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List of Abbreviations

Acronym	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AR	adverse reaction
ARDS	acute respiratory distress syndrome
bAb	binding antibody
BEST	Biologics Effectiveness and Safety
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CoVs	coronaviruses
COVID-19	coronavirus disease 2019
COVID-NET	Coronavirus Disease 2019-Associated Hospitalization Surveillance Network
DHHS	Department of Health and Human Services
ECG	electrocardiogram
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
GGT	gamma glutamyltransferase
GLSM	geometric least square mean
GM	geometric mean
GMFR	geometric mean fold ratio
GMR	geometric mean ratio
GMT	geometric mean titer
HAART	highly active anti-retroviral therapy
HELLP	hemolysis, elevated liver enzymes, low platelet count
HIV	human immunodeficiency virus
HLT	High Level Term
IA	interim analysis
ICU	intensive care unit
ID_{50}	50% inhibitory dose
ID_{80}	80% inhibitory dose
IM	intramuscular
IP	investigational product
KPSC	Kaiser Permanente Southern California
LLOQ	lower limit of quantification

Acronym	Definition
LNP	lipid nanoparticle
LS	least squares
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
mITT	modified intent to treat
mRNA	messenger ribonucleic acid
MSD	MesoScale Discovery
nAb	neutralizing antibody
polyA	polyadenylated
PP	Per Protocol
PsVNA	pseudovirus neutralization assay
PT	preferred term
RNA	ribonucleic acid
RT-PCR	reverse-transcriptase polymerase chain reaction
S-2P	spike protein with 2 proline substitutions within the heptad repeat 1 domain
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SMQ	standard Medical Dictionary for Regulatory Activities queries
SOC	system organ class
Study P204	Study mRNA-1273-P204
TEAE	treatment-emergent adverse event
TTO	time to onset
ULOQ	upper limit of quantitation
URTI	upper respiratory tract infection
UTR	untranslated region
VE	vaccine efficacy
WHO	World Health Organization

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Executive Summary

Product Development Rationale

The Applicant has developed a rapid response proprietary vaccine platform based on a messenger ribonucleic acid (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.

Based on this technology, the Applicant has developed a COVID-19 vaccine, mRNA-1273, that is currently authorized for immunization of adults 18 years of age and older in the United States (US), and for individuals 12 years of age and older in more than 41 countries, including the EU, Canada, and Japan.

Intended Use

This submission intends to extend the use of mRNA-1273 to include active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 6 years to 11 years of age.

Clinical/Pathophysiology of Condition

Since the beginning of the COVID-19 pandemic, hospitalizations and deaths associated with COVID-19 have occurred more frequently in adults (Ayoub et al 2021; CDC 2021c; Hay et al 2020); however, COVID-19 can also lead to severe outcomes in children and adolescents (Kim et al 2020; Havers et al 2021). From the start of the pandemic to May 2021, approximately 2.6 million cases of COVID-19 have been reported among children 5 to < 9 years of age and approximately 3.8 million have been reported among children 10 to 14 years of age in 105 countries (Unicef 2021). In the US, an excess of 2670 hospitalizations among children 5 to 17 years of age have been observed through 21 October 2021 with 28.5% requiring intensive care unit interventions and more than 500 deaths observed (CDC 2021c). A large cohort study found that children under 16 years of age with COVID-19 are at 37 times higher risk of myocarditis than the uninfected age and gender-matched control population (Boehmer et al 2021). Additionally, there is evidence of "long-COVID-19" in children even after mild infection (Dembiński et al 2021). Children and adolescents also can develop a life-threatening hyperinflammatory state, termed multisystem inflammatory syndrome in children (MIS-C), 4 to 6 weeks after infection with primary COVID-19 (Vogel et al 2021), often presenting with

persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021d). More than 5217 cases and 46 deaths meeting case definition of MIS-C have been reported in the US (CDC 2021m).

Changes in social policy, individual behavior, and viral dynamics are moving the burden of disease into younger age groups. Schools have opened at the same time as relaxed mask mandates and an increase in the number of cases caused by the highly transmissible B.1.617.2 Delta variant of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (CDC 2021e). Before the Delta wave of the pandemic, persons 17 years of age and younger comprised the lowest weekly cases and death rates per 100,000 population; however, in the current Delta wave, persons 12 years to 17 years of age have the highest case rates, followed closely by persons 5 years to 11 years of age (CDC 2021f). The hospitalization rate for children and adolescents has also increased with the spread of the Delta variant; rates rose each week to 1.4 per 100,000 children during the week ending 14 August 2021, which was 4.7 times the rate during the week ending 26 June 2021 and approached the peak hospitalization rate of 1.5 per 100,000 observed during the week ending 09 January 2021 (Delahoy et al 2021).

COVID-19 cases among students may lead to consequences such as school closures and remote learning (CDC 2021l), which can be detrimental to the education and mental health of students (AAP 2021). Vaccinating children 6 years to < 12 years of age with mRNA-1273 has the potential to help schools remain open for in-person education. Young children attending school represent a type of institutional setting in which the risk of virus transmission is high. If children are not vaccinated, they will remain a large, susceptible group capable of being infected with the virus and transmitting it to others. A mathematical modeling study demonstrated the importance of vaccinating children and adolescents and found that including these populations for vaccination could reduce overall COVID-related mortality across all age groups by 57% and reduce cases of "long COVID" by 75% (Shiri et al 2021).

Clinical Development of mRNA-1273 in Children

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

Study P204 is being conducted in 2 parts. In Part 1, participants received mRNA-1273 in an open-label and dose-escalation fashion. Safety and immunogenicity data from Part 1 for each age

group are reviewed to select the preferred dose for each age group (50 µg and 100 µg dose levels were explored in children between 6 years and <12 years). Part 2 of the study is a placebo-controlled, observer-blind, randomized (3:1, mRNA-1273:placebo) evaluation of the selected dose in up to 4000 participants in each of the 3 age groups (for a total of up to 12,000 children in Study P204).

The primary objectives of P204 are: (1) evaluate the safety and reactogenicity of 2 doses of mRNA-1273 28 days apart in each age group and (2) infer the effectiveness of the selected dose level in each age group based on noninferiority of neutralizing antibody (nAb) responses compared with those of young adults (18 to 25 years in the pivotal efficacy study mRNA-1273-P301 [hereafter P301]). Secondary objectives are to evaluate the persistence of immune response, the incidence of SARS-CoV-2 infection regardless of symptoms, the incidence of asymptomatic SARS-CoV-2 infection and the incidence of COVID-19 (defined as clinical symptoms consistent with COVID-19 and positive reverse transcription polymerase chain reaction [RT-PCR] for SARS-CoV-2) after receipt of mRNA-1273 or placebo.

Timing of the Application

Data are available for the 6 years to <12 years of age group from both open-label Part 1 and blinded Part 2 as of a data snapshot performed on 06 October 2021. This submission was triggered by

- the availability of immunogenicity data from Part 1 participants in the 6 years to < 12-year age group who received the selected dose of mRNA-1273 (2 50 µg doses, 28 days apart)
- a median 2 months of follow-up after dose 2 for at least 1000 participants who received mRNA-1273
- at least 7 days follow-up after dose 2 for at least 3000 participants who received mRNA-1273 with a median 21 days of follow-up after dose 2.

Overall, safety data are available for the 4753 participants enrolled in the 6 years to <12 year age group. This includes data from a total of 3387 participants who received at least 1 dose of mRNA-1273 50 µg (380 in Part 1 and 3007 in Part 2) and 995 placebo participants in Part 2. Safety data are also presented for the 371 participants who received at least 1 dose of mRNA-1273 100 µg in Part 1. The size of the safety database supports detection of an adverse event (AE) occurring at a rate of 0.1% with a 95% probability.

The median duration of follow-up after dose 2 was 111 days (Q1 104, Q3 117) for the 50 µg group (n=380) and 106 days (Q1 104, Q3 117) for the 100 µg group (n=371) for Part 1 and

20 days (Q1 15, Q3 26) for Part 2 (n=4002 in Safety Set). Data are available for 749 Part 1 participants (379 mRNA-1273 50 µg and 370 mRNA-1273 100 µg) with at least 56 days of follow-up after dose 2 and 639 Part 2 participants (474 mRNA-1273 50 µg and 165 placebo) with at least 28 days of follow-up after dose 2. At the time of the data snapshot (06 October 2021), 3758 participants had received at least 1 dose of mRNA-1273, and 749 had been followed for at least 2 months after dose 2.

This submission includes the immunogenicity data from 134 participants who received mRNA-1273 50 µg in Part 1 of Study P204.

Dose Selection

After review of available safety and immunogenicity data obtained from recipients of the 100 and 50 µg doses in Part 1, the 50 µg dose was advanced to Part 2 for children between 6 years and < 12 years, based in part on lower rates of fever and solicited adverse reactions.

Effectiveness of 50 µg mRNA-1273 in Children Between 6 Years and <12 Years Inferred Based on Noninferiority of nAb Responses Compared with Young Adults in Pivotal P301 Study

Study P204 included prespecified noninferiority criteria allowing inference of effectiveness in pediatric populations based on comparison of nAb responses to those obtained among young adults (18 to 25 years old) in the pivotal Phase 3 efficacy Study P301. Immunogenicity results (nAb levels measured with the validated pseudovirus neutralization assay [PsVNA]) are provided for the Per-Protocol (PP) Immunogenicity Subset(n=134) from recipients of 50 µg of mRNA-1273 in Part 1 (open-label phase) of Study P204.

The prespecified success criteria for the primary immunogenicity objective were met. Specifically, the noninferiority of the co-primary immunogenicity endpoints (geometric mean titer [GMT] and seroresponse rate in Study P204 participants 6 years to <12 years old) were demonstrated as compared with those in young adults (18- to 25-year-olds) in Study P301. In addition, the criterion on the point estimator of geometric mean ratio (GMR) also met. The GMR of pediatric (Study P204) to young adult (Study P301) nAb titers at Day 57 was 1.510 (95% CI: 1.263, 1.804), meeting the noninferiority success criterion (ie, lower bound of the 95% CI for GMR ≥ 0.67 and GMR point estimate > 0.8). The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 0.6% (95% CI: -2.8%, 2.8%), meeting the noninferiority success criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%). Effectiveness of 2 doses of 50 µg of mRNA-1273 administered to children 6 years to < 12 years of age was successfully inferred by

immunobridging to young adults (18 to 25 years of age) in Study P301 who received 2 100 µg doses of mRNA-1273.

Efficacy

In the Part 1 50 µg group starting 14 days after dose 2 in the PP Set for Efficacy, there was 1 case of asymptomatic SARS-CoV-2 infection (occurring at 28 days after dose 2 in a 7-year-old male), which was detected at the Day 57 prespecified study visit.

In Part 2 starting 14 days after dose 2 in the PP Set for Efficacy, there was 1 case (0.1%) of COVID-19 in the placebo group (incidence rate 8.58 per 1000 person-years) and none in the mRNA-1273 group. The case in the placebo group met both the Centers for Disease Control (CDC) case definition of COVID-19 and the "P301 case definition" of COVID-19. There were no cases of asymptomatic SARS-CoV-2 infection in either treatment group starting 14 days after dose 2 in the PP Set for Efficacy. The paucity of cases (of COVID-19 or SARS-CoV-2 infection) is not unexpected based on the limited follow-up period and the 3:1 mRNA-1273:placebo randomization ratio, given the known robust efficacy of mRNA-1273.

Although there were few cases in the PP population (from Day 14 after dose 2), VE in Part 2 in the mITT1 for COVID-19 cases using the "CDC case definition" occurring 14 days or more after dose 1 was 93.0% (95% CI: 75.1%, 98.7%); and VE for COVID-19 cases using the "P301 case definition" occurring 14 days or more after dose 1 was 100% (95% CI: 89.3%, not estimable [NE]). These results show an early onset of protection after vaccination with mRNA-1273 and were similar to the high, protective efficacy observed in the pivotal P301 study in adults, where 94.1% VE (95% CI: 89.3%, 96.8%) was observed 14 days after dose 2 in the final blinded analysis. Additionally, VE in Part 2 of the mITT1 for asymptomatic SARS-CoV-2 infections occurring 14 days or more after dose 1 was 65.0% (95% CI: 16.1%, 85.3%). These results were highly consistent with the 63.0% (95% CI: 56.6%, 68.5%) VE against asymptomatic infection observed in the pivotal P301 study, obtained in this pediatric population at a time when the major circulating variant was delta.

Summary of Unblinded Safety Data

Study P204 collected solicited adverse reactions (ARs) for 7 days after each injection (Parts 1 and 2), unsolicited AEs for 28 days after each injection, serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and AEs leading to withdrawals through the last day of study participation.

In Part 1 in the 50 µg group, the most common solicited local AR after any dose was injection site pain (96.8%). The majority of solicited local ARs were grade 1 to grade 2 in severity, occurred within the first 1 to 2 days after each dose, and generally persisted for a median of 3 days. The most frequent grade 3 solicited local ARs in this group included injection site pain (2.6%) and erythema (1.1%). There were no grade 4 solicited local ARs reported. The most common solicited systemic ARs after any dose were fatigue (68.9%) and headache (60.0%). The majority of solicited systemic ARs were grade 1 to grade 2 in severity. The most common grade 3 systemic ARs after any dose in this group were fatigue (7.9%), headache (3.7%), and fever (2.9%). There were no grade 4 solicited systemic ARs in the 50 µg group of Part 1. The majority of the solicited systemic ARs in participants in the 50 µg group of Part 1 occurred within the first 1 to 2 days after each dose and generally persisted for a median of 2 days. The safety data in the 50 µg group is supplemented by the data from the 100 µg group.

The most commonly reported unsolicited AEs in Part 1 were injection site erythema, upper respiratory infection, oropharyngeal pain, nasal congestion, cough, headache, nasopharyngitis, urinary tract infection, rhinorrhoea, otitis externa, injection site lymphadenopathy, fatigue, and vomiting. All events occurred in less than 5% of participants. No SAEs assessed by the investigator as related to study vaccine and no deaths were reported in Part 1. Additionally, no cases of myocarditis or pericarditis and no cases of MIS-C were reported.

In Part 2 (blinded evaluation of 50 µg mRNA-1273:placebo with 3:1 randomization ratio), the profile of solicited ARs was generally consistent with that observed in clinical trials of mRNA-1273 in adults (Studies P301). 50 µg of mRNA-1273 was generally well tolerated, with solicited ARs (overall) occurring more often in the mRNA-1273 group (95.6% and 97.0%) than in the placebo (68.5% and 66.8%) group, after first and second dose, respectively. As in previous studies, slightly higher rates of solicited ARs occurred after dose 2 and most solicited ARs overall were mild to moderate – indeed the excess solicited ARs overall observed in the mRNA-1273 group compared with the placebo group were largely due to mild to moderate (grades 1 and 2) solicited ARs. The incidence of any (local or systemic) grade 3 solicited ARs after any dose of 50 µg mRNA-1273 was 16.9% and after any dose of placebo was 3.3%. No grade 4 solicited ARs were reported among recipients of 50 µg of mRNA-1273 and only 1 grade 4 solicited AR was observed (grade 4 fever) in a placebo recipient. This event of grade 4 fever was due to a data entry error in the daily eDiary. The actual temperature was 100.0°F (grade 0).

After the first dose, the most frequent solicited local ARs were injection site pain (93.1%) and axillary swelling or tenderness (15.5%) and the most frequent solicited systemic ARs were fatigue (43.3%) and headache (31.2%). The most frequent grade 3 solicited local ARs were

injection site pain (0.9%) and axillary swelling or tenderness (0.6%), and the most frequent grade 3 solicited systemic ARs were fatigue (1.0%), and headache and fever (both 0.6%).

After the second dose, the most frequent solicited local ARs were injection site pain (94.8%) and erythema (18.8%) and the most frequent solicited systemic ARs were fatigue (64.4%) and headache (54.2%). The most frequent grade 3 solicited local ARs were injection site pain (2.7%) and erythema (1.1%), and the most frequent grade 3 solicited systemic ARs were fatigue (6.3%), headache (4.0%), and fever (3.8%)

The overall reactogenicity profile of mRNA-1273 (50 µg) in Part 2 is aligned with that observed recipients of mRNA-1273 (50 µg) in Part 1.

The rate and severity of solicited ARs among 6 years to <12-year-old recipients of 50 µg mRNA-1273 (Part 2, P204) were compared with those observed among young adult (18 to 25 years of age) recipients of 100 µg mRNA-1273 in the pivotal Phase 3 efficacy study (P301). Overall, the rate of solicited local ARs was slightly higher, but rates of grades 3 and 4 solicited local ARs were lower, in children 6 years to < 12 years of age compared with those of young adults. Overall systemic reactogenicity was similar among 6- to <12-year-old recipients compared with that observed in young adult recipients; the exception was rates of fever, which were higher among children 6 years to <12 years.

Overall, unsolicited AEs Part 2 occurred at similar frequency in the mRNA-1273 group and the placebo group. The most common unsolicited AEs in the mRNA-1273 group were injection site erythema, upper respiratory tract infection (URTI), oropharyngeal pain, cough, rhinorrhoea, nasal congestion, injection site lymphadenopathy, injection site pain, and fatigue. All of these events occurred in less than 3% of participants in this group. The most common AEs reported in the placebo group were oropharyngeal pain, nasal congestion, COVID-19, URTI, headache, rhinorrhoea, cough, and fatigue.

