
Anaemia	2 (<0.1)	2 (<0.1)		4 (<0.1)
Blood loss anaemia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Thrombocytopenia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Anaemia macrocytic	1 (<0.1)	0		1 (<0.1)
Iron deficiency anaemia	1 (<0.1)	0		1 (<0.1)
Thrombocytosis	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Immune system disorders	2 (<0.1)	0		2 (<0.1)
Anaphylactic reaction	1 (<0.1)	0		1 (<0.1)
Cytokine storm	1 (<0.1)	0		1 (<0.1)
Endocrine disorders	0	1 (<0.1)		1 (<0.1)
Basedow's disease	0	1 (<0.1)		1 (<0.1)
Metabolism and nutrition disorders	15 (<0.1)	17 (0.1)		32 (0.1)
Dehydration	4 (<0.1)	4 (<0.1)		8 (<0.1)
Diabetic ketoacidosis	3 (<0.1)	3 (<0.1)		6 (<0.1)
Hyponatraemia	1 (<0.1)	3 (<0.1)		4 (<0.1)
Hypoglycaemia	1 (<0.1)	2 (<0.1)		3 (<0.1)
Type 2 diabetes mellitus	1 (<0.1)	2 (<0.1)		3 (<0.1)
Diabetic complication	0	1 (<0.1)		1 (<0.1)
Failure to thrive	0	1 (<0.1)		1 (<0.1)
Gout	1 (<0.1)	1 (<0.1)		2 (<0.1)
Hyperkalaemia	0	1 (<0.1)		1 (<0.1)
Hypokalaemia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Obesity	0	1 (<0.1)		1 (<0.1)
Diabetes mellitus	1 (<0.1)	0		1 (<0.1)
Diabetes mellitus inadequate control	1 (<0.1)	0		1 (<0.1)
Hypomagnesaemia	1 (<0.1)	0		1 (<0.1)
Metabolic acidosis	1 (<0.1)	0		1 (<0.1)
Psychiatric disorders	13 (<0.1)	13 (<0.1)		26 (<0.1)
Depression	2 (<0.1)	3 (<0.1)		5 (<0.1)
Alcohol withdrawal syndrome	1 (<0.1)	2 (<0.1)		3 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Alcohol abuse	0	1 (<0.1)		1 (<0.1)
Completed suicide	1 (<0.1)	1 (<0.1)		2 (<0.1)
Drug abuse	0	1 (<0.1)		1 (<0.1)
Intentional self-injury	0	1 (<0.1)		1 (<0.1)
Mental status changes	1 (<0.1)	1 (<0.1)		2 (<0.1)
Schizoaffective disorder	1 (<0.1)	1 (<0.1)		2 (<0.1)
Substance-induced mood disorder	0	1 (<0.1)		1 (<0.1)
Substance-induced psychotic disorder	0	1 (<0.1)		1 (<0.1)
Suicidal ideation	0	1 (<0.1)		1 (<0.1)
Suicide attempt	0	1 (<0.1)		1 (<0.1)
Alcoholism	1 (<0.1)	0		1 (<0.1)
Anxiety	1 (<0.1)	0		1 (<0.1)
Anxiety disorder	1 (<0.1)	0		1 (<0.1)
Confusional state	1 (<0.1)	0		1 (<0.1)
Depression suicidal	1 (<0.1)	0		1 (<0.1)
Major depression	2 (<0.1)	0		2 (<0.1)
Mania	1 (<0.1)	0		1 (<0.1)
Schizophrenia	1 (<0.1)	0		1 (<0.1)
Nervous system disorders	27 (0.2)	31 (0.2)		58 (0.2)
Cerebrovascular accident	4 (<0.1)	6 (<0.1)		10 (<0.1)
Syncope	7 (<0.1)	5 (<0.1)	0.71 (0.24, 2.13)	12 (<0.1)
Seizure	1 (<0.1)	3 (<0.1)		4 (<0.1)
Subarachnoid haemorrhage	0	3 (<0.1)		3 (<0.1)
Embolic stroke	0	2 (<0.1)		2 (<0.1)
Transient ischaemic attack	2 (<0.1)	2 (<0.1)		4 (<0.1)
Aphasia	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Autonomic nervous system imbalance	0	1 (<0.1)		1 (<0.1)
Carotid artery stenosis	0	1 (<0.1)		1 (<0.1)
Carotid artery thrombosis	0	1 (<0.1)		1 (<0.1)
Cauda equina syndrome	0	1 (<0.1)		1 (<0.1)
Cervical radiculopathy	0	1 (<0.1)		1 (<0.1)
Dizziness	1 (<0.1)	1 (<0.1)		2 (<0.1)
Facial paralysis	0	1 (<0.1)		1 (<0.1)
Hemiparesis	0	1 (<0.1)		1 (<0.1)
Lumbar radiculopathy	0	1 (<0.1)		1 (<0.1)
Multiple sclerosis	1 (<0.1)	1 (<0.1)		2 (<0.1)
Optic neuritis	0	1 (<0.1)		1 (<0.1)
Spinal cord compression	0	1 (<0.1)		1 (<0.1)
Amyotrophic lateral sclerosis	1 (<0.1)	0		1 (<0.1)
Arachnoid cyst	1 (<0.1)	0		1 (<0.1)
Basal ganglia haemorrhage	1 (<0.1)	0		1 (<0.1)
Encephalopathy	2 (<0.1)	0		2 (<0.1)
Hydrocephalus	1 (<0.1)	0		1 (<0.1)
Ischaemic stroke	1 (<0.1)	0		1 (<0.1)
Loss of consciousness	1 (<0.1)	0		1 (<0.1)
Migraine	1 (<0.1)	0		1 (<0.1)
Nerve compression	1 (<0.1)	0		1 (<0.1)
Paraesthesia	1 (<0.1)	0		1 (<0.1)
Speech disorder	1 (<0.1)	0		1 (<0.1)
Eye disorders	1 (<0.1)	0		1 (<0.1)
Retinal detachment	1 (<0.1)	0		1 (<0.1)
Retinal tear	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Cardiac disorders	43 (0.3)	36 (0.2)		79 (0.3)
Myocardial infarction	9 (<0.1)	7 (<0.1)	0.78 (0.30, 2.01)	16 (<0.1)
Atrial fibrillation	10 (<0.1)	6 (<0.1)	0.60 (0.23, 1.59)	16 (<0.1)
Cardiac failure congestive	3 (<0.1)	4 (<0.1)		7 (<0.1)
Acute coronary syndrome	0	3 (<0.1)		3 (<0.1)
Acute myocardial infarction	6 (<0.1)	3 (<0.1)		9 (<0.1)
Coronary artery disease	3 (<0.1)	3 (<0.1)		6 (<0.1)
Atrial flutter	2 (<0.1)	2 (<0.1)		4 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	2 (<0.1)		3 (<0.1)
Pericarditis	2 (<0.1)	2 (<0.1)		4 (<0.1)
Acute left ventricular failure	2 (<0.1)	1 (<0.1)		3 (<0.1)
Angina unstable	0	1 (<0.1)		1 (<0.1)
Bradycardia	0	1 (<0.1)		1 (<0.1)
Cardiac arrest	0	1 (<0.1)		1 (<0.1)
Cardiac failure	2 (<0.1)	1 (<0.1)		3 (<0.1)
Cardiac failure acute	1 (<0.1)	1 (<0.1)		2 (<0.1)
Coronary artery occlusion	0	1 (<0.1)		1 (<0.1)
Pericardial effusion	1 (<0.1)	1 (<0.1)		2 (<0.1)
Stress cardiomyopathy	0	1 (<0.1)		1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)		1 (<0.1)
Ventricular extrasystoles	0	1 (<0.1)		1 (<0.1)
Angina pectoris	1 (<0.1)	0		1 (<0.1)
Arrhythmia	1 (<0.1)	0		1 (<0.1)
Atrioventricular block complete	1 (<0.1)	0		1 (<0.1)
Atrioventricular block second degree	1 (<0.1)	0		1 (<0.1)
Paroxysmal arrhythmia	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Sinus tachycardia	2 (<0.1)	0		2 (<0.1)
Vascular disorders	15 (<0.1)	15 (<0.1)		30 (<0.1)
Deep vein thrombosis	1 (<0.1)	4 (<0.1)		5 (<0.1)
Haematoma	0	2 (<0.1)		2 (<0.1)
Hypertension	2 (<0.1)	2 (<0.1)		4 (<0.1)
Hypertensive urgency	1 (<0.1)	2 (<0.1)		3 (<0.1)
Aortic aneurysm	1 (<0.1)	1 (<0.1)		2 (<0.1)
Arteriosclerosis	0	1 (<0.1)		1 (<0.1)
Axillary vein thrombosis	0	1 (<0.1)		1 (<0.1)
Embolism venous	0	1 (<0.1)		1 (<0.1)
Hypotension	2 (<0.1)	1 (<0.1)		3 (<0.1)
Polyarteritis nodosa	0	1 (<0.1)		1 (<0.1)
Venous thrombosis limb	0	1 (<0.1)		1 (<0.1)
Aortic stenosis	1 (<0.1)	0		1 (<0.1)
Arterial haemorrhage	1 (<0.1)	0		1 (<0.1)
Fibromuscular dysplasia	1 (<0.1)	0		1 (<0.1)
Hypertensive emergency	2 (<0.1)	0		2 (<0.1)
Peripheral artery aneurysm	1 (<0.1)	0		1 (<0.1)
Peripheral artery occlusion	1 (<0.1)	0		1 (<0.1)
Thrombophlebitis superficial	1 (<0.1)	0		1 (<0.1)
Respiratory, thoracic and mediastinal disorders	35 (0.2)	25 (0.2)		60 (0.2)
Acute respiratory failure	10 (<0.1)	7 (<0.1)	0.70 (0.28, 1.77)	17 (<0.1)
Pulmonary embolism	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Dyspnoea	0	5 (<0.1)		5 (<0.1)
Pleural effusion	2 (<0.1)	2 (<0.1)		4 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Respiratory failure	1 (<0.1)	2 (<0.1)		3 (<0.1)
Atelectasis	0	1 (<0.1)		1 (<0.1)
Chronic obstructive pulmonary disease	8 (<0.1)	1 (<0.1)	0.12 (0.02, 0.77)	9 (<0.1)
Emphysema	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pneumothorax	2 (<0.1)	1 (<0.1)		3 (<0.1)
Pulmonary mass	0	1 (<0.1)		1 (<0.1)
Acute respiratory distress syndrome	1 (<0.1)	0		1 (<0.1)
Asthma	1 (<0.1)	0		1 (<0.1)
Epistaxis	1 (<0.1)	0		1 (<0.1)
Hypoxia	3 (<0.1)	0		3 (<0.1)
Laryngeal oedema	1 (<0.1)	0		1 (<0.1)
Organising pneumonia	1 (<0.1)	0		1 (<0.1)
Pleuritic pain	1 (<0.1)	0		1 (<0.1)
Pneumonia aspiration	1 (<0.1)	0		1 (<0.1)