MAAEs occurring within 28 days of any dose were more frequently reported in the mRNA-1273 group (1.0%) compared with the placebo group (0.3%) in Part 2. In the mRNA-1273 group, SAEs occurring within 28 days of any dose were reported in 2 (< 0.1%) participants with the PTs appendicitis and cellulitis orbital. No SAEs were reported within 28 days of any dose in the placebo group.

Based on observations of cases of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines from post-authorization data, the majority of the cases have been reported in young males shortly after the second dose of the vaccine. Individuals tend to recover within a short time following standard treatment and rest (Gargano et al 2021a). No events of

myocarditis or pericarditis were reported in this clinical trial at the time of the data snapshot. Evaluation of the PTs within the Cardiomyopathy SMQ or within the algorithm created following the CDC Working Case Definition for Acute Myocarditis and Acute Pericarditis did not yield any cases suggestive of possible myocarditis or pericarditis.

No SAEs assessed by the investigator as related to study vaccine and no deaths were reported in Part 2. Additionally, no cases of MIS-C were reported at the time of the data snapshot.

Benefit/Risk Conclusion

The data presented in this submission include inferred effectiveness by bridging to efficacy data in the pivotal study P301 as well as direct observation of early efficacy in the mITT1 population and support the extension of the use of mRNA-1273 to children 6 years to < 12 years for the prevention of COVID-19. The observed efficacy against infection with SARS-CoV-2 (with or without symptoms) at a time when the SARS-CoV-2 delta variant predominated also suggests a benefit in the prevention of transmission. Results are generally consistent with the safety profile observed in young adults (18 to 25 years of age) in Study P301. No cases of myocarditis or pericarditis were reported and additional thorough search of the safety database for specific PT did not identify any cases suggestive of these disorders. The immunogenicity, safety, and efficacy data from Study P204, support administration of mRNA1273 as 2 50 µg doses administered 28 days apart in children 6 years to < 12 years of age. Considering the ongoing public health emergency due to SARS-CoV-2, the burden of disease in children 6 years to < 12 years of age, and the effectiveness and safety data from clinical Study P204 presented herein, the Applicant considers that the known and potential benefits of the mRNA-1273 outweigh the known and potential risks for mRNA-1273.

2.5.2 PRODUCT DEVELOPMENT RATIONALE

2.5.2.1 Pharmacologic Class of Agent

2.5.2.1.1 mRNA Platform

The Applicant has developed a rapid response proprietary vaccine platform based on a messenger ribonucleic acid (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 (NCT03382405), human metapneumovirus and parainfluenza virus type 3 (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 (Rozenski et al 1999, Karikó et al 2005). 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 (Kozak 1991, Fechter and Brownlee 2005).

Each mRNA molecule contains noncoding, or untranslated, sequences that may carry instructions for the cell regarding how to handle the mRNA (Figure 1).

Figure 1: Structure of mRNA

Abbreviations: PolyA = polyadenylated; UTR = untranslated region.

The 3' untranslated region (UTR) is at the end of the open reading frame and is followed by the polyadenylated (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 initiation of translation of the target protein.

2.5.2.1.2 mRNA-1273 Mechanism of Action

The Applicant 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, the Applicant 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 (SARS) CoV-1. This preclinical 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 Applicant to leverage the scientific understanding and apply it to the approach used in the development of mRNA-1273. That approach utilizes the Applicant'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 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). It has been confirmed that the stabilized SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the prefusion conformation (Wrapp et al 2020).

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. After IM injection, 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 14.9-63.0 hours in Sprague Dawley rats (Moderna 2021). 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 (Nelson et al 2020). In addition, the LNP-encapsulated mRNA is taken up by cells in the body, primarily antigen presenting cells at the injection site and in the draining lymph nodes. The mRNA interacts with cellular translational machinery, resulting in translation of the encoded spike antigen. This antigen is both properly folded and presented on the surface of these cells as well as cleaved into peptide fragments by the cellular proteasome and displayed on major histocompatibility complex class 1 and 2 molecules. Naïve or memory B-cells interact with the displayed conformational spike protein, resulting in the induction of memory B-cells, affinity maturation of existing memory B-cell pools, and generation of long-lived plasma cells in the bone marrow. These function to secrete antibodies (Abs) that bind to and neutralize SARS-CoV-2 viruses. The peptide fragments displayed on major histocompatibility complex class 1 and 2 molecules interact and activate $CD8^+$ and $CD4^+$ T-cells, which function to eliminate infected cells and support B-cell responses. mRNA-1273 induces T-helper 1-biased CD4 T-cell responses in humans (Jackson et al 2020).

2.5.2.2 Intended Use

This submission intends to extend the use of mRNA-1273 to include active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 6 years through 11 years of age.

Each primary series dose of mRNA-1273 is 0.25 mL.

mRNA-1273 is administered as a primary series of 2 doses (0.25 mL each) 1 month apart to children 6 through 11 years of age.

2.5.2.3 Clinical/Pathophysiology of Condition

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. Coronaviruses are also zoonotic, with different species causing disease in other mammals, such as bats and cats.

An outbreak of COVID-19 caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally (WHO 2020). This virus is not known to have previously caused disease in humans. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020 and declared COVID-19 a pandemic on 11 March 2020.

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 contact with fomites (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 the distinctive symptoms of loss of taste or smell.

2.5.2.3.1 Unmet Medical Need

2.5.2.3.1.1 Direct Medical Impact of COVID-19 on the Proposed Indicated Population

As of 21 October 2021, confirmed COVID-19 mortality has surpassed 4.9 million deaths worldwide and over 731,000 deaths in the US, with COVID-19 cases numbered nearly 243 million worldwide and over 45 million in the US (Johns Hopkins University 2021). Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults (Hay et al 2020; Ayoub et al 2021; CDC 2021c); however, COVID-19 can also lead to severe outcomes in children and adolescents (Kim et al 2020; Havers et al 2021). From the start of the pandemic to May 2021, approximately 2.6 million cases of COVID-19 have been reported among children 5 to 9 years of age and approximately 3.8 million cases have been reported among children 10 to 14 years of age in 105 countries (Unicef 2021). In the US, due to COVID-19, an excess of 2670 hospitalizations among children 5 years to 17 years of age have been observed through 21 October 2021 with 28.5% requiring intensive care unit interventions and more than 500 deaths observed (CDC 2021c).

While the burden of COVID-19 disease has largely affected adult populations, changes in social policy, individual behavior, and viral dynamics are moving the burden of disease into younger age groups. Schools have opened for in-person learning, and many children have returned to early educational programs and kindergartens. The opening of these institutions is occurring at the same time as relaxed mask mandates and an increase in the number of cases caused by the highly transmissible B.1.617.2 Delta variant of SARS-CoV-2 (CDC 2021e). An evaluation of case trends, by age, demonstrates a rapid change in demographics when comparing the winter 2020-2021 COVID-19 wave to the current Delta wave in the US. Before the Delta wave, persons 17 years of age and younger comprised the lowest weekly cases and death rates per 100,000 population; however, in the current Delta wave, adolescents 12 to 17 years of age have the highest case rates, followed closely by children 5 years to 11 years of age (CDC 2021f).

A distinctive manifestation of SARS-Co-V-2 in children and adolescents is development of a life-threatening hyperinflammatory state 4 to 6 weeks after infection with primary COVID-19. Termed multisystem inflammatory syndrome in children (MIS-C) (Vogel et al 2021), this often presents with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021d). Additionally, a large cohort study found that children under 16 years of age with COVID-19 are at 37 times higher risk of myocarditis than the uninfected age and gender-matched control population (Boehmer et al 2021). There is also evidence of chronic sequelae known as "long-COVID-19" in children even after mild infection; this includes fatigue, muscle and joint pain, insomnia, respiratory problems, and palpitations that may be seen up to 6 months after infection (Dembiński et al 2021). More than 5217 cases and 46 deaths meeting case definition of MIS-C have been reported in the US (CDC 2021m).

A recent paper published by the US CDC using data from the Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) reported on indicators of severe COVID-19 among children and adolescents (Delahoy et al 2021). COVID-NET is a database of COVID-19–associated hospitalizations in 99 counties across 14 states, and the study described pediatric hospitalization from 01 March 2020 through 14 August 2021. During 01 March 2020 to 14 August 2021, the cumulative incidence of COVID-19–associated hospitalizations was 49.7 per 100,000 children and adolescents. COVID-NET reported hospitalization rates were highest among children 0 to 4 years of age (69.2 per 100,000 children) followed by adolescents 12 to 17 years of age (63.7 per 100,000 children) and children 5 years to 11 years of age (24.0 per 100,000 children). The lowest weekly hospitalization rates in 2021 were observed during the weeks ending 12 June 2021 to 03 July 2021 (0.3 per 100,000 children and adolescents each week). In the following 6-week period after the Delta variant became predominant, rates rose each week to 1.4 per 100,000 children during the week ending 14 August 2021, which was 4.7 times the rate during the week ending 26 June 2021 and approached the peak hospitalization rate of 1.5 per 100,000 children observed during the week ending 09 January 2021.

Since March 2020, approximately 1 in 4 hospitalized children and adolescents with COVID-19 has required intensive care, although the proportions with indicators of severe disease during the period when the Delta variant predominated were generally similar compared with those earlier in the pandemic. The authors of studies of MIS-C and "long-COVID" in children report the observed indicators (insomnia [18.6%], respiratory symptoms [including pain and chest tightness] [14.7%], nasal congestion [12.4%], fatigue [10.8%], muscle [10.1%] and joint pain [6.9%], and concentration difficulties [10.1%]) of severe COVID-19 among children and adolescents, as well as the potential for serious longer-term sequelae (eg, MIS-C) (Buonsenso et al 2021; Feldstein et al 2020), and underscore the importance of implementing multipronged

preventive measures to reduce severe COVID-19 disease, including nonpharmaceutical interventions and vaccination among eligible age groups.

COVID-NET data indicate that vaccination was highly effective in preventing COVID-19–associated hospitalizations in adolescents (Delahoy et al 2021). Among adolescents 12 to 17 years of age, the only pediatric age group for whom a COVID-19 vaccine is currently approved, hospitalization rates were approximately 10 times higher in unvaccinated compared with fully vaccinated adolescents, indicating that vaccines were highly effective at preventing serious COVID-19 illness in this age group during a period when the Delta variant predominated. As of 31 July 2021, 32% of US adolescents had completed a COVID-19 vaccination series (Murthy et al 2021); increasing vaccination coverage among adolescents, as well as expanding eligibility for COVID-19 vaccination to younger age groups if approved and recommended, is expected to reduce severe COVID-19–associated outcomes among children and adolescents.

2.5.2.3.1.2 Social Impact and Effect on Education of the Proposed Indicated Population

During the COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control outbreaks; therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, has been infected household contacts.

Evidence is emerging to suggest that children and adolescents may be disproportionately contributing to the number of new cases, as schools re-open for varying degrees of in-person learning (CDC 2021c; SAGE 2020). The efficiency of SARS-CoV-2 transmission in schools has recently been documented in an outbreak in elementary school students and their close contacts after exposure to an unvaccinated infected teacher. The attack rate was 50%. Of 22 students tested for SARS-CoV-2, 12 tested positive, as did 6 of 18 students in a separate grade, and 8 additional family members (Lam-Hine et al 2021). Cases among students may lead to larger consequences for the schools they attend. In the first month since the start of the school year 2021 (02 August to 17 September 2021), there have been at least 248 public districtwide closures and 384 individual school closures for ≥ 1 day attributable to COVID-19; this has thus far affected 15% of all schools, almost 60,000 teachers in 44 states and the education of almost 1 million students in the US (CDC 2021l).

The effects of school closures and remote learning can be severe. According to the American Academy of Pediatrics, schools and school-supported programs are fundamental to child development and well-being. Remote learning was detrimental to the education of students, exacerbated the mental health crisis among children, and highlighted inequalities in education

(AAP 2021). Particularly for 6- to < 12-year-olds, school is essential for learning critical academic skills such as reading, writing, and math as well as social skills; missing out on these crucial elementary school years may have long lasting consequences for their future educational achievements.

2.5.2.3.1.3 The Role of Children in Community Transmission

The vast majority of infected children have mild or unrecognized disease, and this population may play important epidemiologic roles by potentiating spread of infection through communities (Li et al 2020).

A study by Han et al (2020) and colleagues provide data accumulated from 22 centers throughout South Korea reported that not all infected children have symptoms, and even those with symptoms are not necessarily recognized in a timely fashion. In this study, the authors estimate that 85 infected children (93%) would have been missed using a testing strategy focused on testing of symptomatic patients alone. A surveillance strategy that tests only symptomatic children will fail to identify children who are silently shedding virus while moving about their community and schools.

The viral load of asymptomatic and symptomatic cases does not appear to differ (Lee et al 2020, Hurst et al 2020). Infectious virus is cultured from both, and the likelihood of successfully culturing virus is unrelated to age, including individuals 0 to 20 years of age (Singanayagam et al 2020).

Based on these review, children likely play a role in community transmission, given the large number of contacts children have in childcare centers and schools (Hyde 2020) and the increasing proportion of pediatric cases as described in Section 2.5.2.3.1.1. Young children attending school represent a type of institutional setting in which the risk of virus transmission is high. If children are not vaccinated, they will remain a large, susceptible group capable of being infected with the virus and transmitting it to others. A mathematical modeling study demonstrated the importance of vaccinating children and adolescents and found that including these populations for vaccination could reduce overall COVID-related mortality across all age groups by 57% and reduce cases of “long COVID” by 75% (Shiri et al 2021).

2.5.2.3.1.4 Importance of Vaccinating the Pediatric Population

Immunization with a safe and effective COVID-19 vaccine is a critical component of the strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning. Overall, the evidence suggests that the burden of COVID-19 has begun to increase in younger age groups based on the number and proportion of cases.

There is an urgent unmet medical need to prevent COVID-19 cases, MIS-C, "long-COVID-19," hospitalizations, and deaths in pediatric patients. Vaccinating children 6 years to < 12 years of age with mRNA-1273 has the potential to address this unmet medical need.

Additionally, infections among school children lead to school closures and educational disruptions for entire communities, especially in areas where other measures such as wearing a mask are not enforced. Vaccinating children 6 years to < 12 years of age with mRNA-1273 has the potential to help schools remain open for in-person education. Young children attending school represent a type of institutional setting in which the risk of virus transmission is high. If children are not vaccinated, they will remain a large, susceptible group capable of being infected with the virus and transmitting it to others.

As the COVID-19 pandemic continues and more transmissible variants become dominant, Moderna proposes that mRNA-1273 should be authorized for use in persons 6 years to < 12 years of age based on the data generated at the 50 µg dose in Study P204 to protect children from the direct sequelae of COVID-19, to reduce the frequency of educational disruptions, and as a part of the world's action plan to curb the pandemic.

2.5.2.4 mRNA-1273 in Adults and Adolescents

2.5.2.4.1 Study mRNA-1273-P301

The pivotal study of mRNA-1273 in adults is mRNA-1273-P301 (hereafter Study P301), a Phase 3 efficacy, safety, and immunogenicity study that provides the primary clinical evidence of vaccine efficacy (VE) and safety in adults ≥ 18 years of age. The study was designed as a randomized, observer- and participant-blind, placebo-controlled study of the efficacy, safety, and immunogenicity of 2 doses of mRNA-1273 100 µg compared with placebo (Part A, Blinded Phase). In this study, more than 30,000 participants were randomized and > 96.7% participants received dose 2 of mRNA-1273. Vaccine efficacy was observed to be 94.1% with a median of 9 weeks of efficacy follow-up and remained high and durable with observed VE of 93.2% after 5.3 months of median efficacy follow-up. The safety profile was observed to be clinically acceptable (Baden et al 2021; El Sahly et al 2021). Data from this study supported the US Emergency Use Authorization (18 December 2020), the Canadian Interim Order (23 December 2020), the European Medicines Agency Conditional Marketing Authorization (06 January 2021) and numerous other marketing authorizations worldwide, for use of mRNA-1273 to prevent COVID-19. These data also supported the US BLA, which is currently under review.

2.5.2.4.2 Study mRNA-1273-P203

mRNA-1273 is being studied in adolescents 12 to < 18 years of age in the US in Study mRNA-1273-P203 (hereafter Study P203), a Phase 2/3, randomized, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study is to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group.

Study participants were randomly assigned to receive 2 injections (28 days apart) of either 100 µg of mRNA-1273 vaccine or placebo in a 2:1 randomization ratio (Part A, the Blinded Phase of Study P203). The protocol stipulated vaccine effectiveness to be inferred based upon either: (i) proportion of study participants with serum Ab levels (on Study Day 57) that meet or exceed an Ab level conferring protection from COVID-19, or in the absence of such an accepted threshold of protection, (ii) by demonstrating the noninferiority of both the (a) geometric mean (GM) value of serum Ab and (b) the seroresponse rate from adolescent participants compared with those observed in a subset of young adults (18 to 25 years of age) enrolled in the ongoing adult study (Study P301), where VE of 94.1% was demonstrated. At the time the analysis for the adolescent regulatory file submission was performed, a serum Ab threshold of vaccine protection against COVID-19 (ie, an Ab based correlate of protection) had not been established; therefore, the second method to evaluate VE was used. The coprimary endpoints were considered to have been met if the lower bound of the 95% confidence interval (CI) for the GM ratio (GMR) of adolescent (Study P203) to young adult (Study P301) nAb titers was > 0.67 and the lower bound of the 95% CI for the seroresponse rate difference was > -10%. Positive seroresponse was defined as a change in PsVNA 50% inhibitory dose (ID_{50}) from below the lower limit of quantification (LLOQ) at baseline to above the LLOQ or at least a 3.3-fold rise if baseline was at or above the LLOQ.

Upon availability of another COVID-19 vaccine authorized for emergency use in adolescents in the US, the study transitioned to Part B, the Open-label Observational Phase of this study. In this part, participants who were of eligible age for a COVID-19 vaccine authorized for emergency use, could request unblinding and those having received placebo could seek the authorized vaccine. Upon unblinding, previous placebo recipients who sought an alternative vaccine were removed from the study.

The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the 1.5-fold noninferiority criterion (ie, lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb seroresponse rates at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the 10% noninferiority criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%). Since both coprimary

endpoints of Study P203 met the prespecified success criteria for noninferiority, the primary immunogenicity objective is considered to have been met.

In addition, direct clinical benefit in the reduction in COVID-19 cases was demonstrated. COVID-19, defined using either of 2 case definitions (including the definition utilized in the adult efficacy study), prevented disease starting 14 days after dose 1. Applying the same case definition and interval (starting 14 days after dose 2) as that used in the adult efficacy study, VE was 100% (lower bound, 95%CI: 28.9%), with 4 cases in the placebo group and 0 cases in the vaccine group. These results are consistent with results obtained in the pivotal adult efficacy study (Study P301).

The CDC case definition of COVID-19, requiring only one symptom and laboratory confirmation, allowed assessment of VE against a higher number of cases as expected, and using a definition well-suited to adolescents for whom COVID-19 is typically less severe. Applying this case definition, VE of 93.3% (95% CI: 47.9%, 99.9%) was demonstrated 14 days after dose 2. This benefit was also evident starting as soon as 14 days after dose 1, with a VE of 92.7% (95% CI: 67.8%, 99.2%), based on accrual of a total of 15 cases (2 cases [3.83 per 1,000 person-years] in mRNA-1273 group and 13 cases [52.47 per 1,000 person-years] in the placebo group.

The available safety and efficacy data of mRNA-1273 in adults and adolescents support the evaluation of mRNA-1273 in children <12 years of age.

2.5.2.4.3 Post-Authorization Use of mRNA-1273

Since December 2020, mRNA-1273 and other COVID-19 vaccines have been available, under EUA in the US and approvals worldwide, including a conditional marketing authorization in the EU (6 January 2021). mRNA-1273 was fully approved in Canada on 16 September 2021. A Biologics License Application (BLA) for the full licensure of mRNA-1273 for active immunization to prevent COVID-19 in individuals 18 years of age and older was submitted to the US FDA on 25 August 2021. As of 30 September 2021, 518,902,500 doses of mRNA-1273 had been distributed worldwide; globally, an estimated 124,399,577 people are considered to be fully vaccinated after receiving a 2-dose primary series of mRNA-1273 (Monthly Safety Report 09). A third dose in immunocompromised individuals has been granted emergency authorization in the US (13 August 2021), and has been approved in Europe (06 October 2021), and other countries. A booster dose of mRNA-1273 50 µg is authorized in the US as of 20 October 2021 for people 65 years and older, people 18 to 64 years who are at high risk of severe COVID-19, and people 18 to 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2, and in the EU as of 29 October 2021 for people ≥18 years of age.

mRNA-1273 is also indicated for use in adolescents 12 years of age and older in Canada, Europe, United Kingdom, Switzerland, Japan, Australia, Saudi Arabia, Taiwan, Israel, Singapore, and 12 other countries; an EUA for use in adolescents was submitted to the US FDA on 10 June 2021. Approximately 1.5 million doses globally have been administered to people < 18 years of age (Monthly Safety Report 09).

Observational studies demonstrate high effectiveness of mRNA-1273 against most variants of concern; however, decreased effectiveness of mRNA-1273 against the Delta variant has been shown (Bruxvoort et al 2021a; Bruxvoort et al 2021b). An interim analysis (IA) from Study P901, a Moderna collaboration with Kaiser Permanente Southern California (KPSC) (Long-term Effectiveness study, prospective cohort with individuals ≥ 18 years old vaccinated starting in December 2020 and followed through end June 2021 for the IA) showed effectiveness of 2 doses of mRNA-1273 against COVID-19 diagnosis was 87.4% (99.3% CI: 84.8%, 89.6%). Vaccine effectiveness against COVID-19 hospitalization and hospital death was 95.8% (99.3% CI: 90.7%, 98.1%) and 97.9% (99.3% CI: 66.9%, 99.9%), respectively. Vaccine effectiveness was higher against symptomatic (88.3% [98.3% CI: 86.1%, 90.2%]) than asymptomatic SARS-CoV-2 infection (72.7% [98.3% CI: 53.4%, 84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups (Bruxvoort et al 2021b). The most common variants circulating in the KPSC population during this analytic period were, in decreasing order, Delta, Alpha, Epsilon, and Gamma.

Additionally, a test-negative case-control analysis was conducted using SARS-CoV-2 positive specimens collected during 01 March 2021 to 27 July 2021 from all KPSC members ≥ 18 years old. Two-dose VE was 86.7% (95% CI: 84.3%, 88.7%) against Delta infection, 98.4% (95% CI: 96.9%, 99.1%) against Alpha, 90.4% (95% CI: 73.9%, 96.5%) against Mu, and 96% to 98% against other identified variants. VE against Delta declined from 94.1% (95% CI: 90.5%, 96.3%) 14 to 60 days after vaccination to 80.0% (95% CI: 70.2%, 86.6%) 151 to 180 days after vaccination. Waning was less pronounced for non-Delta variants. VE against Delta hospitalization was 97.6% (92.8-99.2%) (Bruxvoort et al 2021a). These data support the effectiveness of mRNA-1273 against variants of concern.

2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age

Study mRNA-1273-P204 (hereafter Study P204) is an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age. The study population includes 3 age groups (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years). This submission will focus on children 6 years to < 12 years of age. As described below, this

2-part study (Part 1 open-label dose selection and Part 2 placebo-controlled expansion) is evaluating up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 in each age group. In the expansion phase (Part 2), participants receive mRNA-1273 or placebo administered as 2 IM injections approximately 28 days apart at the selected dose level (Table 1).

The study is being conducted in 2 parts. Part 1 of the study is open-label and involves dose-escalation and age de-escalation to select the preferred dose for each age group based on safety, tolerability, and immunogenicity results. Approximately 1275 participants in total have been enrolled in Part 1 of the study, with the highest number enrolled in the oldest age group. Part 2 of the study is a placebo-controlled observer-blind evaluation of the selected dose in up to a total of 12,000 participants (up to 4000 participants in each of the 6 years to < 12 years, 2 years to < 6 years, and the 6 months to < 2 years of age groups). No participants in Part 1 participate in Part 2 of the study. The sample size was increased in an amendment to the Study P204 protocol (23 July 2021) based on FDA advice to enhance the probability of detecting less common AEs. With the updated sample size of 4000 participants in each age group in Part 2 of the study, the probability of detecting an AE occurring at a rate of 0.1% in the vaccine group is 95%.

The primary objectives are to evaluate the safety and reactogenicity of up to 3 dose levels of mRNA-1273 administered as 2 doses 28 days apart in 3 age groups, and to infer the effectiveness of the selected dose level in each age group based on immunogenicity. Secondary objectives are to evaluate the persistence of immune response, the incidence of SARS-CoV-2 infection regardless of symptoms, the incidence of asymptomatic SARS-CoV-2 infection, and the incidence of COVID-19 (defined as clinical symptoms consistent with COVID-19 and positive RT-PCR for SARS-CoV-2) after vaccination with mRNA-1273 or placebo.

This submission presents the data from Study P204 for the 6 years to < 12-year age group.

Table 1: Study mRNA-1273-P204 Design

	Part 1			Part 2	
Age Group	**mRNA-1273 25 µg**	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n=3,000)	Study Arm 9 (n=1,000)
2 to < 6 years	Study Arm 7 (n=75)	Study Arm 3 (n=75) Study Arm 4 (n=75)		Study Arm 10 (n= up to 3,000)	Study Arm 11 (n= up to 1,000)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n= up to 3,000)	Study Arm 13 (n= up to 1,000)

2.5.2.6 Timing of the Application

Data are available for the 6 years to <12 years of age group from both open-label Part 1 and blinded Part 2 as of a data snapshot performed on 06 October 2021. This submission was triggered by

- the availability of immunogenicity data from Part 1 participants in the 6 years to < 12-years age group who received the selected dose of mRNA-1273 (2 50 µg doses, 28 days apart)
- a median 2 months of follow-up after dose 2 for at least 1000 participants who received mRNA-1273
- at least 7 days follow-up after dose 2 for at least 3000 participants who received mRNA-1273 with a median 21 days' follow-up after dose 2.

This analysis (data snapshot 06 October 2021) from the ongoing P204 study includes the immunogenicity data from 134 participants who received mRNA-1273 50µg in Part 1 of Study P204 in addition to the 67 Part 1 participants whose data were used for dose selection. Safety data are included from a total of 3387 participants who received at least 1 dose of mRNA-1273 50 µg in Study P204 (380 participants in Part 1 and 3007 participants in Part 2) and 995 participants who received at least 1 dose of placebo. The median duration of follow-up is 111 days (Q1 104, Q3 117) after dose 2 for the Part 1 50 µg group and 20 days (Q1 15, Q3 26) after dose 2 for the Part 2 group. The safety database in children 6 years to < 12 years of age is sufficient to have a 95% probability of detecting an AE occurring at a rate of 0.1% during the observed timeframe. Additionally, safety data are presented for 371 participants who received at least 1 dose of mRNA-1273 100 µg in Part 1 of Study P204. Data are available for 749 Part 1 participants (379 mRNA-1273 50 µg and 370 mRNA-1273 100 µg) with at least 56 days of follow-up after dose 2 and 639 Part 2 participants (474 mRNA-1273 50 µg and 165 placebo) with at least 28 days of follow-up after dose 2 (Table 2).

Table 2: Overview of Participant Disposition and Duration Part 1 and Part 2 (Safety Set)

	mRNA-1273 (50 µg and 100 µg) (n=3758)	Placebo (n=995)	Total
Received Dose 1	3758	995	4753
Received Dose 2	3737	969	4706
Follow-up since Dose 2:			
≥7 days	3708	962	4670[a]
≥21 days	2259	489	2748
≥1 month	1224	165	1389[b]
≥2 months	749	0	749
≥3 months	749	0	749

a. Median follow-up of >21 days after dose 2
b. Median follow-up of > 2 months after dose 2.
Source: Study P204 Table 14.1.5.1 and Table 14.1.5.2

2.5.2.7 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 P204 protocol and statistical analysis plan (SAP) have been designed in accordance with both US FDA general guidance on COVID-19 vaccine development (DHHS 2020; DHHS 2021) and product-specific guidance. Study P204 protocol development, pediatric study plan and pediatric investigation plan 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 country. Clinical protocol and study design elements were developed in collaboration with the US National Institutes of Health and conducted in accordance with consensus ethical principles derived from international guidelines including principles provided by the Declaration of Helsinki, as well as guidelines described in the Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonisation Good Clinical Practice Guidelines.

2.5.3 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.4 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 are critical for expanding population coverage for the mRNA-1273 development program in comparison to the pivotal study in which efficacy was established (Study P301).

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 validated analytical methods used for the assessment of clinical endpoints in the clinical studies of mRNA-1273 discussed in this EUA is provided in Table 3.

Immunoassays for Study P204 were validated for use in the assessment of clinical samples. In P204 as well as P301 and P203 2 assays employed: (i) PsVNA for measure of functional neutralizing antibody (nAb) and (ii) MesoScale Discovery (MSD) Multiplex (S, N, RBD) for measure of binding antibody (bAb). Both assays were validated and considered acceptable for use in the assessment of clinical samples.

Table 3: Overview of Bioassays for the Assessment of Clinical Endpoints

Assay Name	Methodology	Study Number(s)	Development Status (Performing Laboratory)[a]
MSD multiplex anti-S	MSD multiplex	204 and 301	Validated (PPD Vaccine Laboratories)
SARS-CoV-2 Pseudotyped Virus Neutralization	PsV neutralization	204 and 301	Validated (Duke University Medical Center)

Abbreviations: IgG = immunoglobulin G; MSD = MesoScale Discovery; PsV = pseudotyped virus; S = spike; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus that causes COVID-19.
[a] Commercially available assays were validated by the laboratory performing the assay with the study samples.

2.5.5 OVERVIEW OF EFFICACY

This section presents the data from Study P204 for the 6 years to < 12 year age group.

2.5.5.1 Study Populations

2.5.5.1.1 Analysis Sets

Analysis sets from Study P204 that are referenced in this EUA amendment are defined in Table 4. A complete list of analysis sets with corresponding definitions are provided in the Study P204 SAP (Module 5.3.5.1).

Table 4: Study P204 Analysis Sets

Analysis Set	Description
Randomization Set	All participants who are randomized in Part 2, regardless of the participants' treatment status in the study
FAS	All enrolled participants who received at least 1 dose of IP (Part 1) All randomized participants who received at least 1 dose of IP (Part 2)
Per-Protocol Set for Efficacy	All participants in the FAS who meet all the following criteria: • received planned doses of IP per schedule • complied with the 2nd dose injection timing • had no major protocol deviations that impact key or critical efficacy data • had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline
Per Protocol Immunogenicity Subset	A subset of participants in the FAS who meet all the following criteria: • have baseline (Day 1) SARS-CoV-2 status available • have baseline and at least 1 post-injection Ab assessment for the analysis endpoint • received planned doses of IP per schedule • complied with the immunogenicity window based on the 2nd dose injection timing • had a negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid protein at baseline • are not receiving HAART (for participants who have a diagnosis of HIV) • had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint • had no major protocol deviations that impact critical or key study data
mITT	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline
mITT1	All participants in the mITT Set excluding those who received the wrong treatment.
Safety Set	All enrolled participants (Part 1) All randomized participants who received any study injection (Part 2)
Solicited Safety Set	All participants in the safety set who contributed any solicited AR data, ie, had at least 1 post-baseline solicited safety assessment
First Injection Solicited Safety Set	All participants in the Solicited Safety Set who have received the first study injection and have contributed any solicited AR data from the time of first study injection through the following 6 days
Second Injection Solicited Safety Set	All participants in the Solicited Safety Set who have received the second study injection and have contributed any solicited AR data from the time of second study injection through the following 6 days

Abbreviations: Ab = antibody; AR = adverse reaction; bAb = binding antibody; FAS = full analysis set; HAART = highly active anti-retroviral therapy; HIV = human immunodeficiency virus; IP = investigational product; mITT = modified intent-to-treat; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

The number of participants in each analysis set for Part 1 referenced in this document and reasons for exclusions from the PP Immunogenicity Subset are presented in Table 5. Of note, the PP Immunogenicity Subset used for immunogenicity analyses to assess noninferiority in this submission excludes participants whose data were used for dose selection.

Table 5: Number of Participants in Each Analysis Set by Dose Level in Part 1 (FAS)

	mRNA-1273 50 µg	**mRNA-1273 100 µg**
FAS[a], n	380	371
Immunogenicity Subset[b], n	145	
PP Immunogenicity Subset[b], n (%)	134 (92.4)	
Excluded from PP Immunogenicity Subset	11 (7.6)	
Reason for Exclusion[c]		
Positive Baseline SARS-CoV-2 Status	10 (6.9)	
Did not Receive Dose 2 per Schedule	1 (0.7)	
Safety Set[d], n	380	371
Solicited Safety Set[d], n (%)	380 (100)	371 (100)
First Injection Solicited Safety Set	378 (99.5)	369 (99.5)
Second Injection Solicited Safety Set	379 (99.7)	371 (100)

Abbreviations: FAS = full analysis set; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

a. Numbers are based on planned treatment group.

b. Numbers are based on planned treatment group, and percentages are based on the number of participants in the Immunogenicity Subset, which includes participants in Part 1 whose data were not used in dose selection.

c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.

d. Numbers are based on actual treatment group, and percentages are based on the number of safety participants.

Source: Study P204 Table 14.1.2.1.1.1, Study P204 Table 14.1.2.3.1, and Study P204 Table 14.1.2.3.1.1

The number of participants in each analysis set for Part 2 referenced in this document and reasons for exclusion from the PP Set for Efficacy are provided in Table 6.