Pulmonary fibrosis	1 (<0.1)	0		1 (<0.1)
Pulmonary infarction	1 (<0.1)	0		1 (<0.1)
Gastrointestinal disorders	25 (0.2)	36 (0.2)		61 (0.2)
Colitis	4 (<0.1)	3 (<0.1)		7 (<0.1)
Gastrointestinal haemorrhage	2 (<0.1)	3 (<0.1)		5 (<0.1)
Nausea	3 (<0.1)	3 (<0.1)		6 (<0.1)
Small intestinal obstruction	3 (<0.1)	3 (<0.1)		6 (<0.1)
Abdominal pain	2 (<0.1)	2 (<0.1)		4 (<0.1)
Abdominal pain upper	0	2 (<0.1)		2 (<0.1)
Diarrhoea	1 (<0.1)	2 (<0.1)		3 (<0.1)
Duodenal ulcer perforation	0	2 (<0.1)		2 (<0.1)
Hiatus hernia	1 (<0.1)	2 (<0.1)		3 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Intestinal obstruction	0	2 (<0.1)		2 (<0.1)
Vomiting	2 (<0.1)	2 (<0.1)		4 (<0.1)
Crohn's disease	0	1 (<0.1)		1 (<0.1)
Diverticular perforation	0	1 (<0.1)		1 (<0.1)
Duodenal ulcer	0	1 (<0.1)		1 (<0.1)
Gastritis	2 (<0.1)	1 (<0.1)		3 (<0.1)
Gastrooesophageal reflux disease	0	1 (<0.1)		1 (<0.1)
Inguinal hernia	0	1 (<0.1)		1 (<0.1)
Intra-abdominal fluid collection	0	1 (<0.1)		1 (<0.1)
Large intestine perforation	0	1 (<0.1)		1 (<0.1)
Oesophageal rupture	0	1 (<0.1)		1 (<0.1)
Oesophageal spasm	0	1 (<0.1)		1 (<0.1)
Pancreatitis	2 (<0.1)	1 (<0.1)		3 (<0.1)
Pancreatitis acute	0	1 (<0.1)		1 (<0.1)
Rectal prolapse	0	1 (<0.1)		1 (<0.1)
Retroperitoneal haemorrhage	0	1 (<0.1)		1 (<0.1)
Abdominal hernia	1 (<0.1)	0		1 (<0.1)
Abdominal pain lower	2 (<0.1)	0		2 (<0.1)
Duodenal ulcer haemorrhage	1 (<0.1)	0		1 (<0.1)
Gastric perforation	1 (<0.1)	0		1 (<0.1)
Gastric ulcer haemorrhage	1 (<0.1)	0		1 (<0.1)
Tooth socket haemorrhage	1 (<0.1)	0		1 (<0.1)
Hepatobiliary disorders	5 (<0.1)	6 (<0.1)		11 (<0.1)
Cholecystitis	3 (<0.1)	3 (<0.1)		6 (<0.1)
Bile duct stone	0	2 (<0.1)		2 (<0.1)
Cholelithiasis	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Biliary dyskinesia	1 (<0.1)	0		1 (<0.1)
Cholecystitis acute	1 (<0.1)	0		1 (<0.1)
Skin and subcutaneous tissue disorders	2 (<0.1)	3 (<0.1)		5 (<0.1)
Alopecia areata	0	1 (<0.1)		1 (<0.1)
Angioedema	1 (<0.1)	1 (<0.1)		2 (<0.1)
Rash	0	1 (<0.1)		1 (<0.1)
Rash vesicular	0	1 (<0.1)		1 (<0.1)
Dermatitis bullous	1 (<0.1)	0		1 (<0.1)
Musculoskeletal and connective tissue disorders	28 (0.2)	24 (0.2)		52 (0.2)
Osteoarthritis	12 (<0.1)	8 (<0.1)	0.67 (0.28, 1.58)	20 (<0.1)
Intervertebral disc protrusion	2 (<0.1)	3 (<0.1)		5 (<0.1)
Back pain	0	2 (<0.1)		2 (<0.1)
Spinal stenosis	2 (<0.1)	2 (<0.1)		4 (<0.1)
Flank pain	1 (<0.1)	1 (<0.1)		2 (<0.1)
Fracture nonunion	0	1 (<0.1)		1 (<0.1)
Muscular weakness	1 (<0.1)	1 (<0.1)		2 (<0.1)
Musculoskeletal chest pain	1 (<0.1)	1 (<0.1)		2 (<0.1)
Neck pain	0	1 (<0.1)		1 (<0.1)
Rheumatoid arthritis	0	1 (<0.1)		1 (<0.1)
Spinal osteoarthritis	3 (<0.1)	1 (<0.1)		4 (<0.1)
Spondylolisthesis	0	1 (<0.1)		1 (<0.1)
Vertebral foraminal stenosis	0	1 (<0.1)		1 (<0.1)
Arthritis	1 (<0.1)	0		1 (<0.1)
Cervical spinal stenosis	1 (<0.1)	0		1 (<0.1)
Joint stiffness	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Osteonecrosis	1 (<0.1)	0		1 (<0.1)
Polymyalgia rheumatica	1 (<0.1)	0		1 (<0.1)
Rhabdomyolysis	1 (<0.1)	0		1 (<0.1)
Renal and urinary disorders	11 (<0.1)	10 (<0.1)		21 (<0.1)
Acute kidney injury	6 (<0.1)	5 (<0.1)		11 (<0.1)
Nephrolithiasis	1 (<0.1)	5 (<0.1)		6 (<0.1)
Chronic kidney disease	2 (<0.1)	1 (<0.1)		3 (<0.1)
Renal impairment	1 (<0.1)	0		1 (<0.1)
Urinary retention	1 (<0.1)	0		1 (<0.1)
Pregnancy, puerperium and perinatal conditions	2 (<0.1)	1 (<0.1)		3 (<0.1)
Abortion spontaneous	1 (<0.1)	1 (<0.1)		2 (<0.1)
Ectopic pregnancy	1 (<0.1)	0		1 (<0.1)
Reproductive system and breast disorders	6 (<0.1)	6 (<0.1)		12 (<0.1)
Pelvic pain	0	2 (<0.1)		2 (<0.1)
Benign prostatic hyperplasia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Dysfunctional uterine bleeding	0	1 (<0.1)		1 (<0.1)
Ovarian cyst	2 (<0.1)	1 (<0.1)		3 (<0.1)
Uterine haemorrhage	0	1 (<0.1)		1 (<0.1)
Breast pain	1 (<0.1)	0		1 (<0.1)
Endometrial hyperplasia	1 (<0.1)	0		1 (<0.1)
Pelvic prolapse	1 (<0.1)	0		1 (<0.1)
Congenital, familial and genetic disorders	1 (<0.1)	0		1 (<0.1)
Talipes	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
General disorders and administration site conditions	12 (<0.1)	15 (<0.1)		27 (<0.1)
Death	2 (<0.1)	4 (<0.1)		6 (<0.1)
Non-cardiac chest pain	2 (<0.1)	3 (<0.1)		5 (<0.1)
Chest pain	2 (<0.1)	2 (<0.1)		4 (<0.1)
Swelling face	1 (<0.1)	2 (<0.1)		3 (<0.1)
Asthenia	0	1 (<0.1)		1 (<0.1)
Drug withdrawal syndrome	0	1 (<0.1)		1 (<0.1)
Generalised oedema	0	1 (<0.1)		1 (<0.1)
Multiple organ dysfunction syndrome	0	1 (<0.1)		1 (<0.1)
Oedema peripheral	0	1 (<0.1)		1 (<0.1)
Feeling hot	1 (<0.1)	0		1 (<0.1)
Incarcerated hernia	2 (<0.1)	0		2 (<0.1)
Pyrexia	1 (<0.1)	0		1 (<0.1)
Systemic inflammatory response syndrome	2 (<0.1)	0		2 (<0.1)
Investigations	1 (<0.1)	3 (<0.1)		4 (<0.1)
Hepatic enzyme increased	0	2 (<0.1)		2 (<0.1)
Heart rate irregular	0	1 (<0.1)		1 (<0.1)
Transaminases increased	1 (<0.1)	0		1 (<0.1)
Injury, poisoning and procedural complications	29 (0.2)	27 (0.2)		56 (0.2)
Hip fracture	3 (<0.1)	3 (<0.1)		6 (<0.1)
Cervical vertebral fracture	0	2 (<0.1)		2 (<0.1)
Craniocerebral injury	0	2 (<0.1)		2 (<0.1)
Fall	5 (<0.1)	2 (<0.1)		7 (<0.1)
Road traffic accident	1 (<0.1)	2 (<0.1)		3 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Subdural haematoma	0	2 (<0.1)		2 (<0.1)
Back injury	0	1 (<0.1)		1 (<0.1)
Concussion	0	1 (<0.1)		1 (<0.1)
Facial bones fracture	0	1 (<0.1)		1 (<0.1)
Femoral neck fracture	0	1 (<0.1)		1 (<0.1)
Femur fracture	2 (<0.1)	1 (<0.1)		3 (<0.1)
Gastrointestinal procedural complication	0	1 (<0.1)		1 (<0.1)
Head injury	0	1 (<0.1)		1 (<0.1)
Humerus fracture	0	1 (<0.1)		1 (<0.1)
Incarcerated incisional hernia	0	1 (<0.1)		1 (<0.1)
Incision site pain	0	1 (<0.1)		1 (<0.1)
Joint injury	1 (<0.1)	1 (<0.1)		2 (<0.1)
Overdose	0	1 (<0.1)		1 (<0.1)
Post procedural haemorrhage	1 (<0.1)	1 (<0.1)		2 (<0.1)
Procedural haemorrhage	1 (<0.1)	1 (<0.1)		2 (<0.1)
Rib fracture	3 (<0.1)	1 (<0.1)		4 (<0.1)
Skin laceration	1 (<0.1)	1 (<0.1)		2 (<0.1)
Superficial injury of eye	0	1 (<0.1)		1 (<0.1)
Tendon rupture	1 (<0.1)	1 (<0.1)		2 (<0.1)
Traumatic liver injury	0	1 (<0.1)		1 (<0.1)
Upper limb fracture	0	1 (<0.1)		1 (<0.1)
Wound dehiscence	0	1 (<0.1)		1 (<0.1)
Wrist fracture	0	1 (<0.1)		1 (<0.1)
Ankle fracture	1 (<0.1)	0		1 (<0.1)
Cartilage injury	1 (<0.1)	0		1 (<0.1)
Gun shot wound	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Immunisation anxiety related reaction	1 (<0.1)	0		1 (<0.1)
Pelvic fracture	1 (<0.1)	0		1 (<0.1)
Post procedural fever	1 (<0.1)	0		1 (<0.1)
Post procedural haematoma	1 (<0.1)	0		1 (<0.1)
Post-traumatic pain	1 (<0.1)	0		1 (<0.1)
Sternal fracture	1 (<0.1)	0		1 (<0.1)
Thoracic vertebral fracture	1 (<0.1)	0		1 (<0.1)
Tracheal haemorrhage	1 (<0.1)	0		1 (<0.1)
Traumatic haemothorax	2 (<0.1)	0		2 (<0.1)
Social circumstances	1 (<0.1)	0		1 (<0.1)
Sexual abuse	1 (<0.1)	0		1 (<0.1)
Product issues	1 (<0.1)	0		1 (<0.1)
Lead dislodgement	1 (<0.1)	0		1 (<0.1)