Table 6: Number of Participants in Each Analysis Set by Dose Level in Part 2 (Randomization Set)

	mRNA-1273 50 µg	Placebo
Randomization Set[a], n	3009	1002
FAS[a], n (%)	3005 (99.9)	997 (99.5)
PP Set for Efficacy[a], n (%)	2638 (87.7)	852 (85.0)
Excluded from PP Set for Efficacy, n (%)	371 (12.3)	150 (15.0)
Reason for Exclusion[b], n (%)		
Randomized but Not Dosed	4 (0.1)	5 (0.5)
Baseline SARS-CoV-2 Status Positive or Missing	315 (10.5)	117 (11.7)
Discontinued Study Treatment or Participation Without Receiving Dose 2	7 (0.2)	9 (0.9)
Did not Receive Dose 2 and Passed Window	11 (0.4)	13 (1.3)
Received Incorrect Vaccination	12 (0.4)	2 (0.2)
Received Dose 2 Out of Window	20 (0.7)	4 (0.4)
Had Other Major Protocol Deviations	2 (<0.1)	0
mITT[a], n (%)	2690 (89.4)	880 (87.8)
mITT1[a], n (%)	2678 (89.0)	878 (87.6)
Safety Set[c], n	3007	995
Solicited Safety Set[c], n (%)	3007 (100)	995 (100)
First Injection Solicited Safety Set	3005 (>99.9)	994 (99.9)
Second Injection Solicited Safety Set	2986 (99.3)	968 (97.3)

Abbreviations: FAS = full analysis set; mITT = modified intent-to-treat; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Percentages are based on the number of participants in the Randomization Set in Part 2.
[a.] Numbers are based on planned treatment group, and percentages are based on the number of randomized participants.
[b.] A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.
[c.] Numbers are based on actual treatment group, and percentages are based on the number of safety participants.
Source: Study P204 Table 14.1.2.1.2.1 and Study P204 Table 14.1.2.5

2.5.5.1.2 Study Duration and Disposition

In Part 1, at the time of the data snapshot (06 October 2021), 380 participants in the 50 µg group and 371 participants in the 100 µg group received dose 1 and 379 participants in the 50 µg group and 371 participants in the 100 µg group received dose 2 (Table 7). One (0.3%) participant in the 50 µg group discontinued study vaccine due to an AE of urticaria papular (verbatim term: delayed skin reaction, urticaric and papular rash; left arm, elbows, feet and hands) on Day 9 following dose 1 (Section 2.5.6.1.4.3). A total of 4 (0.5%) participants in Part 1 withdrew from the study. One (0.3%) participant in the 50 µg group withdrew consent. In the 100 µg group, 1 (0.3%) participant was lost to follow-up and 2 (0.5%) participants withdrew consent.

Table 7: Participant Disposition by Dose Level in Part 1 (FAS)

	mRNA-1273 50 µg N=380 n (%)	mRNA-1273 100 µg N=371 n (%)	Total N=751 n (%)
Received first injection	380 (100)	371 (100)	751 (100)
Received second injection	379 (99.7)	371 (100)	750 (99.9)
Did not receive any injection	0	0	0
Completed study vaccine schedule	379 (99.7)	371 (100)	750 (99.9)
Discontinued study vaccine[a]	1 (0.3)	0	1 (0.1)
Reason for discontinuation of study vaccine			
Adverse event	1 (0.3)[b]	0	1 (0.1)
Completed study[c]	0	0	0
Withdrew from study	1 (0.3)	3 (0.8)	4 (0.5)
Reasons for withdrawal from study			
Lost to follow-up	0	1 (0.3)	1 (0.1)
Withdrawal of consent	1 (0.3)	2 (0.5)	3 (0.4)

Abbreviations: FAS = full analysis set.
Percentages are based on the number of participants enrolled in Part 1 who receive at least 1 injection of study IP.
[a.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[b.] One participant had an adverse event of urticaria papular (verbatim term: delayed skin reaction, urticaric and papular rash; left arm, elbows, feet and hands)on Day 9 following dose 1 (Section 2.5.6.1.4.3).
[c.] Study Completion is defined as a participant who completed 12 months of follow-up after the last injection received, included participants who complete the first injection but not second injection. The study is ongoing; no participants have completed 12 months of follow-up.
Source: Study P204 Table 14.1.1.1.1

In Part 1, the median duration of follow-up was 140 days (Q1 134, Q3 145) for the 50 µg group and 135 days (Q1 133, Q3 143) for the 100 µg group after dose 1 and 111 days (Q1 104, Q3 117) for the 50 µg group and 106 days (Q1 104, Q3 113) for the 100 µg group after dose 2 (Table 8). In the Part 1 50 µg group, 379 (99.7%) participants have been followed for 2 months (56 days) or more after dose 2.

Table 8: Summary of Study Duration by Dose Level in Part 1 (Safety Set)

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
≥ 7 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 35 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 56 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 7 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 28 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 56 days since second injection, n (%)	379 (99.7)	370 (99.7)	749 (99.7)
Study Duration from Dose 1, days			
Median (Min, Max)	140.0 (128, 206)	135.0 (76, 169)	138.0 (76, 206)
Study Duration from Dose 2, days			
Median (Min, Max)	111.0 (0, 177)	106.0 (41, 139)	108.0 (0, 177)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set for Part 1.
Source: Study P204 Table 14.1.5.1

From the Part 1 data, the 50 µg dose was selected for further study in Part 2 (Section 2.5.5.2.2.1).

In Part 2, at the time of the data snapshot (06 October 2021), 3007 participants in the mRNA-1273 group and 995 participants in the placebo group had received dose 1 and 2987 participants in the mRNA-1273 group and 969 participants in the placebo group had received dose 2 (Study P204 Table 14.1.5.2).

A total of 12 (0.3%) participants discontinued study vaccine, including 6 (0.2%) participants in the mRNA-1273 group and 6 (0.6%) participants in the placebo group. Reasons for discontinuation of study vaccine in the mRNA-1273 group were physician decision -2 (<0.1%) participants, withdrawal of consent - 2 (<0.1%) participants, and other - 2 (<0.1%) participants. Although none of the participants were coded as discontinuing due to an AE, 1 of the 2 participants who discontinued due to physician decision had an AE of rash, verbatim term: generalized rash [all over body]) on Day 10 (Section 2.5.6.1.4.3.2). In addition to the 12 participants coded as discontinuing study vaccine, an additional participant had AEs of urticaria (verbatim term: hives all over the body) on Day 24 and wheezing on Day 29 that were coded in the AE section of the electronic case report form (eCRF) as leading to discontinuation of study vaccine (Section 2.5.6.1.4.3.2). Reasons for discontinuation in the placebo group were AE - 1 (<0.1%) participant, physician decision - 1 (<0.1%) participant, withdrawal of consent - 3 (0.3%) participants, and other - 1 (<0.1%) participant. The participant who discontinued study vaccine due to an AE in the placebo group had COVID-19 infection on Day 25. This participant's Dosing Discontinuation Form was erroneously reported with in the clinical database with "Adverse Event" being the primary reason for dosing discontinuation; however, the action taken was "dose delayed" and the participant continues in the study.

A total of 20 (0.5%) participants in Part 2 withdrew from the study, including 9 (0.3%) participants in the mRNA-1273 group and 11 (1.1%) participants in the placebo group. Reasons for study withdrawal in the mRNA-1273 group were withdrawal of consent - 6 (0.2%) participants, AE - 1 (<0.1%) participant, physician decision - 1 (<0.1%) participant, and other - 1 (<0.1%) participant. One participant in the mRNA-1273 group withdrew from study due to an AE of inflammatory bowel disease (work-up for abdominal symptoms ongoing for many years is underway), which was assessed as not related and began 21 days after dose 2. Reasons for study withdrawal in the placebo group were withdrawal of consent - 9 (0.9%) participants and other - 2 (0.2%) participants.

Table 9: Participant Disposition by Dose Level in Part 2 (Randomization Set)

	mRNA-1273 50 µg N=3009 n (%)	Placebo N=1002 n (%)	Total N=4011 n (%)
Received first injection[a]	3005 (99.9)	997 (99.5)	4002 (99.8)
Received second injection	2985 (99.2)	971 (96.9)	3956 (98.6)
Did not receive any injection	4 (0.1)	5 (0.5)	9 (0.2)
Completed study vaccine schedule	2985 (99.2)	971 (96.9)	3956 (98.6)
Discontinued study vaccine[b]	6 (0.2)	6 (0.6)	12 (0.3)
Reason for discontinuation of study vaccine			
Adverse event	0[c]	1 (<0.1)[c]	1 (<0.1)
Physician decision	2 (<0.1)[d]	1 (<0.1)	3 (<0.1)
Withdrawal of consent	2 (<0.1)[e]	3 (0.3)	5 (0.1)
Other	2 (<0.1)[f]	1 (<0.1)	3 (<0.1)
Completed study[g]	0	0	0
Withdrew from study	9 (0.3)	11 (1.1)	20 (0.5)
Reasons for withdrawal from study			
Adverse event	1 (<0.1)[h]	0	1 (<0.1)
Physician decision	1 (<0.1)	0	1 (<0.1)
Withdrawal of consent	6 (0.2)	9 (0.9)	15 (0.4)
Other	1 (<0.1)	2 (0.2)	3 (<0.1)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Randomization Set for Part 2.
[a.] Two participants who were randomized to the placebo group received mRNA-1273 50 µg due to a dosing error.
[b.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[c.] One participant in the mRNA-1273 group had AEs of urticaria (verbatim term: hives all over the body) on Day 24 and wheezing on Day 29 that were coded in the AE section of the eCRF as leading to discontinuation of study vaccine d. One participant in the mRNA-1273 group discontinued study vaccine due to physician decision due to an adverse event of rash (verbatim term: generalized rash [all over body]) on Day 10 (Section 2.5.6.1.4.3.2). One participant discontinued study vaccine due to physician decision because the participant became aggressive and violent when the vaccinator went to give study injection.
[e.] Two participants in the mRNA-1273 group discontinued study vaccine due to withdrawal of consent: 1 denied nasal swab and withdrew consent and 1 no longer wanted to comply with study procedures.
[f.] Two participants in the mRNA-1273 group discontinued study vaccine for other reasons; both refused vaccination.
[g.] Study Completion is defined as a participant who completed 12 months of follow up after the last injection received, included participants who complete the first injection but not second injection.
[h.] One participant in the mRNA-1273 group withdrew from study due to an AE of inflammatory bowel disease, which was reported 21 days after dose 2. This event was assessed as not related by the investigator.
Source: Study P204 Table 14.1.1.1.2 and Study P204 Listing 16.2.7.1.2

In Part 2, the median duration of follow-up was 50 days (Q1 45.0, Q3 56.0) after dose 1 and 20 days (Q1 15.0, Q3 26.0) after dose 2 (Table 10). In Part 2, 2958 (98.4%) participants in the mRNA-1273 group and 962 (96.7%) participants in the placebo group have been followed for 7 days or more after dose 2. Further, 474 (15.8%) participants in the mRNA-1273 group and 165 (16.6%) participants in the placebo group have been followed for 1 month (28 days) or more after dose 2.

Table 10: Summary of Study Duration in Part 2 (Safety Set)

	mRNA-1273 50 µg N=3007	Placebo N=995	Total N=4002
Received first injection, n (%)	3007 (100)	995 (100)	4002 (100)
Received second injection, n (%)	2987 (99.3)	969 (97.4)	3956 (98.9)
≥ 7 days since first injection, n (%)	3007 (100)	995 (100)	4002 (100)
≥ 35 days since first injection, n (%)	3004(>99.9)	990 (99.5)	3994 (99.8)
≥ 56 days since first injection, n (%)	763 (25.4)	250 (25.1)	1013 (25.3)
≥ 7 days since second injection, n (%)	2958 (98.4)	962 (96.7)	3920 (98.0)
≥ 28 days since second injection, n (%)	474 (15.8)	165 (16.6)	639 (16.0)
Study Duration from Dose 1, days			
Median (Min, Max)	50.0 (29, 59)	50.0 (14, 59)	50.0 (14, 59)
Study Duration from Dose 2, days			
Median (Min, Max)	21.0 (0, 30)	20.0 (0, 30)	20.0 (0, 30)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set for Part 2.
Source: Study P204 Table 14.1.5.2

2.5.5.1.3 Demographics and Baseline Characteristics

Participant demographics and baseline characteristics in the Part 1 Safety Set are provided in Table 11. In Part 1, 48.9% were male and 51.1% were female; 58.3% were White non-Hispanic, and 40.9% were from Communities of Color.

Table 11: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Safety Set)

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
Age, years			
Mean (SD)	8.6 (1.66)	8.6 (1.62)	8.6 (1.64)
Median	9.0	9.0	9.0
Min, Max	6, 11	6, 11	6, 11
Sex, n (%)			
Male	195 (51.3)	172 (46.4)	367 (48.9)
Female	185 (48.7)	199 (53.6)	384 (51.1)
Race, n (%)			
White	266 (70.0)	284 (76.5)	550 (73.2)
Black	33 (8.7)	13 (3.5)	46 (6.1)
Asian	26 (6.8)	25 (6.7)	51 (6.8)
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.1)
Multiracial	39 (10.3)	31 (8.4)	70 (9.3)
Other	3 (0.8)	10 (2.7)	13 (1.7)
Not Reported	12 (3.2)	4 (1.1)	16 (2.1)
Unknown	0	2 (0.5)	2 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	72 (18.9)	69 (18.6)	141 (18.8)
Not Hispanic or Latino	304 (80.0)	296 (79.8)	600 (79.9)
Not Reported	3 (0.8)	3 (0.8)	6 (0.8)
Unknown	1 (0.3)	3 (0.8)	4 (0.5)

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
Race and Ethnicity Group[a], n (%)			
White, non-Hispanic	208 (54.7)	230 (62.0)	438 (58.3)
Communities of Color	168 (44.2)	139 (37.5)	307 (40.9)
Missing	4 (1.1)	2 (0.5)	6 (0.8)
Weight, kg			
Mean (SD)	34.93 (12.472)	34.86 (11.834)	34.89 (12.153)
Median	32.05	32.27	32.18
Min, Max	16.8, 86.4	16.5, 85.6	16.5, 86.4
Baseline SARS-CoV-2 Status[b], n (%)			
Negative	327 (86.1)	322 (86.8)	649 (86.4)
Positive	28 (7.4)	30 (8.1)	58 (7.7)
Missing	25 (6.6)	19 (5.1)	44 (5.9)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set for Part 1.
[a.] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
[b.] 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.
Source: Study P204 Table 14.1.3.1.1

Participant demographics and baseline characteristics in the Part 1 PP Immunogenicity Subset are provided in Table 12 and were generally comparable to the Part 2 Safety Set (Table 13). Participant demographics and baseline characteristics in the young adult (18 to 25 years old) P301 PP Immunogenicity Subset is provided in Table 12. Representation of communities of color was similar in the P204 Part 2 Safety Set and the P301 young adult (18 to 25 years old) P301 PP Immunogenicity Subset.

Table 12: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Per Protocol Immunogenicity Subset)

	P204 (6-<12 years) mRNA-1273 50 µg N=134	P301 (18-25 years) mRNA-1273 100 µg N=296
Age, years		
Mean (SD)	8.7 (1.48)	22.4 (2.19)
Median	9.0	23.0
Min, Max	6, 11	18, 25
Sex, n (%)		
Male	79 (59.0)	143 (48.3)
Female	55 (41.0)	153 (51.7)
Race, n (%)		
White	85 (63.4)	207 (69.9)
Black	12 (9.0)	29 (9.8)
Asian	13 (9.7)	30 (10.1)
American Indian or Alaska Native	0	3 (1.0)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
Multiracial	18 (13.4)	14 (4.7)

	P204 (6-<12 years) mRNA-1273 50 µg N=134	P301 (18-25 years) mRNA-1273 100 µg N=296
Other	0	8 (2.7)
Not Reported	6 (4.5)	3 (1.0)
Unknown	0	0
Ethnicity, n (%)		
Hispanic or Latino	24 (17.9)	79 (26.7)
Not Hispanic or Latino	109 (81.3)	215 (72.6)
Not Reported	1 (0.7)	0
Unknown	0	2 (0.7)
Race and Ethnicity Group[a], n (%)		
White, non-Hispanic	68 (50.7)	145 (49.0)
Communities of Color	65 (48.5)	151 (51.0)
Missing	1 (0.7)	0
Weight, kg		
Mean (SD)	34.81 (10.714)	77.59 (19.280)
Median	32.76	73.64
Min, Max	19.4, 75.0	44.0, 158.2

Abbreviations: max = maximum; min = minimum; SD = stable disease.
Percentages are based on the number of participants in the Per Protocol Immunogenicity Subset for Part 1.
[a.] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
Source: Study P204 Table 14.1.3.4.1

Participant demographics and baseline characteristics in the Part 2 Safety Set were representative of the intended target population and were generally balanced between the mRNA-1273 group and placebo group (Table 13).