A treatment-emergent adverse event (TEAE) 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 subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Section 2.7.4 Table 18.

Table 14 Study 301 Participant Incidence of Serious Treatment-Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Part A (Safety Set)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	4 (<0.1)	12 (<0.1)		16 (<0.1)
Number of unsolicited adverse events	13	15		28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (<0.1)		1 (<0.1)
B-cell small lymphocytic lymphoma	0	1 (<0.1)		1 (<0.1)
Endocrine disorders	0	1 (<0.1)		1 (<0.1)
Basedow's disease	0	1 (<0.1)		1 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)	0		1 (<0.1)
Hypomagnesaemia	1 (<0.1)	0		1 (<0.1)
Nervous system disorders	1 (<0.1)	3 (<0.1)		4 (<0.1)
Autonomic nervous system imbalance	0	1 (<0.1)		1 (<0.1)
Cerebrovascular accident	0	1 (<0.1)		1 (<0.1)
Multiple sclerosis	0	1 (<0.1)		1 (<0.1)
Paraesthesia	1 (<0.1)	0		1 (<0.1)
Cardiac disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pericardial effusion	0	1 (<0.1)		1 (<0.1)
Pericarditis	0	1 (<0.1)		1 (<0.1)
Acute myocardial infarction	1 (<0.1)	0		1 (<0.1)
Atrial fibrillation	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pleural effusion	0	1 (<0.1)		1 (<0.1)
Organising pneumonia	1 (<0.1)	0		1 (<0.1)
Respiratory failure	1 (<0.1)	0		1 (<0.1)
Gastrointestinal disorders	0	1 (<0.1)		1 (<0.1)
Nausea	0	1 (<0.1)		1 (<0.1)
Vomiting	0	1 (<0.1)		1 (<0.1)
Skin and subcutaneous tissue disorders	0	2 (<0.1)		2 (<0.1)
Alopecia areata	0	1 (<0.1)		1 (<0.1)
Angioedema	0	1 (<0.1)		1 (<0.1)
Musculoskeletal and connective tissue disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Rheumatoid arthritis	0	1 (<0.1)		1 (<0.1)
Polymyalgia rheumatica	1 (<0.1)	0		1 (<0.1)
Renal and urinary disorders	1 (<0.1)	0		1 (<0.1)
Acute kidney injury	1 (<0.1)	0		1 (<0.1)
General disorders and administration site conditions	1 (<0.1)	2 (<0.1)		3 (<0.1)
Swelling face	1 (<0.1)	2 (<0.1)		3 (<0.1)
Feeling hot	1 (<0.1)	0		1 (<0.1)
Injury, poisoning and procedural complications	2 (<0.1)	0		2 (<0.1)
Immunisation anxiety related reaction	1 (<0.1)	0		1 (<0.1)
Procedural haemorrhage	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)

A treatment-emergent adverse event (TEAE) 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 subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Section 2.7.4 Table 19.

2.5.5.6.2.2 Study 201

In Study 201, one SAE (preferred term pneumonia) was reported through Day 57 in a 65-year-old participant in the mRNA-1273 50 µg group (Section 2.7.4.2.3.3.2). The pneumonia was not considered by the investigator to be related to IP or any study procedure and multiple tests for SARS-CoV-2 were negative. A case narrative for the participant is provided in Study 201 Primary Analysis CSR, Section 15.

Safety follow-up through Day 209 in Study 201 showed SAEs reported for 5 participants in the 50 µg mRNA-1273 group, 2 participants in the 100 µg mRNA-1273 group, and 0 participants in the placebo group (Section 2.7.4.2.3.4; Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.13.2). None of the SAEs were considered by the investigator to be related to IP.

2.5.5.6.2.3 Study 101

At the time of the data cutoff for the Study 101 Day 119 CSR, no SAEs had occurred (Section 2.7.4.2.4.3.2). One SAE of clear renal cell carcinoma was reported in the Study 101 Day 209 CSR Addendum, in a participant ≥71 years of age in the 100 µg dose group (Section 2.7.4.2.4.4; Study 101 CSR Addendum 1 [Day 209], Section 7.3.2). The event was not considered by the investigator to be related to IP.

2.5.5.6.3 Discontinuation From Study Vaccine

2.5.5.6.3.1 Study 301 Part A

In Study 301, at least one unsolicited TEAE that was reported as leading to discontinuation from IP in Part A was reported for 74 participants (0.5%) in the mRNA-1273 group and 109 participants (0.7%) in the placebo group (Section 2.7.4.2.1.4.4). The most frequently reported TEAE leading to discontinuation from IP was COVID-19 (14 participants [< 0.1%] in the mRNA-1273 group vs. 53 participants [0.3%] in the placebo group).

2.5.5.6.3.2 Study 201

In Study 201, at the time of the database lock for the primary analysis, 2 participants had discontinued IP due to an unsolicited TEAE (1 each in the mRNA-1273 50 µg [pneumonia SAE] and placebo [COVID-19] groups) (Section 2.7.4.2.3.3.3.1).

2.5.5.6.3.3 Study 101

In Study 101, AEs leading to IP discontinuation were reported in 3 participants. Of these, 1 mild AE of urticaria (25 µg group, age group 18 to 55 years) was deemed by the investigator to be related to mRNA-1273 (Section 2.7.4.2.4.3.3.1).

2.5.5.6.4 Medically Attended Treatment-emergent Adverse Events

An MAAE was defined as an AE that led to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (including unscheduled visits to the study site). Medically attended AEs were collected throughout the duration of the study.

2.5.5.6.4.1 Study 301 Part A

In Study 301 Part A, the participant incidence of unsolicited MAAEs was balanced between the mRNA-1273 and placebo groups (22.8% and 27.2%, respectively) (Section 2.7.4.2.1.4.3). COVID-19 was the most common MAAE and was reported more frequently in the placebo group (5.9%) than in the mRNA-1273 group (0.5%). The incidence of other common (≥ 1.0% in either group) MAAEs was balanced between the groups: upper respiratory tract infection (1.2% mRNA-1273 vs. 1.4% placebo); urinary tract infection (0.9% mRNA-1273 vs. 1.2% placebo); and hypertension (1.2% mRNA-1273 vs. 1.4% placebo).

2.5.5.6.4.2 Study 201

At least one MAAE was reported for 112 participants (28.0%) in the combined mRNA-1273 groups (including 74 [37.0%] for 50 µg and 38 [19.0%] for 100 µg) and 64 participants [32.0%]) in the placebo group and no imbalances were observed in the types of events reported (Section 2.7.4.2.3.4).

2.5.5.6.4.3 Study 101

In Study 101, 33 MAAEs were reported in 24 participants through Day 119 (Section 2.7.4.2.4.3.3.3). All MAAEs were deemed not related to mRNA-1273 except for moderate abdominal discomfort reported by 1 participant in the 250 µg group (age group: 18 to 55 years) on Day 26 after the second injection. A total of 29 new MAAEs were reported through Day 209, of which most were reported as resolved (Section 2.7.4.2.4.4). Those MAAEs that were not resolved as of the database lock will continue to be followed as the study is still ongoing.

2.5.5.6.5 Vaccine-associated Enhanced Respiratory Disease: COVID-19 and Severe COVID-19

In Study 301, the DSMB continuously monitored case counts of COVID-19 and severe COVID-19 (based on prespecified criteria) for any indication of higher disease incidence and/or severity in the mRNA-1273 group compared with that in the placebo group that might have suggested a risk of vaccine harm in the form of VAERD (Section 2.7.4.2.1.4.5). The prespecified criteria for VAERD have not been met at any time during the study. Fewer cases of COVID-19 or severe COVID-19 have been observed in participants who received mRNA-1273 than in those who received placebo (Table 6).

A reduced level of viral replication (viral load) was found in COVID-19 cases in mRNA-1273 recipients compared with that in placebo recipients (Section 2.7.3.2.1.1). In contrast to the a priori hypothetical concern for risk of more severe disease (VAERD) being observed in vaccine recipients, those participants who received mRNA-1273 and experienced COVID-19 had milder disease compared with participants who received placebo and experienced COVID-19 (based on symptom scores during the 28 days after onset) (Study 301 Part A CSR, Section 6.3.1). In addition, as a further sign of the absence of VAERD, the point estimates for VE were highest for severe disease, lower for any disease, and lowest for asymptomatic infection (Table 6).

2.5.5.6.6 Analysis of Adverse Events of Interest

2.5.5.6.6.1 Study 301 Part A

As described in Section 2.5.5, ad hoc analyses of AEs of interest were performed in Study 301 by searching the database using SMQs or CMQs for the following events of interest: anaphylactic reaction, angioedema, arthritis, cardiomyopathy, CNS vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, vasculitis, autoimmune disorders, dermal filler reaction post vaccination.

Potential imbalances were observed for hypersensitivity (2.2% mRNA-1273 group; 1.8% placebo group) (Section 2.7.4.2.1.4.6). Hypersensitivity events for which larger imbalances between the groups were observed were consistent with reactogenicity of the vaccine; injection site urticaria and injection site rash were reported for 0.3% and 0.2% of mRNA-1273 participants, respectively, compared with <0.1% each in placebo participants.

In the anaphylaxis SMQ, 9 events were reported for 5 participants (< 0.1%) in the mRNA-1273 group and 18 events were reported for 8 participants (< 0.1%) in the placebo group (Section 2.7.4.2.1.4.6). No anaphylaxis was reported within 30 minutes after any injection (Section 2.7.4.2.1.3.5). Anaphylactic reaction of unknown cause was reported for 2 participants in the mRNA-1273 group as nonserious moderate events approximately 2 months after the second dose; both were considered by the investigator to be not related to IP and resolved on the same day with concomitant medications (Section 2.7.4.2.1.4.6).

In the dermal filler post-vaccination CMQ, 20 participants (0.1%) in the mRNA-1273 group and 14 participants (< 0.1%) in the placebo group had at least one TEAE, and no imbalance was apparent for any individual PT. None of the participants had reported dermal filler reaction post-vaccination in their medical history. When queried specifically after the interim analysis for history of dermal filler use, 325 participants (2.1%) in the mRNA-1273 group and 234 participants (1.5%) in the placebo group reported history of dermal filler use.

In the CNS vascular disorders SMQ, 21 participants (0.1%) in the mRNA-1273 group and 11 participants (< 0.1%) in the placebo group experienced at least one TEAE. For all events in the category, the difference between the mRNA-1273 and placebo groups was more pronounced among participants ≥ 65 years of age (11 participants vs. 4 participants, respectively) than among participants ≥ 18 to < 65 years of age (10 participants vs. 7 participants, respectively). Imbalances were also noted for subarachnoid hemorrhage (4 participants vs. 0 participants, respectively) and subdural hematoma (3 participants vs. 0 participants, respectively), but these events were related to trauma (with precipitating events not considered by the investigator to be related to mRNA-1273) and are not indicative of a vascular disorder. No cases of thrombosis with thrombocytopenia syndrome were reported.

In the hematopoietic cytopenia SMQ, thrombocytopenia was reported for 5 participants in the mRNA-1273 group and 1 participant in the placebo group. The events were not associated with thrombosis and none were considered by the investigator to be related to IP. One participant in each group had an SAE of grade 4 thrombocytopenia. For the participant in the mRNA-1273 group, the SAE occurred approximately 40 days after the second dose and at the same time the participant had severe bacterial pyelonephritis, acute renal failure, and nephrolithiasis. The other thrombocytopenia TEAEs in the mRNA-1273 group were all mild and occurred on Days 25, 57, 60, and 153.

No other potential imbalances were identified among other SMQ or CMQ categories.

2.5.5.6.6.2 Study 201

In Study 201, ad hoc analyses of AEs of interest were performed by searching the database for the following SMQs: angioedema, arthritis, convulsions, demyelination, hypersensitivity, peripheral neuropathy, and vasculitis (Section 2.5.5). The incidence of hypersensitivity was similar between the mRNA-1273 total group (11/400 [2.8%]) and placebo group (6/200 [3.0%]). More participants in the mRNA-1273 50 µg group (9/200 [4.5%]) reported hypersensitivity TEAEs than in the mRNA-1273 100 µg group (2/200 [1.0%]) (Section 2.7.4.2.3.3.3.3).

2.5.5.7 Rates of Adverse Events in Subgroups

Study 301 Part A data for solicited ARs and unsolicited AEs were summarized by subgroups based on age group, baseline SARS-CoV-2 status, race, ethnicity, sex, risk factors for severe COVID-19, and autoimmune disorders at baseline. Subgroup summaries were not provided for Studies 201 or 101, but data presentations by age-based enrollment or randomization cohort permit summaries by subgroups based on age group. Age group boundaries differed slightly across studies, as follows:

- Study 301 age groups were 18 to < 65 years and ≥ 65 years; age subgroups were 18 to < 65 years, 65 to < 75 years, 75 to < 85 years, and ≥ 85 years.
- Study 201 age groups were 18 to <55 years and ≥ 55 years.
- Study 101 age groups were 18 to 55 years, 56 to 70 years, and ≥ 71 years.

2.5.5.7.1 Study 301 Part A

2.5.5.7.1.1 Solicited Adverse Reactions in Subgroups

Age Group

In Study 301, the incidence of solicited local and systemic ARs after either injection in the mRNA-1273 group was lower among older adults (≥ 65 years) than among younger adults (≥ 18 to < 65 years) (Section 2.7.4.5.1.1.1). No differences were apparent between the age subgroups for the most frequently reported ARs, AR severity, or duration of solicited local or systemic ARs after the first or second injection.

Baseline SARS-CoV-2 Status

In the Safety Set, 347 participants in the mRNA-1273 group and 337 participants in the placebo group had positive baseline SARS-CoV-2 status (Section 2.7.4.5.1.2). Results among participants

with negative baseline status reflect those of the overall population. Participants who were SARS-CoV-2 positive at baseline had rates of solicited ARs similar to those among baseline negative participants (Study 301 CSR Part A, Table 7-8 and Table 7-9).

Race and Ethnicity

Compared with those who reported White race, participants who reported Black or African American race appeared to have lower incidence of solicited local ARs overall and for all reactions except axillary swelling or tenderness after the first injection, while the incidence of systemic ARs appeared to be similar between the subgroups (Section 2.7.4.5.1.3.1). After the second injection, participants who reported Black or African American race appeared to have a lower incidence of local and systemic ARs compared with those who reported White race. Numbers of other subgroups by race were too low for meaningful comparison.

Sex

In Study 301 after both the first and second injections, female participants appeared to have a higher incidence of local and systemic ARs compared with male participants (Section 2.7.4.5.1.4.1).

2.5.5.7.1.2 Unsolicited Adverse Events in Subgroups

Age Group

In Study 301, analysis of unsolicited TEAEs by age group did not reveal any clinically relevant imbalances between the mRNA-1273 and placebo groups compared with the overall population (Section 2.7.4.5.1.1.2). The incidence of unsolicited TEAEs was similar in both the younger (≥ 18 to < 65 years; 29.7% of 22,826 participants) and older (≥ 65 years; 30.6% of 7520 participants) age groups; this was also true for TEAEs assessed as treatment-related by the investigator.

Baseline SARS-CoV-2 Status

Among participants with positive baseline SARS-CoV-2 status, incidence of TEAEs was numerically lower in the mRNA-1273 group (22.2%) than in the placebo group (27.3%) and compared with the incidence in the overall mRNA-1273 population (Section 2.7.4.5.1.2.2). Incidence was similarly lower for severe TEAEs, SAEs, MAAEs, and TEAEs considered related (as assessed by the investigator) to treatment.

Race and Ethnicity

In Study 301, the incidence of unsolicited TEAEs was similar across the race and ethnicity groups (Section 2.7.4.5.1.3.2).

Sex

In Study 301, the observed incidence of unsolicited TEAEs during the 28-day follow-up was higher in females (35.5% of 7266 participants in the mRNA-1273 group) and lower in males (27.4% of 7918 participants in the mRNA-1273 group) (Section 2.7.4.5.1.4.2). The reported TEAEs by preferred term were similar for both sexes, and the most common TEAEs were headache, fatigue, headache, myalgia, and arthralgia.

Risk Factors for Severe COVID-19 and Comorbidities

The incidence of unsolicited TEAEs up to 28 days after any IP administration in the mRNA-1273 group was 34.5% in the At Risk subgroup (3448 participants) and 30.4% in the Not At Risk subgroup (11,736 participants) groups (Section 2.7.4.5.1.5). As expected based on their medical history and comorbidities, SAEs were reported at a higher rate among participants in the At Risk group (1.0% in the mRNA-1273 group) compared with those in the Not At Risk group (0.5% in the mRNA-1273 group).

Among participants with HIV, the incidence of unsolicited TEAEs up to 28 days after any IP administration was generally similar between the mRNA-1273 group (35/94 participants [37.2%]) and the placebo group (38/91 participants [41.8%] (Section 2.7.4.5.1.5).

Participants with Autoimmune Disorders at Baseline

Among the 2296 participants for whom an autoimmune disorder was reported at baseline, the incidence of unsolicited TEAEs up to 28 days after any injection was 35.0% compared with 30.0% in the overall population. However, even in this large population of participants with at least one autoimmune disorder at baseline, no notable difference in TEAE incidence was observed between the mRNA-1273 group (36.7% of 1152 participants) and the placebo group (33.2% of 1144 participants) (Section 2.7.4.5.1.6).

2.5.5.7.2 Study 201

In Study 201, no differences were apparent between the age cohorts for the most frequently reported ARs, AR severity, or duration of solicited local or systemic ARs after the first or second injection (Section 2.7.4.5.1.1.1).

Age group cohorts were too small in Study 201 for meaningful comparisons of unsolicited TEAEs, but findings were not inconsistent with those of Study 301 (Section 2.7.4.5.1.1.2).

2.5.5.7.3 Study 101

Solicited ARs were summarized only by age group for Study 101 as discussed in Section 2.5.5.4.3.

Unsolicited AEs were summarized by age group for Study 101. Results are summarized in Section 2.5.5.5.1.3.

2.5.5.8 Relatedness of Adverse Events to Study Vaccine

2.5.5.8.1 Study 301 Part A

More participants in the mRNA-1273 group (13.6%) than in the placebo group (8.2%) had unsolicited TEAEs during the 28-day follow-up that were assessed by the investigator as related to IP (Section 2.7.4.2.1.3.4). Most of the imbalance is in events that were also solicited ARs (injection site events, headache, nausea, vomiting, pyrexia, chills) or were similar to ARs (lymphadenopathy, neck pain, back pain, and musculoskeletal pain).

2.5.5.8.2 Study 201

In Study 201, more participants had unsolicited TEAEs assessed by the investigator as treatment-related up to Day 57 in the mRNA-1273 total group (43/400 participants [10.8%] with 80 events) than in the placebo group (13/200 participants [6.5%] with 18 events) (Section 2.7.4.2.3.2.4). The incidence of treatment-related TEAEs was higher in the mRNA-1273 100 µg group than in the 50 µg group, (27/200 participants [13.5%] versus 16/200 [8.0%], respectively). The higher incidence of treatment-related TEAEs reported by participants who received mRNA-1273 at 100 µg was attributed to the higher frequency of injection site reactions (eg, injection site pain, erythema, induration, swelling) that were reported as unsolicited TEAEs.

2.5.5.8.3 Study 101

In Study 101, unsolicited AEs were deemed related to mRNA-1273 in 33%, 13%, and 23% of participants who were 18 to 55 years of age, 56 to 70 years of age, and ≥ 71 years of age (Section 2.7.4.2.4.2.4).

2.5.5.9 Study 301 Part B

As described in Section 2.5.1.4.2, after EUA was granted for mRNA-1273 and another mRNA COVID-19 vaccine, Part B, the open-label observational phase of the study, was initiated. The Study 301 CSR Addendum 1 (Part B) includes open-label unblinded data from the PDV through the data cutoff (26 Mar 2021) for participants who completed the PDV. Unblinding was performed at the PDV and any subsequent treatment was open-label. Safety data were collected during this period for SAEs, MAAEs, TEAEs leading to discontinuation from study participation, and pregnancies. The Study 301 Part B safety data are consistent with findings in Part A; no new safety signals were detected (Section 2.7.4.2.2).

2.5.5.9.1 Study 301 Part B Safety

Safety results from Study 301 Part B were consistent with those from Part A (Section 2.7.4.2.2.2).

A total of 12 participants died in Part B: 1 participant in the placebo group, 3 participants in the placebo-mRNA-1273 group, and 8 participants in the mRNA-1273 group (Table 15; Section 2.7.4.2.2.2).