Table 13: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set)

	mRNA-1273 50 µg N=3007 n (%)	Placebo N=995 n (%)	Total N=4002 n (%)
Age, years			
Mean (SD)	8.5 (1.65)	8.5 (1.64)	8.5 (1.65)
Median	8.0	9.0	9.0
Min, Max	6[a], 11	6, 11	6[a], 11
Sex, n (%)			
Male	1554 (51.7)	481 (48.3)	2035 (50.8)
Female	1453 (48.3)	514 (51.7)	1967 (49.2)
Race, n (%)			
White	1955 (65.0)	667 (67.0)	2622 (65.5)
Black	308 (10.2)	92 (9.2)	400 (10.0)
Asian	296 (9.8)	99 (9.9)	395 (9.9)
American Indian or Alaska Native	14 (0.5)	3 (0.3)	17 (0.4)
Native Hawaiian or Other Pacific Islander	4 (0.1)	0	4 (<0.1)
Multiracial	326 (10.8)	97 (9.7)	365 (10.8)
Other	62 (2.1)	23 (2.3)	65 (1.9)
Not Reported	28 (0.9)	12 (1.2)	40 (1.2)
Unknown	9 (0.3)	1 (0.1)	9 (0.3)
Missing	5 (0.2)	1 (0.1)	5 (0.1)

	mRNA-1273 50 µg N=3007 n (%)	Placebo N=995 n (%)	Total N=4002 n (%)
Ethnicity, n (%)			
Hispanic or Latino	558 (18.6)	180 (18.1)	738 (18.4)
Not Hispanic or Latino	2419 (80.4)	806 (81.0)	3225 (80.6)
Not Reported	23 (0.8)	5 (0.5)	28 (0.7)
Unknown	7 (0.2)	4 (0.4)	11 (0.3)
Race and Ethnicity Group[b], n (%)			
White, non-Hispanic	1539 (51.2)	535 (53.8)	2074 (51.8)
Communities of Color	1460 (48.6)	456 (45.8)	1916 (47.9)
Missing	8 (0.3)	4 (0.4)	12 (0.3)
Weight, kg			
Mean (SD)	33.33 (11.279)	33.52 (11.432)	33.38 (11.316)
Median	30.60	30.91	30.73
Min, Max	14.0, 112.0	14.2, 99.8	14.0, 112.0
Baseline SARS-CoV-2 Status[c], n (%)			
Negative	2692 (89.5)	878 (88.2)	3570 (89.2)
Positive	257 (8.5)	87 (8.7)	344 (8.6)
Missing	58 (1.9)	30 (3.0)	88 (2.2)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = stable disease.
Percentages are based on the number of participants in the Safety Set for Part 2.
[a.] One participant's age was incorrectly entered in the database as 5 years of age. The site has confirmed that the participant was indeed 6 years of age at the time of informed consent.
[b.] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
[c.] 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.
Source: Study P204 Table 14.1.3.2

2.5.5.2 Vaccine Effectiveness and Efficacy

This section contains an overview of immunogenicity and efficacy data for the ongoing Study P204 age group of 6 years to < 12 years of age. In this pediatric submission, mRNA-1273 effectiveness is inferred based on meeting prespecified criteria of noninferiority compared with Ab responses obtained from young adults (18 to 25 years) in the pivotal P301 study, which established the efficacy of mRNA-1273. Efficacy was evaluated as a secondary objective.

2.5.5.2.1 Statistical Methods Used for P204

The statistical methods for Study P204 are provided in the SAP (version 2.0, 22 September 2021) (Module 5.3.5.1).

The protocol stated that the primary immunogenicity objective of Study P204 is to infer the effectiveness of mRNA-1273 based on the primary endpoint of either:

- The proportion of participants with a serum Ab level at Day 57 ≥ Ab threshold of protection if an acceptable threshold of protection has been established
- If an acceptable threshold of protection has not been established, the GM value of serum Ab level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301)

Day 57 (1 month after the second dose) was chosen for the timepoint of immunogenicity analysis because Abs tend to peak approximately 28 days after vaccination. This timepoint was used for immunogenicity in the pivotal adult study (Study P301) in which the VE has been established (Section 2.5.2.4.1). This timepoint was also used for immunobridging in the adolescent study (Study P203).

At the time of analysis for this submission, a serum Ab threshold of vaccine protection against COVID-19 had not been established. Therefore, the primary objective to infer the effectiveness of mRNA-1273 was evaluated by comparing the GM value of serum Ab level and seroresponse rates from Study P204 vaccine recipients at Day 57 to those obtained from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the pivotal study (Study P301), which established the efficacy of mRNA-1273.

An analysis of covariance model was conducted with Ab at Day 57 in log scale as the dependent variable and a group variable (a pediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable. The GM values of the pediatric age group at Day 57 were estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) was estimated by the ratio of GLSM from the model. The corresponding 2-sided 95% CI of GMR was provided to assess the difference in immune response for the pediatric age group (6 to <12 years of age, Study P204) compared with the young adults (18 to 25 years of age) in Study P301 at Day 57. The noninferiority of GM in 6 to <12 years of age group is considered demonstrated if the lower bound of the 95% CI of the GMR is ≥ 0.67 based on the noninferiority margin of 1.5. In addition, the GMR point estimate > 0.8 (minimum threshold) is required for the success criteria of the immunogenicity objective based on GMT. In addition, GMR with 95% CI calculated using t-distribution was provided to assess if the 2 methods are consistent in the analysis results.

The number and percentage of participants with seroresponse due to vaccination was provided with 2-sided 95% CI using the Clopper-Pearson method at each post baseline time point with Day 57 being of the primary interest. The seroresponse rate difference with 95% CI using the Miettinen-Nurminen (score) confidence limits at Day 57 was provided between children

receiving mRNA-1273 in Study P204 and young adults 18 to 25 years of age receiving mRNA-1273 from Study P301. The noninferiority of seroresponse rate in 6 to <12 years of age group is considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is > -10% based on the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Secondary objectives of Study P204 include evaluation of the incidence of SARS-CoV-2 infection, the incidence of asymptomatic SARS-CoV-2 infection, and the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. Definitions of infection are provided in Section 2.5.5.2.2.3. The number and percentage of participants who had an event are provided. The incidence rate was calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate was calculated using the exact method (Poisson distribution) and adjusted by person-time. Person-time is defined in Part 2 as the total time from randomization date to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earliest.

2.5.5.2.2 Results

2.5.5.2.2.1 Dose Selection

The study began with dosing participants in the 6 years to < 12-year age group in Part 1 with 50 µg of mRNA-1273. After at least 75 participants had completed Day 8 (1 week after dose 1 of mRNA-1273 50 µg), an internal safety team reviewed the available safety data and agreed with the prespecified protocol plans to proceed with the 100 µg arm in Part 1 in the 6 years to < 12-year age group.

Review of the reactogenicity profile of the 50 µg dose was comparable to what had been observed young adults (18- to 25-year-olds) who had received 100 µg in Study P301 (note: reactogenicity data for the current data snapshot in Study P204 can be found in Section 2.5.6.1.2). The 100 µg dose was more reactogenic in 6 years to < 12-year-old participants than in older populations as evidenced by an increased fever rate.

A preplanned immunogenicity data review for dose selection compared the GM nAbs and seroresponse rate of the 6 to <12 years of age Dose Selection PP Immunogenicity Subset 50 µg Group in Study P204 with those from previously generated results of the immunogenicity subset of 18- to 25-year-old participants in the pivotal Study P301 (Module 5.3.5.1). In children 6 years to < 12 years old in the immunogenicity subset, the nAb GMT (measured by PsVNA ID_{50}) was 1204.647 at Day 57, 28 days after dose 2 (Table 14). All (100%) children achieved seroresponse. The immunogenicity data from the Dose Selection PP Immunogenicity Subset 50 µg Group of Study P204 were similar to those of the pivotal Study P301 immunogenicity subset (Study P301

established the efficacy of mRNA-1273 in adults). Using the PsVNA ID_{50}, the GMR of the pediatric (Study P204) 50 µg group (n=67) to young adult (Study P301, n=296) nAb titers at Day 57 was 0.93 (95% CI 0.74, 1.16). The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 1.4% (95% CI: -4.1%, 3.4%). Based on the combined assessments of safety, reactogenicity, tolerability, and immunogenicity, the 50 µg dose was selected for evaluation in Part 2 (randomized, placebo-controlled portion) of Study P204 in the 6 years to < 12-year age group.

Of note, one P301 participant PPD) had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunizations values in the PsVNA ID_{50} are uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.

Table 14: Part 1 Dose-Finding Analysis of Pseudovirus Neutralizing Antibody Level and Seroresponse Rate at Day 57 by Pseudovirus Neutralizing Assay (ID_{50}) (Dose Selection PP Immunogenicity Subset 50 µg Group)

	Study P204 6 years to < 12 Years mRNA-1273 50 µg N=67	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N=296**
Baseline GMT	9.250	9.506
GMT Observed at Day 57	1204.647	1301.312
GMFR (95% CI)[a] at Day 57 from Baseline	130.232 (113.205, 149.820)	136.896 (122.266, 153.276)
GMT (model based) (95% CI) at Day 57	1204.647 (986.657, 1470.798)	1301.312 (1183.412, 1430.959)
GMR (P204 vs P301; model-based) (95% CI)[b]	0.93 (0.74, 1.16)	
Participants achieving seroresponse, n (%)[c] at Day 57	67 (100)	292 (98.6)
95% CI[d]	94.6, 100.0	96.6, 99.6
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	1.4 (-4.1, 3.4)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Of note, one P301 participant PPD) had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunizations values in the PsVNA ID50 are

uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.
a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
b. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
d. 95% CI is calculated using the Clopper-Pearson method.
e. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: Module 5.3.5.1

Similarly, assessment of the PsVNA results applying a cutoff of 80% inhibitory dose (ID_{80}), showed similar results with a GMR of pediatric participants to young adults at Day 57 of 0.966 (95% CI: 0.795, 1.175) and difference in seroresponse rate of 1.4% (95% CI: -4.1%, 3.4%) (Module 5.3.5.1).

As part of the dose-finding immunogenicity assessment, anti-Spike bAb was also measured using the MSD platform (Table 15). The GMR of bAb specific to SARS-CoV-2 spike protein measured by MSD at Day 57 of children 6 years to <12 years of age in the Dose Selection PP Immunogenicity Subset 50 µg Group (Study P204) compared with young adults (Study P301) was 1.295 (95% CI: 1.041, 1.612). The difference in seroresponse rates by binding antibody specific to SARS-CoV-2 spike protein by MSD between children (Study P204) and young adults (Study P301) at Day 57 was 0.7% (95% CI: -4.7%, 2.6%).

Taken together, results of the nAb and the bAb assay in the dose-finding immunogenicity assessment supported the selection of the 50 µg dose for advancement to Part 2 as both suggested that 50 µg would meet noninferiority criteria in the PP Immunogenicity Subset.

Table 15: Part 1 Dose-Finding Analysis of Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD and Seroresponse Rate at Day 57: ANCOVA Model (Dose Selection PP Immunogenicity Subset 50 µg Group)

Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD	**Study P204 6 years to < 12 Years mRNA-1273 50 µg GMT 95% CI N=67**	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg GMT 95% CI N=280**	**GMR Study P204 vs Study P301 95% CI[a]**
	333103.348 273637.564, 405491.992	257131.438 233549.311, 283094.717	1.295 1.041, 1.612
Seroresponse by Binding Antibody Specific to SARS-CoV-2 Spike Protein by MSD[b]	**Study P204 6 years to < 12 Years mRNA-1273 50 µg n (%) 95% CI[c] N=67**	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg n (%) 95% CI[c] N=-280**	**Difference in Seroresponse Rate (%) 95% CI[d]**
	67 (100) 94.6, 100.0	278 (99.3) 97.4, 99.9	0.7 -4.7, 2.6

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMT = geometric mean titer estimated by geometric least squares mean; GMR = geometric mean ratio; ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; MSD = MesoScale Discovery; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
[a.] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b.] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
[c.] 95% CI is calculated using the Clopper-Pearson method.
[d.] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: Module 5.3.5.1

The GMR of pediatric (Study P204) 100 µg group (n=57) to young adult (Study P301, n=296) nAb titers at Day 57 was 1.45 (95% CI 1.15, 1.84). The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 1.4% (95% CI: -5.0%, 3.4%) (Module 5.3.5.1).

2.5.5.2.2.2 Immunogenicity

Results are provided in this section for the PP Immunogenicity Subset for the 50 µg group from Part 1 of Study P204 using the validated PsVNA. These results consist of all available data from the 50 µg group up until data snapshot (06 October 2021), excluding data from the Dose-Finding Immunogenicity Subset (n=67) used to determine dose selection (described above). Technicians at Duke University Medical Center who performed PsVNA were blinded to the associated study visits of samples.

Table 16 summarizes the analysis of serum nAb levels (PsVNA ID_{50} assay) at Day 57 for children 6 years to < 12 years of age in Study P204 compared with those at Day 57 for young adults (18 to 25 years of age) in Study P301. Figure 2 illustrates PsVNA ID_{50} nAb titers for pediatric participants in Study P204 and young adult participants in Study P301. Of note, one P301 participant PPD had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunizations values in the PsVNA ID_{50} are uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.

In the PP Immunogenicity Subset (n=134), baseline nAb GMT (measured by PsVNA ID_{50}) in children 6 years to < 12 years old in Study P204 was below the LLOQ and GMT was 1964.601 (95% CI 1722.357, 2240.915) at Day 57, 28 days after dose 2, with 99.3% of children achieving seroresponse (Table 16). The GM fold-rise from baseline at D57 was 209.466 (95% CI: 182.947, 239.829), indicating robust immunogenicity response of 50 µg of mRNA-1273 in children ages of 6 years to <12 years.

The prespecified success criteria for the primary immunogenicity objective are met based on the co-primary immunogenicity endpoints (Table 16). The immunobridging in children 6 years to < 12 years old in Study P204 is demonstrated as compared with young adults in Study P301. As part of the noninferiority comparison, the GMR of nAb titers at Day 57 of children 6 years to <12 years of age (Study P204) compared with young adults (Study P301) was 1.510 (95% CI: 1.263, 1.804), meeting the noninferiority success criterion (ie, lower bound of the 95% CI for GMR ≥ 0.67). In addition, the criterion on the point estimator of GMR > 0.8 was also met. The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 0.6% (95% CI: -2.8%, 2.8%), meeting the noninferiority success criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%).

Since both coprimary endpoints met the prespecified success criteria for the primary immunogenicity objective (Section 2.5.5.2.1), the immunobridging in children 6 years to < 12 years old (Study P204) is considered to have been demonstrated as compared with young adults in Study P301, where robust efficacy was demonstrated.

Table 16: Co-primary Immunobridging (Pseudovirus Neutralizing Antibody Level by Pseudovirus Neutralizing Assay [ID_{50}])

	Study P204 6 years to < 12 Years mRNA-1273 50 µg N=134	Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N=296
Baseline GMT	9.379	9.506
GMT Observed at Day 57	1964.601	1301.312
GMFR (95% CI)[a] at Day 57 from Baseline	209.466 (182.947, 239.829)	136.896 (121.266, 153.276)
GMT (model based) (95% CI) at Day 57	1964.601 (1694.578, 2277.651)	1301.312 (1178.086, 1437.427)
GMR (P204 vs P301; model-based) (95% CI)[b]	1.510 (1.263, 1.804)	
Participants achieving seroresponse, n (%)[c] at Day 57	133 (99.3)	292 (98.6)
95% CI[d]	95.9, 100.0	96.6, 99.6
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	0.6 (-2.8, 2.8)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.

P301 mRNA-1273 group includes young adults (18-25 years of age).

The ULOQ for selected P301 participants tested previously was different.

Of note, one P301 participant PPD had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunizations values in the PsVNA ID50 are uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.

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

[b.] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

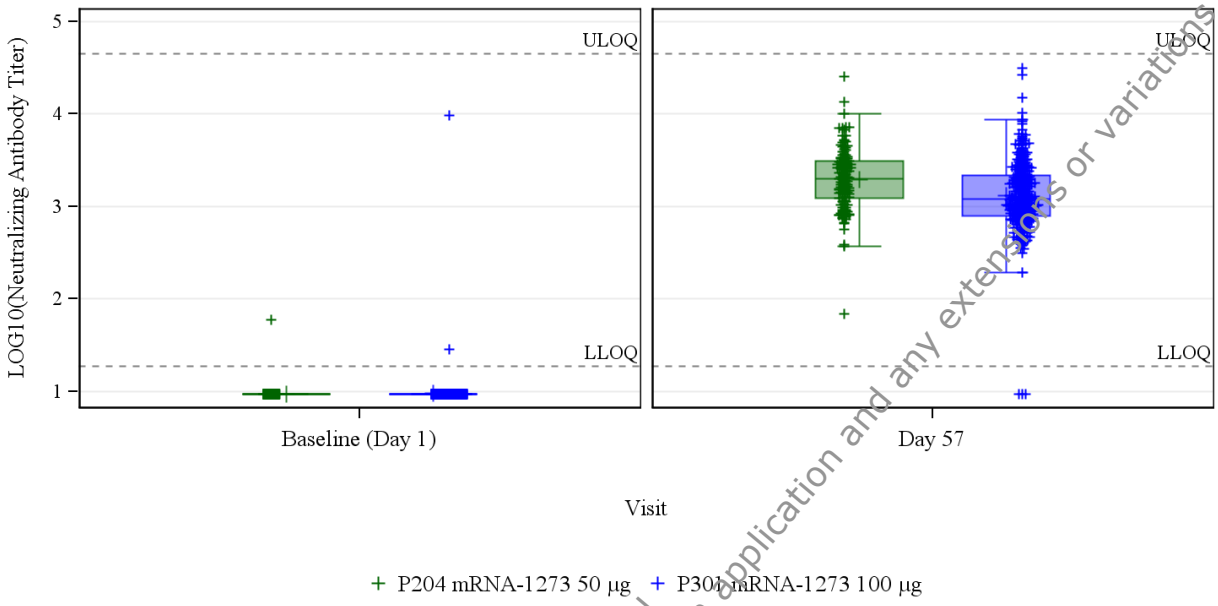
[c.] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.