Table 15 Study 301 Participants with Serious Adverse Events Resulting in Death (Part B; Open-Label Phase; Safety Set)

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Sudden death	182	Not related
mRNA-1273	Cardiac arrest	155	Not related
mRNA-1273	Myocardial infarction	95	Not related
mRNA-1273	Acute myocardial infarction	184	Not related
mRNA-1273	Cerebrovascular accident	212	Not related
mRNA-1273	Head injury	180	Not related
mRNA-1273	Pulmonary embolism, pulseless electrical activity, gastrointestinal hemorrhage	138	Not related
mRNA-1273	Pulmonary mass[b]	136	Not related
Placebo–mRNA-1273	Cardiac failure congestive, gastrointestinal hemorrhage, anticoagulation drug level above therapeutic	27[c]	Not related
Placebo–mRNA-1273	Accidental overdose	10[c]	Not related
Placebo–mRNA-1273	Cerebrovascular accident	44[c]	Not related
Placebo	Ventricular arrhythmia	128	Not related

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]

Abbreviation: IP = investigational product.

[a] Relationship is based on investigator assessment.

[b] This participant's event began during Part A but the fatal outcome occurred during Part B.

[c] This is the number of days since the first dose of mRNA-1273 in Part B.

Source: Section 2.7.4 Table 22.

At least 1 SAE was reported for 296 participants (1%) in Study 301 Part B (Section 2.7.4.2.2.2.2), 141 (0.9%) in the mRNA-1273 group, 7 (0.3%) in the placebo group, and 148 (1.2%) in the placebo-mRNA-1273 group (Study 301 CSR Addendum 1 [Part B] Table 14.3.1.32.1.1). Serious AEs that were considered by the investigator to be related to treatment were reported only in the placebo-mRNA-1273 group and included severe paresthesia, severe muscular weakness, spontaneous abortion, and moderate autoimmune thyroiditis (see Section 2.7.4.2.2.2.2 for details). Anaphylactic reaction was reported for 2 participants in the placebo-mRNA-1273 group and 1 participant in the mRNA-1273 group (see Section 2.7.4.2.2.2.2 for details).

Six participants in the placebo-mRNA-1273 group discontinued IP due to an SAE; none of the events were considered related to IP (Section 2.7.4.2.2.2.2).

2.5.5.10 Pregnancy

Pregnant women were excluded from enrollment in the clinical trials. Pregnancies were reported in Study 301 and Study 201 and are summarized below.

2.5.5.10.1 Study 301 Part A

According to the Study 301 safety database, 27 pregnancies were reported during Part A: 16 pregnancies in the mRNA-1273 group and 11 pregnancies in the placebo group (Table 16). Of the outcomes known as of 04 May 2021, 1 participant in the placebo group experienced a live birth. Five participants (2 in the mRNA-1273 group and 3 in the placebo group) experienced spontaneous abortion/miscarriage. Two participants (1 in each group) underwent elective termination of pregnancy.

Table 16 Study 301: Incidence of Pregnancies Reported in Part A and Outcomes (Safety Set)

	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Number of pregnancies	11	16	27
Known pregnancy outcomes	5	3	8
Live born	1[a, b]	0	1
Spontaneous abortion/miscarriage	3	2	5
Elective termination	1	1	2[c]
Other maternal/gestational complications	1[a, b]	0	1
Unknown outcome/lost to follow-up	2[d, e]	1[d]	3

[a] Baby was born at 37 weeks with congenital anomalies of bilateral talipes equinovarus and hydronephrosis.

[b] The mother of the baby with talipes equinovarus and hydronephrosis had polyhydramnios and gestational diabetes.

[c] There were no reported pregnancy complications in either group.

[d] No response to follow up requests in 1 subject in each group with expected dates of delivery prior to data cut off of 04 May 2021.

[e] One subject was categorized as study lost to follow-up.

Source: Section 2.7.4 Table 36.

2.5.5.10.2 Study 301 Part B

According to the Study 301 safety database, 37 pregnancies were reported during Part B; 19 pregnancies in the placebo-mRNA-1273 group and 18 pregnancies in the mRNA-1273 group (Table 17). Among known outcomes, 4 participants (3 in the placebo-mRNA-1273 group and 1 in the mRNA-1273 group) reported spontaneous abortion/miscarriage.

Table 17 Study 301 Open-Label Phase: Incidence of Pregnancies Reported in Part B and Outcomes (Safety Set; Participants Who Received Placebo in Part A and mRNA-1273 in Part B)

	Placebo (N=2514)	Placebo–100 µg mRNA-1273 (N=12648)	100 µg mRNA-1273 (N=15184)
Number of pregnancies	0	19	18
Known pregnancy outcomes		5	2
Spontaneous abortion/miscarriage		3	1
Elective termination		1[a]	
Unknown outcome/lost to follow-up		1	1

[a] No complications reported with pregnancy.

Source: Section 2.7.4 Table 37.

2.5.5.10.3 Study 201

No pregnancies were reported in Study 201 through Day 57 (Section 2.7.4.5.4.2). Two pregnancies were reported in the Study 201 safety database through Day 209 (1 participant in the mRNA-1273 50 µg group and 1 participant in the mRNA-1273 100 µg group); both resulted in miscarriage/spontaneous abortion and were reported as SAEs that were not considered by the investigator to be related to IP.

2.5.5.10.4 Study 101

No pregnancies were reported in Study 101 (Section 2.7.4.5.4).

2.5.5.10.5 Post-authorization Pregnancies

During post-authorization monitoring, a total of 2,559 cases related to mRNA-1273 use in pregnancy have been reported (Section 2.7.4.6.4.5.1). A total of 560 cases of mRNA-1273 use in lactating women have been reported. Please see Section 2.7.4.6.4.5.1 for details of post-authorization mRNA-1273 use in pregnancy and while breast feeding.

2.5.5.11 Overdose and Dependence Potential

Overdose is unlikely because mRNA-1273 is to be administered by a healthcare professional. The clinical consequence of mRNA-1273 overdose is unknown at this time, and there is no specific antidote for an overdose with mRNA-1273.

No cases of overdose were reported in the 3 mRNA-1273 clinical studies. The highest single dose of mRNA-1273 administered in the clinical studies was 250 µg (given IM twice, 28 days apart) in Study 101 to participants in the 18 to 55 years of age cohort.

No studies have been conducted to assess dependence potential; however, based on the mRNA-1273 mechanism of action, the vaccine is not considered to have dependence potential.

2.5.5.12 Worldwide Marketing Experience/Post-Authorization

mRNA-1273 is not currently marketed in any region. Since December 2020, mRNA-1273 has been available in the US under EUA and has received conditional approvals worldwide. As of 30 Jun 2021, 301,035,380 doses of mRNA-1273 have been distributed worldwide for use in adults 18 years of age and older.

Post-authorization data are summarized in Section 2.7.4.6 based on over 182.7 million doses administered in the post-authorization setting. Since initial authorization in the US and other countries, anaphylaxis, myocarditis, and pericarditis have been added as important identified risks to the risk management plan (RMP). Post-authorization anaphylaxis is discussed in Section 2.7.4.6.4.1, and post-authorization myocarditis and pericarditis are discussed in Section 2.7.4.6.4.2. The important potential risk of vaccine-associated enhanced disease is discussed in Section 2.7.4.6.4.4.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 Therapeutic Context

2.5.6.1.1 Disease or Condition

As described in Section 2.5.1.2.1, an outbreak of COVID-19 began in Wuhan, Hubei Province, China in December 2019, and SARS-CoV-2 quickly spread globally (WHO 2020a). The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 Jan 2020 and declared COVID-19 a pandemic on 11 Mar 2020 (WHO 2020a; WHO 2020b). As of 26 Jul 2021, the WHO dashboard reports 4,162,304 COVID-19 deaths worldwide (WHO 2021a).

Individuals at highest risk of 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 lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, HIV infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease (CDC 2021b). Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19.

The majority of individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill (WHO 2021b). Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae (Carfi et al 2020; Halpin et al 2021). Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury (Puntmann et al 2020; Rajpal et al 2021; Sardari et al 2021; Huang et al 2020; Zhao et al 2020; and Peleg et al 2020).

While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

While most individuals with COVID-19 recover and do not require hospitalization, sequelae lasting weeks or even months after recovery from acute illness have been reported, even in those with mild illness. Some survive an acute COVID-19 infection but experience permanent damage to the lungs, heart, kidneys, or brain that causes ongoing chronic illness. Even among those without permanent organ damage, symptoms including fatigue, body aches, shortness of breath, headache, and difficulties with sleep, concentration, and physical activity may persist for more than 6 months (Logue et al 2021; Havervall et al 2021).

2.5.6.1.2 Prophylactic Therapies

Because the purpose of vaccination is different from that of treatment of infection (Section 2.5.1.2.2), the focus of this section is on vaccines only. In addition to many vaccines that remain under development, several vaccines against COVID-19 are currently available for use under various regulatory provisions in countries around the world, as follows:

- mRNA-based vaccines: Pfizer/BioNTech Comirnaty (BNT162b2); Moderna COVID-19 Vaccine (mRNA-1273; the subject of this application)

- Non-replicating: Adenovirus vaccine: AstraZeneca (Vaxzevria/Covishield); Janssen Vaccines (Johnson & Johnson) (JNJ-78436735; Ad26.COV2.S)

- Recombinant adenovirus vaccines: Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik V (rAd26 and rAd5); Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik Light (rAd26); CanSino Biologics Convidicea (PakVac, Ad5-nCov)

- Inactivated vaccines: Sinovac (CoronaVac); Beijing Institute of Biological Products (BBIBP-CorV); Bharat Biotech ICMR, Ocugen, ViroVax (Covaxin); Wuhan Institute of Biological Products, China National Pharmaceutical Group (WIBP-CorV); Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products (CoviVac); Research Institute for Biological Safety Problems (QazVac); Minhai Biotechnology Co, Kangtai Biological Products Co. Ltd. (Unnamed vaccine candidate); Shifa Pharmed Industrial Group (CovIran Barekat); Chinese Academy of Medical Sciences, Institute of Medical Biology (Unnamed vaccine candidate)

- Peptide vaccine: Federal Budgetary Research Institution State Research Center of Virology and Biotechnology (EpiVacCorona)
- Recombinant vaccine: Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences (ZF2001)
- Protein subunit vaccine: Center for Genetic and Engineering Biotechnology (Abdala); Medigen Vaccine Biologics, Dynavax (MVC-COV1901)
- Conjugate vaccine: Finlay Institute of Vaccines, Pasteur Institute (Soberana 02)

2.5.6.2 Benefits

The efficacy of mRNA-1273 to prevent COVID-19 has been confirmed in adults 18 years and older in Study 301. Analysis of the primary efficacy endpoint on the 04 May 2021 dataset showed a VE of 93.2% (95% CI 91.0%, 94.8%, $p < 0.0001$), based on the hazard ratio for a total of 799 adjudicated COVID-19 cases (55 cases in the mRNA-1273 group and 744 cases in the placebo group). These results are consistent with the results from the interim and primary analyses conducted in November 2020, confirming persistent, high efficacy over a substantially larger case database for a median observation period of over 5.3 months. At the 11 Nov 2020 interim analysis, a total of 95 adjudicated COVID-19 cases (5 cases in the mRNA-1273 group and 90 cases in the placebo group) resulted in VE of 94.5% (95% CI 86.5%, 97.8%, $p < 0.0001$), rejecting the null hypothesis of VE ≤ 30% and achieving the prespecified efficacy boundary. The subsequent primary analysis conducted on 25 Nov 2020 had a total of 196 adjudicated COVID-19 cases (11 cases in the mRNA-1273 group and 185 cases in the placebo group) and VE was observed to be 94.1% (95% CI 89.3%, 96.8%, $p < 0.0001$), based on the hazard ratio.