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

[e.] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: Study P204 Table 14.2.3.1.3.1, Study P204 Table 14.2.1.1.3.4.1, and Study P204 Table 14.2.1.2.3.4.1

Figure 2: Box Plot of Pseudovirus Neutralizing Antibody ID_{50} (PP Immunogenicity Subset)



Abbreviations: ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Boxplot is based on log-transformed values.
Source: Study P204 Figure 14.2.1.4.6.1

Assessment of the PsVNA results applying a cutoff of 80% inhibitory dose (ID_{80}), showed similar results with a GMR of pediatric participants to young adults at Day 57 of 1.310 (95% CI: 1.119, 1.533) and difference in seroresponse rate again of 0.6% (95% CI: -2.8%, 2.8%) (Study P204 Table 14.2.1.1.3.4.1 and Study P204 Table 14.2.1.2.3.4.1).

Anti-Spike bAb assay data using the MSD platform confirmed the findings of the analyses based on the PsVNA ID_{50} assay (Table 17). The GMR of binding antibody specific to SARS-CoV-2 spike protein measured by MSD at Day 57 of children 6 years to <12 years of age (Study P204) compared with young adults (Study P301) was 1.253 (95% CI: 1.055, 1.488). The difference in seroresponse rates by binding antibody specific to SARS-CoV-2 spike protein by MSD between children (Study P204) and young adults (Study P301) at Day 57 was 0.7% (95% CI: -2.1%, 2.6%).

Table 17: Analysis of Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD and Seroresponse Rate at Day 57: ANCOVA Model (PP Immunogenicity Subset)

Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD	**Study P204 6 years to < 12 Years mRNA-1273 50 µg GMT 95% CI N=133**	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg GMT 95% CI N=280**	**GMR Study P204 vs Study P301 95% CI[a]**
	322157.952 279605.198, 371186.755	257131.438 233213.106, 283502.833	1.253 1.055, 1.488
Seroresponse by Binding Antibody Specific to SARS-CoV-2 Spike Protein by MSD[b]	**Study P204 6 years to < 12 Years mRNA-1273 50 µg n (%) 95% CI[c] N=133**	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg n (%) 95% CI[c] N=280**	**Difference in Seroresponse Rate (%) 95% CI[d]**
	133 (100) 97.3, 100	278 (99.3) 97.4, 99.9	0.7 -2.1, 2.6

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer estimated by geometric least squares mean; LLOQ = lower limit of quantification; LS = least squares; MSD = MesoScale Discovery; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
[a.] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b.] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
[c.] 95% CI is calculated using the Clopper-Pearson method.
[d.] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: Study P204 Table 14.2.1.2.2.4.1 and Study P204 Table 14.2.1.2.2.4.1

In both the dose-finding (N=67) and final analyses (N=134), immunogenicity of the 50 µg dose among children 6 years to <12 years of age was similar to young adults in Study P301 using the PsVNA as well as the anti-spike bAb assay. While there was a difference in the GMTs obtained using the PsVNA ID_{50} in the dose finding and final analyses, a review of the PsVNA assay performance between the 2 sets demonstrated that the assay continued to perform within control and specification limits. The anti-spike bAb assay results were consistent between the 2 groups.

2.5.5.2.2.3 Efficacy

2.5.5.2.2.3.1 Methods Used for Efficacy Evaluations

The incidence rates of COVID-19 (ie, symptomatic SARS-CoV-2 infection), SARS-CoV-2 infections (asymptomatic or symptomatic infections), and asymptomatic SARS-CoV-2 infections were assessed as secondary endpoints.

COVID-19 cases were assessed using each of the 2 definitions:

1. the "CDC case definition," which requires at least 1 prespecified clinical symptom and a positive RT-PCR

2. a "P301 case definition" used in the pivotal Phase 3 study in adults (P301) and based on either at least 2 prespecified systemic symptoms or at least 1 respiratory symptom and a positive RT-PCR

Use of the "P301 case definition" allowed alignment of COVID-19 case assessment with that in the pivotal adult study (Study P301). Use of the "CDC case definition," defined by a single symptom, tailored the assessment of COVID-19 to children, a population typically with a milder clinical presentation than adults. Definitions of COVID-19 cases and SARS-CoV-2 infections used in Study P204 and included in this submission are presented in Table 18.

A formal approach to surveil for COVID-19 cases and to identify SARS-CoV-2 infections (regardless of symptoms) was used. Surveillance for symptoms consistent with COVID-19 was conducted via telephone calls or eDiary prompts starting at enrollment and performed biweekly through Day 71 and monthly thereafter (see also clinical protocol Section 7.3.2 [Surveillance for COVID-19 Symptoms]). During the study, participants who had symptoms suggesting COVID-19 were asked to arrange an unscheduled illness visit at the study site. At the illness visit, participants were to be clinically assessed and a SARS-CoV-2 RT-PCR test (nasal swab) was to be performed. A "*SARS-CoV-2 or COVID-19 Symptom Assessment Page*" in the eCRF was to be completed: (i) for every participant with relevant clinical symptoms assessed at any study visit (ie, scheduled or unscheduled illness visit), or (ii) if symptoms were described during a safety call.

In Study P204, the COVID-19 case definition for efficacy endpoints requires the following: (i) Positive RT-PCR (central or local laboratory) (Table 18) and (ii) eligible symptoms reported on the "*SARS-CoV-2 or COVID-19 Symptom Assessment Page*" eCRF form. Completion of this Symptom Assessment Page was critical to allowing proper evaluation and verification of potential COVID-19 cases for efficacy endpoints.

Routine assessment for SARS-CoV-2 infection (regardless of symptoms) was performed by performing RT-PCR testing on pre-planned nasal swab samples collected on Day 1 and Day 29 (day of injection) and on Day 43 (if visit is applicable), Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (12 months after dose 2).

Based on these definitions, and using the surveillance and collection procedures defined above, the following results are provided in this section. These are provided for the (i) PP Set for Efficacy in Part 2 (for both mRNA-1273 50 µg and placebo groups) as well as (ii) the mRNA-1273 50 µg group from Part 1. Results are provided both as case numbers and incidence per 1000 person-years in Part 2.

Of note, asymptomatic SARS-CoV-2 is most often identified via samples obtained at prespecified, scheduled study visits from either nasal swab samples (RT-PCR) or serum samples (bAb levels against SARS-CoV-2 nucleocapsid as measured by Roche Elecsys). Asymptomatic SARS-CoV-2 infections may also be identified at unscheduled study visits triggered by potential exposure, with no subsequent development of clinical symptoms (in spite of collection being identified as "unscheduled" or "illness" visit in the database). In addition, serum samples collected at prespecified timepoints for measure of vaccine-induced immunogenicity (variable timepoints based on sub-cohort) were also tested for presence of Ab against non-vaccine Ag (ie, SARS-CoV-2 nucleocapsid). In this way, prior, asymptomatic infection could also be identified.

Adverse event terms that include "COVID" are reviewed in Section 2.5.6.1.4.4.1.

Table 18: Case Definitions in Study mRNA-1273-P204

Endpoint	Definition
COVID-19 "CDC case definition"	At least 1 symptom from a prespecified list of COVID-19 symptoms derived from the US CDC case definition Systemic symptoms: fever (temperature > 38°C/≥ 100.4°F) or chills (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding, **OR** respiratory signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours) **AND** At least 1 positive RT-PCR for SARS-CoV-2.
COVID-19 "P301 case definition"	COVID-19 case will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms as follows: A positive post-baseline PCR result **AND** At least 2 systemic symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** At least 1 of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
SARS-CoV-2 Infection (regardless of symptoms)	A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, **OR** Positive RT-PCR test post-baseline.

Endpoint	Definition
Asymptomatic SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Absent of COVID-19 symptoms **AND** at least 1 from below: bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, **OR** Positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; COVID19 = coronavirus disease 19; PCR = polymerase chain reaction; RT-PCR = reverse-transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Source: Study P204 protocol amendment 4 in Module 5.3.5.1.

2.5.5.2.2.3.2 Efficacy Analyses for Endpoints Starting 14 Days After Dose 2 in the PP Set for Efficacy

This section includes a descriptive analysis of SARS-CoV-2 infections and COVID-19 cases as defined above (Table 18) and occurring 14 days or more after dose 2 in the PP Set for Efficacy.

In the Part 1 50 µg group starting 14 days after dose 2 in the PP Set for Efficacy, there was 1 case of asymptomatic SARS-CoV-2 infection (occurring at 28 days after dose 2 in a 7-year-old male), which was detected at the Day 57 prespecified study visit (Study P204 Table 14.2.5.1.1.2, Study P204 Table 14.2.6.1.1.2.1, Study P204 Table 14.2.7.1.1.2, Study P204 Table 14.2.8.1.1.2, and Study P204 Listing 16.2.6.5.2).

In Part 2 starting 14 days after dose 2 in the PP Set for Efficacy, there was 1 case (0.1%) of COVID-19 in the placebo group (incidence rate 8.58 per 1000 person-years) and none in the mRNA-1273 group (Table 19). The case in the placebo group met both the CDC case definition of COVID-19 and the P301 case definition of COVID-19 (Study P204 Table 14.2.5.1.1.2, Study P204 Table 14.2.7.1.1.2, and Study P204 Table 14.2.8.1.1.2). There were no cases of asymptomatic SARS-CoV-2 infection in either treatment group starting 14 days after dose 2 in the PP Set for Efficacy (Study P204 Table 14.2.6.1.1.2.1). The paucity of cases (of COVID-19 or SARS-CoV-2 infection) is not unexpected based on the limited follow-up period and the 3:1 mRNA-1273:placebo randomization ratio.

Table 19: Summary of Secondary Efficacy Endpoint Analysis Results Starting 14 Days After Dose 2 (PP Set for Efficacy)

Endpoint	Part 2	
	mRNA-1273 50 µg N=2638	Placebo N=852
CDC case definition of COVID-19		
Cases, n (%)	0	1 (0.1)
Incidence rate per 1000 person-years (95% CI)[a,b]	0.000 (NE, 10.221)	8.580 (0.217, 47.803)
P301 case definition of COVID-19		
Cases, n (%)	0	1 (0.1)
Incidence rate per 1000 person-years (95% CI)	0.000 (NE, 10.219)	8.576 (0.217, 47.784)
Asymptomatic SARS-CoV-2 infection		
Cases, n (%)	0	0
Incidence rate per 1000 person-years (95% CI)	0.000 (NE, 10.241)	0.000 (NE, 31.850)
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n (%)	0	1 (0.1)
Incidence rate per 1000 person-years (95% CI)	0.000 (NE, 10.241)	8.634 (0.219, 48.106)

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not estimable; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

[a.] Person-years is defined as the total years from the first injection date for Part 1 and the randomization date for Part 2 to the date of event (CDC Case Definition of COVID-19, P301 case definition of COVID-19, asymptomatic SARS-CoV-2 infection, or SARS-CoV-2 infection, depending upon endpoint), last date of study participation, or efficacy data cutoff date, whichever is the earliest.

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

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

Source: Study P204 Table 14.2.8.1.1.2, Study P204 Table 14.2.7.1.1.2, Study P204 Table 14.2.6.1.1.2.1, and Study P204 Table 14.2.5.1.1.2

2.5.5.2.2.3.3 Efficacy Analyses for Endpoints Starting 14 Days After Dose 1 in the mITT1

This section includes a descriptive analysis of SARS-CoV-2 infections and COVID-19 cases as defined above (Table 18) and occurring at least 14 days after dose 1 in the mITT1. Please note that all summaries of efficacy are in baseline PCR and Elecsys negative participants.

In the Part 1 50 µg group in the mITT1, there was 1 case of asymptomatic SARS-CoV-2 infection as described in Section 2.5.5.2.2.3.2. There were no cases of COVID-19 (Study P204 Listing 16.2.6.5.2).

In Part 2 in the mITT1, VE analyses were conducted using the COVID-19 "CDC case definition," requiring only 1 symptom and reflecting the less severe disease, which is more common in pediatric patients, and a positive RT-PCR. The VE against cases occurring 14 days or more after dose 1 was based on 3 cases (0.1%) in the mRNA-1273 group (incidence rate 11.399 per 1000 person-years) and 14 cases (1.6%) in the placebo group (incidence rate 163.810 per 1000 person-years) (Table 20). Vaccine efficacy was 93.0% (95% CI: 75.1%, 98.7%). These

results show an early onset of protection after vaccination with mRNA-1273 and were similar to the 94.1% VE (95% CI: 89.3%, 96.8%) observed 14 days after dose 2 in the final blinded analysis of the pivotal P301 study (Study P301 55 cases in the mRNA-1273 group and 744 cases in the placebo group).

In Part 2 in the mITT1 for the analysis of COVID-19 meeting the "P301 case definition" for cases occurring 14 days or more after dose 1, there were 0 cases in the mRNA-1273 group and 13 cases (1.5%) in the placebo group (incidence rate 152.027 per 1000 person-years), and VE was 100% (95% CI: 89.3%, NE) (Table 20). Thus, using measures capturing cases by either the "CDC case definition" or the "P301 case definition", results were consistent with those observed in Study P301.

In Part 2 in the mITT1 for the analysis of SARS-CoV-2 infection (regardless of symptoms) occurring 14 days or more after dose 1, VE was based on 16 cases (0.6%) in the mRNA-1273 group (incidence rate 60.958 per 1000 person-years) and 26 cases (3.0%) in the placebo group (incidence rate 306.853 per 1000 person-years) (Table 20). Vaccine efficacy was 80.1% (95% CI: 61.5%, 90.0%). These results were consistent with the 82.0% (95% CI 79.5%, 84.2%) VE against SARS-CoV-2 infection (regardless of symptoms) observed in Study P301.

In Part 2 in the mITT1 for asymptomatic SARS-CoV-2 infection, VE against cases occurring 14 days or more after dose 1 was based on 13 cases (0.5%) in the mRNA-1273 group and 12 cases (1.4%) in the placebo group. Vaccine efficacy was 65.0% (95% CI: 16.1%, 85.3%) (Table 20). These results were consistent with the 63.0% (95% CI: 56.6%, 68.5%) VE against asymptomatic infection observed in Study P301.

Table 20: Summary of Secondary Efficacy Endpoint Analysis Results Starting 14 Days after Dose 1 in Part 2 (mITT1)

Endpoint	Part 2	
	mRNA-1273 50 µg N=2678	Placebo N=878
CDC case definition of COVID-19		
Cases, n/N1 (%)	3/2672 (0.1)	14/877 (1.6)
Incidence rate per 1000 person-years (95% CI)[a,b]	11.399 (2.351, 33.313)	163.810 (89.557, 274.846)
VE based on incidence rate (95% CI)[c]	0.930 (0.751, 0.987)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	0/2672	13/877 (1.5)
Incidence rate per 1000 person-years (95% CI)	0.000 (NE, 14.006)	152.027 (80.948, 259.970)
VE based on incidence rate (95% CI)	1.000 (0.893, NE)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	16/2672 (0.6)	26/877 (3.0)
Incidence rate per 1000 person-years (95% CI)	60.958 (34.843, 98.992)	306.853 (200.447, 449.611)
VE based on incidence rate (95% CI)	0.801 (0.615, 0.900)	

Endpoint	Part 2	
	mRNA-1273 50 µg N=2678	**Placebo N=878**
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	13/2672(0.5)	12/877 (1.4)
Incidence rate per 1000 person-years (95% CI)	49.529 (26.372, 84.695)	141.625 (73.180, 247.390)
VE based on incidence rate (95% CI)	0.650 (0.161, 0.853)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID 19 = coronavirus disease 2019; mITT = modified intent-to-treat; NE = not estimable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.
N1= number of participants at risk at 14 days after dose 1 for specific efficacy endpoint
[a.] Person-years is defined as the total years from the first injection date for Part 1 and the randomization date for Part 2 to the date of event (CDC Case Definition of COVID-19, P301 case definition of COVID-19, asymptomatic SARS-CoV-2 infection, or SARS-CoV-2 infection, depending upon endpoint), last date of study participation, or efficacy data cutoff date, whichever is the earliest.
[b.] Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
[c.] VE, defined as 1 - ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
Source: Study P204 Table 14.2.5.3.1.2, Study P204 Table 14.2.6.3.1.2, Study P204 Table 14.2.7.4.1.2, Study P204 Table 14.2.8.4.1.2

2.5.6 OVERVIEW OF SAFETY

This section contains a summary of the key safety data for Study P204 in pediatric participants 6 years to < 12 years as of the data snapshot of 06 October 2021. The data are presented first for Part 1 (open-label) and then for Part 2 (randomized, observer-blind, placebo-controlled).

Of note, Protocol Amendment 3 (dated 23 July 2021, Module 5.3.5.1) was implemented prior to the start of Part 2 and included enhanced surveillance for symptoms suggestive of possible myocarditis or pericarditis, based on individual symptoms that are components of the US CDC working case definition for myocarditis and pericarditis observed following COVID-19 vaccination (Gargano et al 2021). During the safety calls occurring 7 days following each study injection (and on safety calls thereafter), study staff asked parents or caregivers if the child had experienced chest pain, chest pressure or discomfort, shortness of breath, fast breathing at rest or any pain with breathing, as well as fast-beating, fluttering, or pounding heart. Reports of any one of these symptoms on these safety calls led to staff advising caregivers to seek medical attention and report back to the study investigator. As part of this protocol amendment, investigators were informed of the US CDC working case definition (above). Additionally, source documents were queried for clinical information relevant to AE and included in case descriptions.

The definitions of the Safety Sets for Part 1 and Part 2 are presented in Table 4.

Safety assessment included monitoring of the following:

- Solicited local and systemic ARs that occurred during the 7 days following each injection recorded daily using an eDiary.
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation.
- AESIs including acute myocarditis or pericarditis and MIS-C, SAEs, and MAAEs from first dose on Day 1 through the entire study period. A list of AESIs can be found in Table 33 in Section 2.5.6.1.4.4.1.1.
- Any pregnancies in female participants.
- As noted above, symptoms suggestive of potential myocarditis or pericarditis (above) were sought from participants during safety calls (7 days following each injection and subsequent safety calls) from 28 July 2021 onward.

The focus of the data description in the text for Part 1 is on the 50 µg dose group (ie, the dose selected for evaluation in Part 2; see Section 2.5.5.2.2.1), with additional data provided from the 100 µg dose.

Data are presented for Part 2 for the 50 µg dose and placebo groups (3:1 randomization).

A summary of the duration of subject follow-up time, including safety follow-up for solicited ARs and unsolicited AEs, can be found in Section 2.5.5.1.2.

2.5.6.1 Study P204

2.5.6.1.1 Overview of Safety

2.5.6.1.1.1 Overview of Safety in Part 1 (Open-label)

This section contains a summary of the key safety data for the open-label part of the study. The median participant duration in the study in Part 1 at the time of the data snapshot was 138 days (see Table 8). A total of 379 participants had been followed for ≥ 56 days after the second injection in the 50 µg group. One participant in Part 1 did not receive the second dose of vaccine (Table 8).

In the 50 µg group, the majority of solicited ARs were grade 1 or grade 2 (Table 21).

Unsolicited AEs were reported in 30.5% of participants in the 50 µg group. There were no unsolicited severe treatment-emergent adverse events (TEAEs) in the 50 µg group. Two (0.5%) participants experienced unrelated SAEs in the 28 days after any dose (Table 21 and Section 2.5.6.1.4.1.1).

In the 28-day window following any dose, 2 unrelated SAEs with the PTs foreign body ingestion and palpitations, respectively, were reported. The event of palpitations occurred in a participant with a previous history of palpitations; subsequent to the data snapshot, this event of palpitations was downgraded to nonserious (as investigator did not find the event met SAE criteria) and the onset date was clarified following parent/caregiver inquiry, to greater than 28 days after dose 2. This event of palpitations is described below in Section 2.5.6.1.4.1.

In the 100 µg group, a total of 371 participants were followed for ≥28 days after dose 2 and 370 participants were followed for ≥ 56 days after dose 2 (Table 8). An overview of safety results for the 100 µg group is presented in Table 21. The incidence of grade 3 solicited local and systemic ARs was higher in the 100 µg group compared with the 50 µg group. There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, no cases of MIS-C, and no cases of myocarditis or pericarditis reported during the entire study period (Table 21). A

severe AE of injection site erythema was assessed as related by the investigator and started on study Day 8 and ended on Study Day 15.

Table 21: Overview of Safety (Part 1)

Participants reporting at least one	mRNA-1273 50 µg	mRNA-1273 100 µg
Solicited adverse reactions	**n/N1 (%)**	**n/N1 (%)**
Solicited local adverse reaction within 7 days		
Dose #1	339/378 (89.7)	347/369 (94.0)
Dose #2	355/379 (93.7)	348/371 (93.8)
Grade 3 solicited local adverse reaction (any dose)	14/380 (3.7)	39/371 (10.5)
Grade 4 solicited local adverse reaction (any dose)	0	0
Solicited systemic adverse reaction within 7 days		
Dose #1	207/378 (54.8)	223/369 (60.4)
Dose #2	284/379 (74.9)	313/371 (84.4)
Grade 3 systemic adverse reaction (any dose)	44/380 (11.6)	78/371 (21.0)
Grade 4 systemic adverse reaction (any dose)	0	2/371 (0.5)
Unsolicited adverse events	**n/N1 (%)**	**n/N1 (%)**
Unsolicited adverse event up to 28 days after any dose	116/380 (30.5)	96/371 (25.9)
Related unsolicited AE	41/380 (10.8)	42/371 (11.3)
Severe unsolicited AE	0	1/371 (0.3)
Related severe unsolicited AE	0	1/371 (0.3)
Medically-attended AE	45/380 (11.8)	47/371 (12.7)
SAE up to 28 days after any dose	2[a, b]/380 (0.5)	0
Related SAE	0	0
AESI up to 28 days after any dose	1[b]/380 (0.3)	0
Related AESI	0	0
MIS-C	0	0
Myocarditis or pericarditis	0	0
Deaths	0	0
AE leading to discontinuation of the vaccine up to 28 days after any dose	1[c]/380 (0.3)	0
AE leading to discontinuation of the study up to 28 days after any dose	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MIS-C = multiorgan inflammatory syndrome in children; SAE = serious adverse event

[a.] One participant experienced the SAE of foreign body ingestion.

[b.] One participant in the 50 µg group of Part 1 experienced an event of palpitations that was reported as an AESI and also as an SAE(Note: Subsequent to the data snapshot, the event of palpitations was downgraded to nonserious and the onset date was changed to > 28 days after dose 2) (Section 2.5.6.1.4.4.1.1).

[c.] Adverse event of urticaria papular (Section 2.5.6.1.4.3).

Source: Study P204 Table 14.3.1.1.1.1, Study P204 Table 14.3.1.1.2.1, Study P204 Table 14.3.1.1.3.1, Study P204 Table 14.3.1.7.1.1; Study P204 14.3.1.21.1.1; Study P204 Table 14.3.1.15.2

2.5.6.1.1.2 Overview of Safety in Part 2 (Randomized, Observer-blind, Placebo-controlled)

This section contains a summary of the key safety data for the randomized, observer-blind, placebo-controlled part of the study. The median participant duration in the study in Part 2 at the time of the data snapshot was 50 days (Table 10). Median follow-up from the second injection was 20 days. A total of 474 participants in the mRNA-1273 group and 165 participants in the placebo group had been followed for ≥ 28 days after the second dose. At the time of data snapshot, no participants had been followed for ≥ 56 days after the second dose (Table 10).

In Part 2, both solicited local and systemic ARs were more frequently reported by participants in the mRNA-1273 group compared with the placebo group after each dose. The majority of solicited ARs were grade 1 or grade 2. The frequency of grade 3 solicited reactions in the mRNA-1273 group was higher than in the placebo group after each dose (Table 22).

The incidence of unsolicited TEAEs up to 28 days after any dose was higher in the mRNA-1273 group compared with the placebo group (Table 22). Imbalances in unsolicited TEAEs up to 28 days after any dose were primarily attributable to events related to reactogenicity which continued beyond 7 days.

Unsolicited TEAEs up to 28 days after any dose assessed by the Investigator as related to study vaccine were more frequently reported in the mRNA-1273 group than in the placebo group (Table 22). The incidence of severe unsolicited TEAEs up to 28 days in the mRNA-1273 group, however, was low. No participants in the placebo group experienced severe unsolicited TEAEs.

The percentage of participants in the mRNA-1273 group reporting MAAEs was lower than the percentage of participants reporting MAAEs in the placebo group (Table 22).

There were 2 unrelated SAEs reported in the mRNA-1273 group in the 28 days after any dose: one was an event of orbital cellulitis, and the other one was an event of appendicitis that was also reported as an AESI.

Two participants had AEs that led to discontinuation in the mRNA-1273 group. One had a mild event of rash, and the other one had moderate event of urticaria that started on Day 24 and a mild event of wheezing that on Day 29 that was considered unrelated. The causality for the urticaria and the rash were not reported at data snapshot.

There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, no cases of MIS-C, and no cases of myocarditis or pericarditis reported during the entire study period. (Table 22).

Table 22: Overview of Safety (Part 2)

Participants reporting at least one	mRNA-1273 50 µg	Placebo
Solicited adverse reactions	**n/N1 (%)**	**n/N1 (%)**
Solicited local adverse reaction within 7 days		
Dose #1	2818/3005 (93.8)	481/994 (48.4)
Dose #2	2847/2986 (95.3)	491/968 (50.7)
Grade 3 solicited local adverse reaction (any dose)	166/3007 (5.5)	8/995 (0.8)
Grade 4 solicited local adverse reaction (any dose)	0	0
Solicited systemic adverse reaction within 7 days		
Dose #1	1743/3005 (58.0)	519/994 (52.2)
Dose #2	2332/2986 (78.1)	485/968 (50.1)
Grade 3 systemic adverse reaction (any dose)	401/2602 (13.3)	25/669 (2.5)
Grade 4 systemic adverse reaction (any dose)	0	1/995 (0.1)
Unsolicited adverse events	**n/N1 (%)**	**n/N1 (%)**
Unsolicited adverse event up to 28 days after any dose	716/3007 (23.8)	194/995 (19.5)
Related unsolicited AE	294/3007 (9.8)	37/995 (3.7)
Severe unsolicited AE	9/3007 (0.3)	0
Related severe unsolicited AE	6/3007 (0.2)	0
Medically-attended AE	256/3007 (8.5)	100/995 (10.1)
SAE up to 28 days after any dose	1[a]/3007 (< 0.1)	0
Related SAE	0	0
AESI up to 28 days after any dose	1[b]/3007 (< 0.1)	1/995 (0.1)
Related AESI	0	0
MIS-C	0	0
Myocarditis or pericarditis	0	0
Deaths	0	0
ading to discontinuation of the vaccine up to 28 days after any dose	2[c]/3007 (< 0.1)	0
ading to discontinuation from the study up to 28 days after any dose	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MIS-C = multiorgan inflammatory syndrome in children; PT = preferred term; SAE = serious adverse event

[a.] One participant experienced an SAE with the PT cellulitis orbital.

[b.] One participant experienced an AESI with the PT appendicitis (Study P204 Table 14.3.1.21.2.2).

[c.] Two participants were discontinued from study vaccine due to AEs with the PTs rash and urticaria and wheezing.

Source: Study P204 Table 14.3.1.1.1.2.1, Study P204 Table 14.3.1.1.2.2.1, Study P204 Table 14.3.1.1.3.2.1, Study P204 Table 14.3.1.7.1.2; Study P204 Table 14.3.1.21.1.2

2.5.6.1.2 Solicited Adverse Reactions

In both Parts 1 and 2, solicited local and systemic ARs were assessed. Solicited ARs with an onset within 7 days after each dose (ie, the day of injection and the 6 subsequent days) were recorded daily by a caregiver using an eDiary, which was adapted for use in pediatric populations from the eDiary used in the Study P301 submission for adults ≥ 18 years of age. Adaptations

consisted of removal of reference to prescription (narcotic) pain relievers for pain control and outpatient IV hydration for nausea/vomiting, as these are not standard of care for children. Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness. Solicited systemic ARs assessed included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. The eDiary solicited daily caregiver reporting of ARs using a structured checklist. Caregivers recorded such occurrences in an eDiary on the day of each investigational product (IP) injection and for the 6 days after the day of dosing (Day 1 through Day 7). If an AR persisted beyond Day 7, the caregiver was prompted to continue to record until resolution. Severity grading of reactogenicity occurred automatically based on caregiver entry into the eDiary according to grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Any solicited AR that meets either of the following criteria was also included in the analysis of unsolicited AEs: 1) solicited local or systemic AR lasting beyond 7 days post-injection 2) solicited local or systemic AR meeting SAE criteria. These events will appear in both solicited AR and unsolicited AE tables.

Refer to the Study P204 protocol amendment 5 in Module 5.3.5.1 for additional details on the collection of ARs.

2.5.6.1.2.1 Summary of Solicited Local Adverse Reactions

Toxicity grades for injection site erythema (redness) or swelling (hardness) are defined as: grade 1: 25-50 mm, grade 2; 51-100 mm, grade 3: >100 mm, and grade 4: necrosis or exfoliative dermatitis. Toxicity grades for injection site pain and for axillary (or groin) swelling or tenderness is defined as: grade 1: no interference with activity, grade 2: some interference with activity, grade 3: prevents daily activity, and grade 4: emergency room visit or hospitalization.

2.5.6.1.2.1.1 Summary of Solicited Local Adverse Reactions in Part 1

In the 50 µg group in Part 1 of the study, solicited local ARs were similar in frequency after dose 1 and dose 2 (Table 23). After any dose, the most common solicited local AR was injection site pain (368 [96.8%] participants) (Study P204 Table 14.3.1.1.3.1.1). The majority of solicited local ARs were grade 1 to grade 2 in severity. The most frequent grade 3 solicited local ARs in this group included injection site pain (10 [2.6%] participants) and erythema (4 [1.1%] participants). There were no grade 4 solicited local ARs reported.

The majority of the solicited local ARs in participants in the 50 µg group occurred within the first 1 to 2 days after each dose in both groups (Study P204 Table 14.3.1.3.3.1) and generally persisted for a median of 3 days (Study P204 Table 14.3.1.4.3.1).

Solicited local ARs that persisted beyond 7 days after an injection were also reported as unsolicited TEAEs. In the 50 µg group, the most common solicited local ARs persisting beyond 7 days after dose 1 include erythema (9 [2.4%] participants) and axillary (or groin) swelling or tenderness (8 [2.1%] participants) (Study P204 Table 14.3.1.6.1.1). Solicited local ARs persisting beyond 7 days after dose 2 included injection site pain (4 [1.1%] participants), erythema (1 [0.3%] participants), injection site swelling (hardness) (2 [0.5%] participants), and axillary (or groin) swelling or tenderness (2 [0.5%] participants) (Study P204 Table 14.3.1.6.2.1).

In the 50 µg group, 15 (3.9%) participants reported 17 solicited local ARs with an onset after 7 days after dose 1. The ARs reported were erythema (15 [3.9%] participants) and injection site swelling (hardness) (2 [0.5%] participants). No participants in this group reported solicited local ARs with an onset after 7 days after dose 2 (Study P204 Table 14.3.1.23.1.1.1 and Table 14.3.1.23.1.2.1).

In the 100 µg group, incidence of solicited local ARs was also similar after dose 2 and dose 1 (Table 23). However, the incidence of participants experiencing grade 3 solicited local ARs was more frequent after dose 2 (30 [8.1%] participants) than dose 1 (12 [3.3%] participants). After any dose, the most common solicited local AR was pain. The majority of solicited local ARs were grade 1 to grade 2 in severity. The most common grade 3 or higher solicited local ARs in the 100 µg group included was also injection site pain. There were no grade 4 solicited local ARs in Part 1.

The majority of the solicited local ARs in participants in the 100 µg group occurred within the first 1 to 2 days after any dose (Study P204 Table 14.3.1.3.3.1) and persisted for a median of 3 days (Study P204 Table 14.3.1.4.3.1.)

In the 100 µg group, solicited local ARs persisting beyond 7 days after dose 1 were erythema (6 [1.6%] participants), injection site swelling (hardness) (2 [0.5%] participants), and axillary (or groin) swelling or tenderness (5 [1.4%] participants) (Study P204 Table 14.3.1.6.1.1). Solicited local ARs persisting beyond 7 days after dose 2 in this group were injection site pain (1 [0.3%] participant), erythema (2 [0.5%] participants), injection site swelling (hardness) (2 [0.5%] participants), and axillary (or groin) swelling or tenderness (2 [0.5%] participants) (Study P204 Table 14.3.1.6.2.1).

In the 100 µg group, 10 (2.7%) participants reported solicited local ARs with an onset after Day 7 after dose 1 (Study P204 Table 14.3.1.23.1.1.1). The ARs reported after dose 1 were erythema (10 [2.7%] participants) and swelling (3 [0.8%] participants). As with the 50 µg group, no participants reported solicited local ARs with an onset after day 7 following dose 2 (Study P204 Table 14.3.1.23.1.2.1).

The solicited local ARs of erythema, swelling (hardness), and axillary (or groin) swelling occurred more frequently after both doses in the 100 µg group as compared with the 50 µg group. The frequency of the solicited local AR of pain was relatively similar across both groups after both doses (Table 23).