The Study 301 population included adults with recognized risk factors for complications of COVID-19, including participants of older age and those with underlying medical comorbidities. This study also included racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of mRNA-1273 was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females, and in White participants and communities of color.

Importantly, analysis of the 04 May 2021 dataset also showed that mRNA-1273 100 µg was 98.2% effective in preventing severe COVID-19, with 106 adjudicated cases of severe COVID-19 in the placebo group and 2 adjudicated cases in the mRNA-1273 group. Subgroup analyses of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of

participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, mRNA-1273 was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of mRNA-1273 (VE of 92.8% based on HR).

mRNA-1273 also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0% and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0%.

Study 301 demonstrated that the 100 μg dose level was highly immunogenic through Day 57 as measured by both bAb and nAb in both SARS-CoV-2 baseline-negative and baseline-positive individuals. In SARS-CoV-2 baseline-positive participants, antibody levels at Day 29 were similar to those observed at Day 57 in baseline-negative participants, indicating that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection. Study 201 and Study 101 provided evidence of persistence of immune response through Day 209, 6 months after the second injection of mRNA-1273, although antibody levels at Day 209 were lower than peak values.

2.5.6.2.1 Uncertainties and Limitations of Benefits

While observed VE in Study 301 is very high, and even higher against severe COVID-19, protection cannot be guaranteed for all vaccine recipients. Out of 14,287 participants who received 2 doses of mRNA-1273 approximately 28 days apart, 55 participants (0.4%) experienced symptomatic COVID-19 disease (as assessed by the adjudication committee). The following are uncertainties and limitations of the mRNA-1273 benefits:

- Duration of vaccine protection is unknown beyond 6 months post vaccination. As the analyses in this application are limited to a median of 6 months of follow-up, it is not possible to assess sustained protection over a period longer than 6 months. No waning of protection has been observed in the 6-month observation period.

- mRNA-1273 has not been studied in immunocompromised populations (other than individuals with HIV) or in patients on immunosuppressive medications and therefore the benefit in immunocompromised individuals is unknown. The VE of mRNA-1273 may be lower in immunocompromised individuals.

- If waning of protection is observed with follow-up (ie, after 6 months), a booster dose may be needed.

- Study 301 provided limited information on VE of mRNA-1273 against variants, and the sample size was small. For VOC, the VE point estimate (95% CI) based on the hazard ratio for 16 participants in the placebo group and 3 in the mRNA-1273 group was 82.4% (40.4%, 94.8%). For the California variants B.1.427 and B.1.429 combined, the VE point estimate (95% CI) based on the hazard ratio for 15 participants in the placebo group and 3 in the mRNA-1273 group was 81.2% (36.1%, 94.5%).

- Risk factors for vaccine failure have not been identified, based on available data from Study 301.

Nevertheless, these uncertainties and limitations do not diminish the findings that mRNA-1273 is highly effective in preventing COVID-19, and importantly, in preventing severe COVID-19.

2.5.6.3 Risks

The safety of mRNA-1273 in controlled clinical studies is based largely on data from Study 301. The safety analyses in Study 301 included 30,346 study participants who received at least 1 dose of IP, and the study population was representative of those at risk of SARS-CoV-2 infection and/or at risk of severe COVID-19; 15,184 participants received at least 1 injection of 100 µg mRNA-1273 and 15,162 participants received at least 1 injection of placebo. In the Phase 3 trial, there were male (52.6%) and female (47.4%.) participants, of whom the majority was White (79.2%), followed by Black or African American (10.2%), and Asian (4.6%). A total of 24.8% of participants were ≥ 65 years of age. Participants who were 18 to < 65 years of age and had risk factors for severe COVID-19 made up 16.7% of the overall population. In the total study population, participants had the following risk factors: diabetes (9.6%), severe obesity (7.0%), significant cardiac disease (5.0%), chronic lung disease (4.8%), liver disease (0.7%), and HIV infection (0.6%). The majority of participants were seronegative at baseline for SARS-CoV-2, except for 684 participants (2.3%) with a positive baseline serostatus.

The safety follow-up in Study 301 is based on a median (range) of 183 days (1 to 218 days) post second dose for participants who received both injections; for Study 201 through Day 57 with supplemental safety reported through Day 209; and for Study 101 through Day 119 with supplemental safety data reported through Day 209. Participants in the clinical trials will be followed until 24 months after the second dose (Study 301) or 12 months after the second dose (Study 201 and Study 101).

In summary, the type, incidence, and severity of ARs and TEAEs reported with mRNA-1273 in clinical trials were consistent with the clinical trial data previously submitted in support of

authorization. No unexpected safety findings were identified. In the post-authorization period, a total of 301,035,380 doses have been distributed, and the data show mRNA-1273 has an acceptable safety profile.

Solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with those who received placebo after both the first and second doses. While the severity of solicited symptoms increased after the second mRNA-1273 dose, relative to the first dose, the majority of ARs were mild-to-moderate in severity. The most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the solicited local and systemic ARs occurred within the first 2 days after administration of mRNA-1273 and generally persisted for 1 to 3 days. In the mRNA-1273 group, pain was the most common grade 3 solicited local AR, and grade 3 pain was more common after the second injection than after the first. Fatigue and headache were the most commonly reported grade 3 systemic ARs in the mRNA-1273 group after the first injection and second injection. The local and systemic ARs are considered risks with minimal and temporary clinical impact.

Hypersensitivity events were more common among mRNA-1273 participants than placebo participants, however, most imbalance was due to injection site urticaria and rashes. In Study 301, anaphylaxis, a potentially life-threatening hypersensitivity reaction that can occur after any vaccination was not reported within 30 minutes after injection with mRNA-1273. Participants with a medical history of anaphylaxis were not excluded from Study 301; 0.2% of participants in the mRNA-1273 group had a medical history of anaphylaxis. In Part A, anaphylactic reaction was reported for 2 participants in the mRNA-1273 group as nonserious events of moderate severity that occurred approximately 2 months after the second injection and were considered by the investigator to be not related to IP. Anaphylaxis in closer temporal relationship to mRNA-1273 vaccination has been reported in the post-authorization period, and the risk has been described in the mRNA-1273 Company Core Data Sheet under Special Warnings and Precautions for Use and Adverse Drug Reaction sections together with appropriate risk minimization strategies.

No cases of myocarditis have been reported in Study 301. Pericarditis was reported 4 participants, 2 each in the mRNA-1273 and placebo groups during Part A (all SAEs; Table 13), with 1 female and 1 male participant in each group having an SAE of pericarditis reported. There was no evidence of an increased risk of pericarditis in the mRNA-1273 group. In addition, the careful review of symptoms suggestive of myocarditis did not identify a concern (Section 2.7.4.2.1.3.2.1).

Cases of myocarditis and pericarditis have been spontaneously reported by healthcare professionals or patients during the post-authorization period following the use of mRNA COVID-19 vaccines, including the Moderna COVID-19 vaccine. In view of the large extent of exposure to the vaccine, these cases are considered to be rare occurrences. They suggest increased risks of myocarditis and pericarditis in young males, particularly following the second injection. Onset of symptoms has reportedly been within a few days following receipt of vaccine. Available post--authorization data from short--term follow-up suggest that most cases have been mild, with resolution of symptoms; however, information is not yet available about potential long-term sequelae. The risk has been described in the mRNA-1273 company Core Data Sheet under Special Warnings and Precautions for use and Adverse Drug Reaction sections in the patient leaflet where patients have been informed to seek medical attention in case of symptoms (ie, chest pain, shortness of breath, feeling of having a fast-beating, fluttering, or pounding heart).

In Study 301 the DSMB continuously monitored case counts of COVID-19 and severe COVID-19 (based on prespecified criteria) for any indication of higher disease incidence and/or severity in the mRNA-1273 group compared with the placebo group that might have suggested a risk of vaccine harm in the form of VAERD. The prespecified criteria for VAERD have not been met at any time during the study. Fewer cases of COVID-19 or severe COVID-19 have been observed in participants who received mRNA-1273 than in those who received placebo. A reduced viral load was found in COVID-19 cases in mRNA-1273 recipients compared with placebo recipients. In contrast to the a priori hypothetical concern for risk of more severe disease (VAERD) being observed in vaccine recipients, those participants who received mRNA-1273 and experienced COVID-19 had milder disease compared with participants who received placebo and experienced COVID-19 (based on symptom scores during the 28 days after onset). In addition, as a further sign of the absence of VAERD, the point estimates for VE were highest for severe disease, lower for any disease, and lowest for asymptomatic infection. The available data ie, nonclinical studies, neutralizing capacity of antibodies did not raise a concern regarding VAERD, and these clinical data do not provide a signal for a possible disease enhancement after vaccination with mRNA-1273.

2.5.6.3.1 Uncertainties

- Use in pregnancy and lactation has not been formally evaluated for mRNA-1273, and available data on the vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy or the effects of the vaccine on the breastfed infant or on milk production or excretion. Animal studies do not indicate direct or indirect

harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development. A DART study with mRNA-1273 was completed in December 2020 with no adverse findings. Pregnant women were excluded from the clinical studies included in this submission, although a low number of incidental pregnancies were reported (16 pregnancies in mRNA-1273 recipients in Study 301 Part A; 37 pregnancies in Study 301 Part B; 2 pregnancies in mRNA-1273 recipients in Study 201). The Sponsor is initiating an observational pregnancy outcome study (Study 902; Section 2.5.1.4.2) with prospective data collection to assess maternal and infant outcomes in pregnant women who receive mRNA-1273. Additionally, Study 904 (Section 2.5.1.4.2), a post-authorization active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine includes use in pregnancy. In the post-authorization period, a total of 2559 cases related to use in pregnancy have been reported. The data reviewed do not represent any new safety issues of concern and do not identify a change to the benefit-risk profile for the pregnant or their neonates. Cumulatively, there were 560 cases of use in lactating women/related to lactation, with a total of 579 cumulative lactation related events. Upon review of the lactation related reports, no unusual significant patterns were noted that would change the benefit risk profile of the use of vaccination while breastfeeding.

- In Study 301, subgroup analyses with older adults, participants with risk factors for severe COVID-19, participants with HIV, and participants with autoimmune disorders showed good tolerability and no apparent imbalances in TEAEs were observed. Use of mRNA-1273 in immunocompromised individuals, frail individuals with unstable health conditions, and individuals with autoimmune or inflammatory disorders require further evaluation. As outlined in Section 2.5.1.4.2 and the RMP, the Sponsor has initiated post-authorization real-world safety studies in the US and in Europe that aim to assess use in these populations.

- The mRNA-1273 clinical studies prohibited administration of other vaccines within 28 days before or after any dose of IP, except for the influenza vaccine that was prohibited within 14 days before or after any dose of IP. As such, co-administration with other vaccines, or administration within 14 to 28 days of other vaccines remains to be characterized. The safety of concomitant use with other vaccines is investigated post-authorization in Study 904 (Section 2.5.1.4.2), a post-authorization active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 vaccine.

- Long-term safety data are not yet available; however, 6 months of safety data are included in this submission, and safety follow-up continues in ongoing studies. At the time of this submission, the safety follow-up in Study 301 is based on a median of 6 months of follow-up post second injection. Long-term safety beyond 6 months remains to be characterized through continued follow-up in the ongoing studies as well as through routine pharmacovigilance during post-authorization.

2.5.6.4 Benefit-Risk Assessment

Based on the efficacy results from the Phase 3 study, mRNA-1273 prevents COVID-19 and, importantly, prevents severe COVID-19. The demonstrated clinical benefit of mRNA-1273 is supported by evidence of a robust immune response both in terms of bAbs and nAbs as well as the induction of CD4+ T-cells with a Th-1 dominant phenotype. Based on administration of mRNA-1273 to 15,704 adults across Study 301, Study 201, and Study 101, there have been no emergent safety concerns; the AE profile is predominantly characterized by mild to moderate reactogenicity lasting 2 to 3 days.

Statistically significant VE to prevent COVID-19 was demonstrated in adults ≥ 18 years of age during the ongoing pandemic. Vaccine efficacy was 94.1%, 94.5%, and 93.2% at the interim, primary, and final efficacy analyses, respectively, confirming persistent, high efficacy in a substantially larger case database over a longer median blinded observation period of 5.3 months. These VE point estimates far exceeded regulatory guidance which suggested 50% efficacy with a lower bound CI of at least 30% for vaccines in development during the pandemic (DHHS 2020). Importantly, mRNA-1273 was 98.2% effective in preventing severe COVID-19; this is a clinically relevant result because severe COVID-19 is associated with increased hospitalizations and mortality (CDC 2021b). Subgroup analyses of VE to prevent adjudicated severe COVID-19 showed consistent high efficacy in participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection, patients who are among those at highest risk for the severe complications of COVID-19.

mRNA-1273 also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0%, and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0%.

mRNA-1273 clinical benefit was consistent across subgroups, including: older vs. younger adults; those with or without risk factors for complications of COVID-19; males and females; and in participants who were White as compared with those from communities of color. The

efficacy of mRNA-1273 is supported by the immune response observed in Study 301, Study 201, and Study 101 that was consistent across age groups and persisted over 6 months after the second injection of mRNA-1273 in Study 101 and Study 201.

Vaccination with mRNA-1273 generally resulted in transient local injection site and systemic reactions and were noted to occur at a lower frequency in older adults compared with younger adults. The majority of the ARs were considered risks with minimal and temporary clinical impact.

The incidence of SAEs was low, and rates were similar in the mRNA-1273 and placebo groups. Unsolicited TEAEs in the 28 days after any injection occurred at similar rates in the mRNA-1273 and placebo groups. The higher rate of unsolicited TEAEs considered treatment-related by the investigator among mRNA-1273 participants was largely driven by events that mapped to solicited ARs. Certain AEs of theoretical interest for COVID-19 vaccines were carefully assessed in the blinded study phase of Study 301. mRNA-1273 was highly efficacious in preventing COVID-19 and severe COVID-19, and this efficacy has been sustained, dispelling concerns of VAERD. No significant clinical findings were identified from the SMQ/CMQ searches performed for the analyses of AEs of interest for COVID-19 vaccines.

The safety profile of mRNA-1273 has been well characterized on the basis of controlled clinical study data included in this submission from more than 15,704 participants exposed to mRNA-1273 with a median follow-up of approximately 6 months in the Phase 3 study, Part A and Part B inclusive.

Outside the clinical studies, the number of persons vaccinated with COVID-19 vaccines within the period since authorization has been unprecedented in vaccine history. The rollout of COVID-19 vaccines has also been associated with extensive post-authorization safety monitoring noted as the most intensive safety monitoring in US vaccine history. In addition to surveillance through Vaccine Adverse Event Reporting System and Vaccine Safety Datalink, the CDC implemented a new smart phone tool v-safe to allow individuals to report any AE following COVID-19 vaccination. These efforts have resulted in a uniquely large safety database achieved only within months following authorization, allowing the rapid detection of rare AEs in post-authorization.

A total of 301,035,380 doses of the Moderna COVID-19 vaccine have been distributed in the post authorization period, and the safety data show mRNA-1273 has an acceptable safety profile. In view of this very large exposure in post-authorization, rare cases of anaphylaxis, myocarditis, and pericarditis events have been reported during the post-authorization period from healthcare

professionals and spontaneously reported from patients. These risks, considered manageable, have been described in product labels with their respective risk factors, and minimization measures. They also have been communicated to patients and caregivers in patient leaflets to be alert to signs and symptoms requiring medical attention. The Sponsor also has an RMP with ongoing studies to continue characterizing these important identified risks.

Based on the data presented in this submission, mRNA-1273 administered as two 100 µg doses given 28 days apart is a highly 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 available safety and efficacy data from the 3 clinical studies presented herein, and the ongoing post-authorization surveillance, the Sponsor considers that the known and potential benefits outweigh the known and potential risks for mRNA-1273.

2.5.6.4.1 Risk Management

Risks associated with mRNA-1273 are considered adequately managed with the product labels. An RMP is in place with ongoing studies including the continuation of the ongoing pivotal trial, Study 301, and other observational studies to further characterize important risks as well as the identified uncertainties (ie, use in pregnancy, long-term safety, use in immunocompromised or frail individuals). Routine pharmacovigilance will monitor for potential new ARs.

2.5.6.5 Indication Statement

mRNA-1273 is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

2.5.7 REFERENCES

Agrawal AS, Tao X, Algaissi A, Garron T, Narayanan K, Peng BH, et al. Immunization with inactivated Middle East respiratory syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Hum Vaccin Immunother. 2016;12(9):2351-56.

Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al; mRNA-1273 Study Group. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383(25):2427-38.

Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice

and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-15.

Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-5.

Centers for Disease Control and Prevention (CDC). Science Brief: SARS-CoV-2 Transmission. May 2021a. [cited 2021 Jun 11]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html.

Centers for Disease Control and Prevention (CDC). People with Certain Medical Conditions. May 2021b. [cited 2021 Jun 11]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

Chen Y, Lu S, Jia H, Deng Y, Zhou J, Huang B, et al. A novel neutralizing monoclonal antibody targeting the N-terminal domain of the MERS-CoV spike protein. Emerg Microbes Infect. 2017;6(5):e37.

Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol. 1969;89(4):449–63.

Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. Nature. 2020a; 586(7830):567-71. doi:10.1038/s41586-020-2622-0.

Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med. 2020b;383(16):1544-55. doi: 10.1056/NEJMoa2024671.

Corti D, Zhao J, Pedotti M, Simonelli L, Agnihothram S, Fett C, et al. Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus. Proc Natl Acad Sci U S A. 2015;112(33):10473-8.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics and Evaluation Research (US). Guidance for industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. [cited 2021 Jun 11]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. May 2021. [cited 2021 Jul 14]. Available from:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.

Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol. 2012;12(7):479-91.

Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-534. doi: 10.1016/S1473-3099(20)30120-1.

Escalante E, Golden RL, Mason DJ. Social isolation and loneliness: Imperatives for health care in a post-COVID world. JAMA. 2021;325(6):520–1. doi:10.1001/jama.2021.0100.

Fechter P, Brownlee GG. Recognition of mRNA cap structures by viral and cellular proteins. J Gen Virol. 2005;86(Pt 5):1239-49.

Halpin, SJ, McIvor, C, Whyatt, G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021;93(2):1013-22.

Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. JAMA. 2021;325(19):2015-16.

Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*. 2020;21(1):163. doi:10.1186/s12931-020-01429-6.

Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020;383(20):1920-31.

Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, et al. SARS-CoV-2 transmission from people without COVID-19 symptoms. JAMA Netw Open. 2021;4(1):e2035057. doi:10.1001/jamanetworkopen.2020.35057.

Johnson RF, Bagci U, Keith L, Tang X, Mollura DJ, Zeitlin L, et al. 3B11-N, a monoclonal antibody against MERS-CoV, reduces lung pathology in rhesus monkeys following intratracheal inoculation of MERS-CoV Jordan-n3/2012. Virology. 2016;490:49-58.

Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity. 2005;23(2):165-75.

Kim Y, Lee H, Park K, Park S, Lim JH, So MK, et al. Selection and characterization of monoclonal antibodies targeting Middle East respiratory syndrome coronavirus through a human synthetic fab phage display library panning. Antibodies (Basel). 2019;8(3):42.

Kozak M. An analysis of vertebrate mRNA sequences: intimations of translational control. J Cell Biol. 1991;115(4):887-903.

Logue, JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Netw Open. 2021;4(2): e210830.

Mansfield KE, Mathur R, Tazare J, Henderson AD, Mulick AR, Carreira H, et al. Indirect acute effects of the COVID-19 pandemic on physical and mental health in the UK: a population-based study. Lancet Digit Health. 2021;3(4):e217-e230. https://doi.org/10.1016/S2589-7500(21)00017-0.

Moderna TX, Inc. mRNA-1273. Investigator's brochure, 6th ed. Cambridge (MA); 2021a. 66p.

Moderna TX, Inc. (Cambridge; MA). mRNA-1273. Moderna mRNA-1273 biomarker concordance analysis report for protocol mRNA-1273-P301.; 2021b Apr 29. Protocol No.: mRNA-1273-P301. 25p.

Peleg Y, Kudose S, D'Agati V, Siddall E, Ahmad S, Nickolas T, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. Kidney Int Rep. 2020;5(6):940–45.

Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffman J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11):1265-73.

Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol. 2021;6(1):116-18. doi:10.1001/jamacardio.2020.4916.

Ritchie H, Ortiz-Ospina E, Beltekian D, Mathieu E, Hassell J, Macdonald B, et al. (2021) - "Coronavirus Pandemic (COVID-19)". [Online Resource] Published online at OurWorldInData.org. Available from: https://ourworldindata.org/coronavirus.

Rozenski J, Crain PF, McCloskey JA. The RNA Modification Database: 1999 update. Nucleic Acids Res. 1999;27(1):196-7.

Sardari A, Tabarsi P, Borhany H, Mohiaddin R, Houshmand G. Myocarditis detected after COVID-19 recovery. Eur Heart J Cardiovasc Imaging. 2021; 22(1):131-32. doi: 10.1093/ehjci/jeaa166.

Thomas SJ and Yoon IK. A review of Dengvaxia®: development to deployment. Hum Vaccin Immunother. 2019;15(10), 2295-314.

Tseng C-T, Sbrana E, Iwata-Yoskikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PloS One. 2012;7(4):e35421.

Wang L, Shi W, Chappell JD, Joyce MG, Zhang Y, Kanekiyo M, et al. Importance of neutralizing monoclonal antibodies targeting multiple antigenic sites on the Middle East respiratory syndrome coronavirus spike glycoprotein to avoid neutralization escape. J Virol. 2018;92(10);e02002-17.

Wang L, Shi W, Joyce MG, Modjarrad K, Zhang Y, Leung K, et al. Evaluation of candidate vaccine approaches for MERS-CoV. Nat Commun. 2015;6:7712.

Widjaja I, Wang C, van Haperen R, Gutiérrez-Álvarez J, van Dieren B, Okba NMA, et al. Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. Emerg Microbes Infect. 2019;8(1):516-30.

World Health Organization. Dengue vaccine: WHO position paper, September 2018 – recommendations. Vaccine. 2019;37(35):4848-49.

World Health Organization (WHO). Update 5 – general information on the virus and the outbreak. Feb 2020a. [cited 2021 Jun 11]. Available from: https://www.who.int/publications/m/item/update-5---general-information-on-the-virus-and-the-outbreak.

World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 Mar 2020. Mar 2020b. [cited 2021 Jun 11]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

World Health Organization (WHO). WHO coronavirus disease (COVID-19) dashboard. 2021a. [cited 2021 Jul 27]. Available from: https://covid19.who.int/.

World Health Organization (WHO). Update 54 – Clinical long-term effects of COVID-19. Mar 2021b. [cited 2021 Jun 11]. Available from: https://www.who.int/publications/m/item/update-54-clinical-long-term-effects-of-covid-19.

Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, et al. Prior Immunization with severe acute respiratory syndrome (SARS) – associated coronavirus (SARS-CoV) nucleocapsid

protein causes severe pneumonia in mice infected with SARS-CoV. J Immunol. 2008;181(9):6337-48.

Yu X, Zhang S, Jiang L, Cui Y, Li D, Wang D, et al. Structural basis for the neutralization of MERS-CoV by a human monoclonal antibody MERS-27. Sci Rep. 2015;5:13133.

Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. doi:10.1016/j.eclinm.2020.100463.

2.5.8 APPENDIX

2.5.8.1 Summary of Regulatory Agency Interactions

Correspondence type	Highlights	Milestone and Date
FDA: CBER		
Pre-IND		
Pre-IND meeting (Ref: PTS# PS005499) - written responses and clarifications	Preclinical studies to evaluate vaccine-induced disease enhancement P201 study design Non-clinical and clinical data package to submit prior to Phase 2 initiation	Pre-IND submission 19Mar2020 CBER Preliminary responses 27Mar2020 TC 10Apr2020 Revised responses from CBER 14Apr2020 and 17Apr2020
IND and P201 study		
IND submission and Fasttrack Designation	Fasttrack Designation granted Safe to Proceed (with P021) notification Initiation of mRNA-1273-P201 clinical study 4 Non-hold requests: - Include more enhanced monitoring of subjects who are confirmed to have SARS-CoV-2 infection; - Examine the clinical course and immune response in vaccinated individuals after natural infection; - Explore vaccine efficacy in preventing asymptomatic infection; - Extend study follow-up	MTX IND SN 0001 submitted on 27Apr2020 CBER response dated 6May2020 MTX response to CBER comments submitted on 21May2020 (IND SN 0003)
P301 design		
CBER feedback on P031 Trial Design Proposal	P301 design items discussed: - Data package prior to the start of the proposed pivotal efficacy study(ies); - Definition of VE and success criteria - Size of the safety database to support licensure - Proposed definition for at risk subjects to be included in the Phase 3 Additional points of interest: duration of the safety follow up ; considerations around stratification by age and by health risk level prior to randomization; exploration of the safety and efficacy of vaccine in subjects with previously undetected SARS-CoV-2 infection; clarification of clinical study assays;	MTX P301 proposal submitted 1May2020 (IND SN0002) CBER feedback dated 13May2020 MTX response addressing CBER comments submitted 27May2020 along with a draft mRNA-1273-P301 protocol incorporating CBER's feedback (IND SN 0004)

Correspondence type	Highlights	Milestone and Date
	considerations around bridging data between different neutralization assay platforms; considerations to include, as secondary or exploratory endpoints, an assessment of biomarkers or threshold of antibody levels which may correlate with protection from SARS-CoV-2 infection or development of COVID-19; examination of the immune response in vaccinated individuals after natural infection and to explore other potentially informative biomarkers	
CBER feedback on Phase 3 mRNA-1273-P301 protocol and follow up comments Protocol Amendment 1 (PA 1) Part 1	Discussions on: - The proposed primary endpoint, and the case definition for symptomatic COVID-19; - The VE and success criteria: follow up of discussions and CBER request for the following to be applied in the P3: "*The point estimate for vaccine efficacy (VE) should be at least 50%, in agreement with the minimum requirement given in the WHO Target Product Profile. In addition, a lower bound of >30% (with a point estimate of at least 50%) for the alpha-adjusted CI is necessary to ensure that a vaccine with a true efficacy of only 20-30% will not likely be declared effective. Therefore, we request that both your early and primary efficacy endpoint success criteria be defined as a VE point estimate of at least 50% with the lower bound of the appropriately alpha-adjusted CI around the VE point estimate being > 30%. In addition, we recommend that you apply a multiplicity adjustment to the analysis of the secondary efficacy endpoints to preserve the study-wise Type I error rate*." - The two interim analysis for efficacy proposed in the P3 protocol; - The DSMB and accompanying charter for continuous monitoring of the theoretical risk of enhanced disease	MTX response to CBER comments and mRNA-1273-P301 Phase 3 protocol submitted 27May2020 (IND SN 0004) CBER comments provided on 4Jun2020 regarding the P301 protocol. MTX response to CBER comments submitted on 1Jul2020 for the P301 design with PA 1 (IND SN 0007).
CBER feedback on Phase 3 mRNA-1273-P301 protocol and follow up comments Part 2	Discussion on the continuous monitoring of the theoretical risk of enhanced disease in the P301 study and submission of MTX Analysis Plan for the Data Safety Monitoring Board (version 1.0, 15Jul2020)	CBER follow up comments dating 20Jul2020 (based on IND SN 0007) MTX response to CBER comments submitted on 22Jul2020 (IND SN0015)

Correspondence type	Highlights	Milestone and Date
CBER feedback on Phase 3 mRNA-1273-P301 protocol and follow up comments Part 3	Discussion around the plan for harm monitoring and adaptation of the DSMB charter	CBER request dating 22Jul2020 (TC) MTX response to CBER comments submitted on 23Jul2020 (IND SN0017)
CBER feedback on Phase 3 mRNA-1273-P301 protocol and follow up comments Part 4	Discussions around the operational aspects of the interim analyses; and of different aspects linked to clinical operations (devices used during the study, eDiary Apps in patient's smartphones; telemedicine tools; etc)	CBER comments dated 20Jul2020 MTX response to CBER comments submitted on 5Aug2020 (IND SN 0020)
P301 PA 2	Purpose of Amendment to provide more intensive surveillance of symptoms and severity of cases of COVID-19 after the first dose of investigational product.	5Aug2020 (IND SN 0020)
CBER feedback on Phase 3 mRNA-1273-P301 protocol and follow up comments Part 5	Discussion on the inclusion of subjects with well-controlled HIV infection in the pivotal study.	CBER comments dated 7Aug2020 MTX responses submitted on 20 Aug (IND SN 0023) CBER agreement on 11Aug2020
P301 PA 3	Addition of HIV infection to the risk factors at Screening Addition of intent to enroll racial and ethnic minorities	SN0026 27Aug2020
mRNA-1273-P301 SAP	Statistical Analysis Plan Version 1	SN0036 18Sep2020
P301 PA 4	Alignment with SAP and increase upper limit of stratification for at risk participants to 50%	SN0042 02Oct2020
P301 PA 5	Clarification of eDiary prompts for safety surveillance weekly; Addition of Month 19 safety call	SN0074 19Nov2020
P301 PA 6	Informed all ongoing study participants of the availability of and eligibility criteria of any COVID-19 vaccine available under EUA and to offer participants who originally received placebo in P301 the potential benefit of vaccination against COVID-19, give the primary efficacy endpoint was met per the protocol-defined interim analysis.	SN0092 24Dec2020
P301 PA 7	Added information regarding collection of safety information on suspected cases of anaphylaxis and to include participant history of facial injections or dermal fillers in the eDiary.	SN0106 16Feb2021

Correspondence type	Highlights	Milestone and Date
iPSP		
iPSP	iPSP original submission (22July; SN0014) with a proposed single Phase 2, randomized, observer-blind, placebo-controlled, dose-finding, age-de-escalation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 Investigational Vaccine in healthy infants and toddlers from 6 months of age, children, and adolescents less than 18 years of age at the time of first vaccination (n = approximately 1000). A request for a partial waiver for infants <6 months of age based on the rationale that the vaccine may be unsafe and ineffective in this age group was included. CBER feedback: - CBER does not agree with the waiver request for children below 6 months of age - A study which will only include 100 subjects per dose per age cohort would not provide a safety database large enough to support an indication for use in the pediatric populations. - While vaccine effectiveness in pediatric populations could potentially be inferred from immunogenicity endpoints (e.g., an immunobridging from adult to pediatric populations), further discussion is needed on the appropriate effectiveness endpoints for pediatric studies MTX revised strategy: - proposed 2 pediatric studies (adolescent 12-<18; pediatric 6mos-<12y) and a deferral to start the <6mos study - deferral for completion until after BLA for all age groups - no waiver at this time	Request from CBER on the timeline for the iPSP submission and the plan for the L2L consistency study dated 26Jun2020 MTX submission of the iPSP and the rational to not perform a lot-to-lot consistency study based on an extensive analytical comparability plan dated 22Jul2020 (IND SN 0014) CBER feedback on the iPSP provided on 3Sep2020 MTX submission of revised iPSP dated 06Oct2020 (IND SN 0044) PIP submitted to EMA in parallel

Abbreviations: BLA = Biologics License Application; CBER = Center for Biologics Evaluation and Research; CI = Confidence Interval; COVID-19 = disease caused by the novel 2019 coronavirus; DMSB = data safety monitoring board; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; HIV = human immunodeficiency virus; IND = Investigational New Drug; IND SN = Investigational New Drug Sequence Number; iPSP = initial pediatric study plan; L2L = lot-to-lot consistency; MTX = Moderna Therapeutics; PA = protocol amendment; PIP = pediatric investigational plan; PTS = pre-application tracking system; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus that causes COVID-19 TC = Teleconference; VE = Vaccine Efficacy; WHO = World Health Organization.