Table 23: Summary of Local Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Solicited local adverse reactions – N1	378	369	379	371
Any solicited local adverse reactions	339 (89.7)	347 (94.0)	355 (93.7)	348 (93.8)
95% CI	86.2, 92.6	91.1, 96.2	90.7, 95.9	90.8, 96.0
Grade 1	237 (62.7)	176 (47.7)	201 (53.0)	157 (42.3)
Grade 2	98 (25.9)	159 (43.1)	144 (38.0)	161 (43.4)
Grade 3	4 (1.1)	12 (3.3)	10 (2.6)	30 (8.1)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	12 (3.3)	10 (2.6)	30 (8.1)
Pain – N1	378	369	379	371
Any	336 (88.9)	341 (92.4)	350 (92.3)	346 (93.3)
Grade 1	252 (66.7)	193 (52.3)	233 (61.5)	197 (53.1)
Grade 2	82 (21.7)	138 (37.4)	109 (28.8)	135 (36.4)
Grade 3	2 (0.5)	10 (2.7)	8 (2.1)	14 (3.8)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	10 (2.7)	8 (2.1)	14 (3.8)
Erythema (redness) – N1	378	369	379	371
Any	44 (11.6)	66 (17.9)	81 (21.4)	108 (29.1)
Grade 1	29 (7.7)	35 (9.5)	36 (9.5)	34 (9.2)
Grade 2	13 (3.4)	31 (8.4)	43 (11.3)	58 (15.6)
Grade 3	2 (0.5)	0	2 (0.5)	16 (4.3)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	0	2 (0.5)	16 (4.3)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Swelling (hardness) – N1	378	369	379	371
Any	40 (10.6)	57 (15.4)	81 (21.4)	92 (24.8)
Grade 1	28 (7.4)	34 (9.2)	50 (13.2)	50 (13.5)
Grade 2	10 (2.6)	21 (5.7)	30 (7.9)	36 (9.7)
Grade 3	2 (0.5)	2 (0.5)	1 (0.3)	6 (1.6)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	2 (0.5)	1 (0.3)	6 (1.6)
Axillary (or groin) swelling or tenderness – N1	378	369	379	371
Any	41 (10.8)	54 (14.6)	46 (12.1)	63 (17.0)
Grade 1	34 (9.0)	43 (11.7)	40 (10.6)	46 (12.4)
Grade 2	7 (1.9)	10 (2.7)	6 (1.6)	16 (4.3)
Grade 3	0	1 (0.3)	0	1 (0.3)
Grade 4	0	0	0	0
Grade 3 or above	0	1 (0.3)	0	1 (0.3)

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Pain is injection site pain. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1=25-50 mm; grade 2=51-100 mm; grade 3=>100 mm; grade 4=necrosis or exfoliative dermatitis. Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: grade 1=no interference with activity; grade 2=some interference with activity; grade 3=prevents daily activity; grade 4=emergency room visit or hospitalization.
Source: Study P204 Table 14.3.1.1.1.1 and Table 14.3.1.1.2.1

2.5.6.1.2.1.2 Summary of Solicited Local Adverse Reactions in Part 2

In Part 2 of the study, the incidence of solicited local ARs were more common in the mRNA-1273 group than in the placebo group (

Table 24). The incidence of participants experiencing grade 3 solicited local ARs was higher (121 [4.1%] participants) after dose 2 than after dose 1 (54 [1.8%] participants) in the mRNA-1273 group. After any dose, the most common solicited local AR was injection site pain. The majority of solicited local ARs were grade 1 to grade 2 in severity; however, there was a higher occurrence of grade 3 solicited systemic reactions in the mRNA-1273 group than in the placebo group. The most common grade 3 solicited local AR occurring after any dose in the mRNA-1273 group was injection site pain (100 [3.3%] participants). No grade 4 solicited local

ARs were reported in Part 2 of the study (Study P204 Table 14.3.1.1.3.2.1). After dose 1, more participants in the placebo group reported grade 2 (441 [44.4%]) and grade 3 (25[2.5%]) events of injection site pain than the mRNA-1273 participants (748 [24.9%] and 28 [0.9%], respectively).

The majority of the solicited local ARs in the mRNA-1273 group in Part 2 occurred within the first 1 to 2 days after any dose (Study P204 Table 14.3.1.3.3.2) and persisted for a median of 3 days (Study P204 Table 14.3.1.4.3.2).

Solicited local ARs that persisted beyond 7 days after an injection were also reported as unsolicited TEAEs. In the mRNA-1273 group, solicited local ARs persisting beyond 7 days after dose 1 were injection site pain (27 [0.9%] participants), erythema (30 [1.0%] participants), injection site swelling (hardness) (18 [0.6%] participants), and axillary (or groin) swelling or tenderness (52 [1.7%] participants) (Study P204 Table 14.3.1.6.1.2). Solicited local ARs persisting beyond 7 days after dose 2 in the mRNA-1273 group were injection site pain (18 [0.6%] participants), erythema (13 [0.4%] participants), injection site swelling (hardness) (9 [0.3%] participants), and axillary (or groin) swelling or tenderness (23 [0.8%] participants) (Study P204 Table 14.3.1.6.2.2). In the placebo group, the most common solicited systemic ARs persisting beyond 7 days after dose 1 include injection site pain (9 [0.9%] participants) and axillary (or groin) swelling or tenderness (6 [0.6%] participants) (Study P204 Table 14.1.3.6.1.2). Solicited systemic ARs persisting beyond 7 days after dose 2 in the placebo group were injection site pain (12 [1.2%] participants) and axillary (or groin) swelling or tenderness (3 [0.3%] participants) (Study P204 Table 14.3.1.6.2.2).

In the mRNA-1273 group, 81 (2.7%) participants reported solicited local ARs with onset after 7 days after dose 1 (Study P204 Table 14.3.1.23.1.1.2). Only 3 (< 0.1%) participants reported solicited local ARs with onset after 7 days after dose 2 (Study P204 Table 14.3.1.23.1.2.2). The ARs reported after any dose were injection site swelling (hardness) (22 [0.7%] participants), injection site pain (16 [0.5%] participants), erythema (63 [2.1%] participants), and axillary (or groin) swelling or tenderness (3 [< 0.1%] participants) (Study P204 Table 14.3.1.23.1.3.2).

Only 2 (0.2%) participants in the placebo group reported solicited local ARs with onset after 7 days post any dose (Study P204 Table 14.3.1.23.1.3.2). The ARs reported were injection site pain (2 [0.2%] participants), and axillary (or groin) swelling or tenderness (1 [0.1%] participants).

Table 24: Summary of Solicited Local Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	**Placebo (N=994) n (%)**	**mRNA-1273 50 µg (N=2986) n (%)**	**Placebo (N=968) n (%)**
Solicited local adverse reactions – N1	3005	994	2986	968
Any solicited local adverse reactions	2818 (93.8)	481 (48.4)	2847 (95.3)	491 (50.7)
95% CI	92.9, 94.6	45.2, 51.5	94.5, 96.1	47.5, 53.9
Grade 1	1934 (64.4)	450 (45.3)	1494 (50.0)	446 (46.1)
Grade 2	830 (27.6)	28 (2.8)	1232 (41.3)	40 (4.1)
Grade 3	54 (1.8)	3 (0.3)	121 (4.1)	5 (0.5)
Grade 4	0	0	0	0
Grade 3 or above	54 (1.8)	3 (0.3)	121 (4.1)	5 (0.5)
Pain – N1	3005	994	2986	968
Any	2798 (93.1)	994	2830 (94.8)	481 (49.7)
Grade 1	2022 (67.3)	466 (46.9)	1695 (56.8)	446 (46.1)
Grade 2	748 (24.9)	441 (44.4)	1055 (35.3)	33 (3.4)
Grade 3	28 (0.9)	25 (2.5)	80 (2.7)	2 (0.2)
Grade 4	0	0	0	0
Grade 3 or above	28 (0.9)	0	80 (2.7)	2 (0.2)
Erythema (redness) – N1	3005	994	2986	968
Any	359 (11.9)	12 (1.2)	561 (18.8)	11 (1.1)
Grade 1	242 (8.1)	9 (0.9)	267 (8.9)	7 (0.7)
Grade 2	101 (3.4)	2 (0.2)	261 (8.7)	3 (0.3)
Grade 3	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Grade 4	0	0	0	0
Grade 3 or above	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Swelling (hardness) – N1	3005	994	2986	968
Any	362 (12.0)	11 (1.1)	510 (17.1)	12 (1.2)
Grade 1	261 (8.7)	9 (0.9)	316 (10.6)	12 (1.2)
Grade 2	82 (2.7)	1 (0.1)	174 (5.8)	0
Grade 3	19 (0.6)	1 (0.1)	20 (0.7)	0
Grade 4	0	0	0	0
Grade 3 or above	19 (0.6)	1 (0.1)	20 (0.7)	0
Axillary (or groin) swelling or tenderness – N1	3005	994	2986	968
Any	467 (15.5)	85 (8.6)	536 (18.0)	65 (6.7)
Grade 1	401 (13.3)	82 (8.2)	409 (13.7)	55 (5.7)
Grade 2	63 (2.1)	2 (0.2)	124 (4.2)	8 (0.8)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	Placebo (N=994) n (%)	mRNA-1273 50 µg (N=2986) n (%)	Placebo (N=968) n (%)
Grade 3	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)
Grade 4	0	0	0	0
Grade 3 or above	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Pain is injection site pain. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1=25-50 mm; grade 2=51-100 mm; grade 3=>100 mm; grade 4=necrosis or exfoliative dermatitis. Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: grade 1=no interference with activity; grade 2=some interference with activity; grade 3=prevents daily activity; grade 4=emergency room visit or hospitalization.
Sources: Table 14.3.1.1.1.2.1 and Table 14.1.1.2.2.1

2.5.6.1.2.2 Summary of Solicited Systemic Adverse Reactions

Toxicity grades for fever are defined as: grade 1: 38.0-38.4°C, grade 2: 38.5-38.9°C, grade 3: 39.0-40.0°C, and grade 4: >40.0°C. Toxicity grades for other solicited systemic ARs are defined as: grade 1: no interference with activity (or, for nausea/vomiting: 1-2 episodes/24 hours), grade 2: some interference with activity (or, for nausea/vomiting: >2 episodes/24 hours), grade 3: prevents daily activity, and grade 4: emergency room visit or hospitalization.

2.5.6.1.2.2.1 Summary of Solicited Systemic Adverse Reactions in Part 1

In the 50 µg group of Part 1 of the study, solicited systemic ARs were more common after dose 2 compared with dose 1 (Table 25). After any dose, the most common solicited systemic ARs in this group were fatigue (262 [68.9%] participants) and headache (228 [60.0%] participants) (Study P204 Table 14.3.1.1.3.1). The majority of solicited systemic ARs were grade 1 to grade 2 in severity. The most common grade 3 systemic ARs after any dose in this group were fatigue (30 [7.9%] participants), headache (14 [3.7%] participants), and fever (11 [2.9%] participants). There were no grade 4 solicited systemic ARs in the 50 µg group of Part 1 (Study P204 Table 14.3.1.1.3.1).

The majority of the solicited systemic ARs in participants in the 50 µg group of Part 1 occurred within the first 1 to 2 days after each dose in both groups (Study P204 Table 14.3.1.3.3.1) and generally persisted for a median of 2 days (Study P204 Table 14.3.1.4.3.1).

Solicited systemic ARs that persisted beyond 7 days after an injection were also reported as unsolicited TEAEs. In the 50 µg group of Part 1, solicited systemic ARs persisting beyond 7 days after dose 1 were fever (1 [0.3%] participant), headache (4 [1.1%] participants), fatigue

(4 [1.1%] participants), and nausea/vomiting (3 [0.8%] participants) (Study P204 Table 14.3.1.6.1.1). Solicited systemic ARs persisting beyond 7 days after dose 2 in this group were headache (1 [0.3%] participant), fatigue (3 [0.8%] participants), myalgia (1 [0.3%] participant), arthralgia (1 [0.3%] participant), nausea/vomiting (1 [0.3%] participant), and chills (1 [0.3%] participants) (Study P204 Table 14.3.1.6.2.1).

In the 50 µg group, no participants reported solicited systemic ARs with onset after 7 days after dose 1 (Study P204 Table 14.3.1.23.1.1.1). In this group, 1 (0.3%) participant reported the solicited systemic AR of a fever with an onset after 7 days post dose 2 (Study P204 Table 14.3.1.23.1.2.1).

In the 100 µg group, solicited systemic ARs were more common after dose 2 compared with dose 1 (Table 25). After any dose, the most common solicited systemic ARs were fatigue (277 [74.7%] participants) and headache (254 [68.5%] participants). The majority of solicited systemic ARs were grade 1 to grade 2 in severity. The most common grade 3 or higher solicited systemic ARs in the 100 µg group after any dose were fatigue (46 [12.4%] participants), headache (6.7%), fever (6.2%), and myalgia (5.1%). There were no grade 4 solicited systemic ARs in Part 1 (Study P204 Table 14.3.1.1.3.1).

The majority of the solicited local ARs in participants occurred within the first 1 to 2 days after any dose (Study P204 Table 14.3.1.3.3.1) and generally persisted for a median of 2 days (Study P204 Table 14.3.1.4.3.1).

In the 100 µg group of Part 1, solicited systemic ARs persisting beyond 7 days after dose 1 were fever (1 [0.3%] participant), headache (2 [0.5%] participants), fatigue (1 [0.3%] participant), and arthralgia (1 [0.3%] participant) (Study P204 Table 14.3.1.6.1.1). Solicited systemic ARs persisting beyond 7 days after dose 2 in this group were headache (4 [1.1%] participants), fatigue (5 [1.3%] participants), myalgia (1 [0.3%] participant), arthralgia (1 [0.3%] participant), nausea/vomiting (3 [0.8%] participants), and chills (2 [0.5%] participants) (Study P204 Table 14.3.1.6.2.1).

In the 100 µg group, 2 (0.5%) participants reported solicited systemic ARs with onset after 7 days after dose 1 (Study P204 Table 14.3.1.23.1.1.1). In this group, 2 (0.5%) participants also reported solicited systemic ARs with onset after 7 days after dose 2 (Study P204 Table 14.3.1.23.1.2.1). Systemic ARs reported with an onset more than 7 days after any dose were fever (1 [0.3%] participant), headache (1 [0.3]% participant), and fatigue (2 [0.5%] participants) (Study P204 Table 14.3.1.23.1.3.1).

Frequency, severity, and duration of solicited systemic ARs in Part 1 were key factors in the decision to set the dose level in Part 2 of the study at 50 µg.

Fever was reported more frequently in the 100 µg group after both doses than in the 50 µg group (Table 25); this applied as well to fever of grades 3 and 4. In the 100 µg group, grade 3 fever after dose 2 was reported in 19 (5.1%) participants as compared with 10 (2.6%) participants in the 50 µg group. Additionally, grade 4 fevers after dose 2 were reported in 2(0.5%) participants in the 100 µg group and none in the 50 µg group after either dose.

Similarly, headache was reported more frequently after both doses in the 100 µg group than in the 50 µg group (Table 25). More participants in the 100 µg group experienced headaches of grade 3 severity (5.1%) compared with participants in the 50 µg group experiencing grade 3 severity headaches (2.6%). No participants in either dose group experienced a grade 4 AR of headache.

Myalgia was also reported more frequently after both doses in the 100 µg group than in the 50 µg group (Table 25). Myalgia was also more frequently reported at grade 3 in the 100 µg group than in the 50 µg group. Notably, after dose 1, no grade 3 ARs of myalgia were reported in the 50 µg group as compared with 6 (1.6%) participants in the 100 µg group having reports of grade 3 myalgia. After dose 2, grade 3 myalgia was reported in 13 (3.5%) participants in the 100 µg group experienced, while 1.8% of participants in the 50 µg group experienced this grade of myalgia.

Fatigue was reported at roughly similar frequencies in both dose groups, but the reported severity of fatigue was higher in the 100 µg group than in the 50 µg group (Table 25). After dose 1, grade 3 fatigue was reported in 10 (2.7%) participants in the 100 µg group as opposed to 4 (1.1%) of participants in the 50 µg group. After dose 2, there was an increase in participants experiencing grade 3 fatigue in both dose groups, but, again, the frequency participants experiencing grade 3 fatigue was higher in the 100 µg group (9.7%) than in the 50 µg group (6.9%).

Table 25: Summary of Solicited Systemic Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Solicited systemic adverse reactions – N1	378	369	379	371

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Any solicited systemic adverse reactions	207 (54.8)	223 (60.4)	284 (74.9)	313 (84.4)
95% CI	49.6, 59.9	55.2, 65.5	70.3, 79.2	80.3, 87.9
Grade 1	135 (35.7)	120 (32.5)	112 (29.6)	111 (29.9)
Grade 2	64 (16.9)	86 (23.3)	136 (35.9)	136 (36.7)
Grade 3	8 (2.1)	17 (4.6)	36 (9.5)	64 (17.3)
Grade 4	0	0	0	2 (0.5)
Grade 3 or above	8 (2.1)	17 (4.6)	36 (9.5)	66 (17.8)
Fever – N1	378	369	379	371
Any	11 (2.9)	24 (6.5)	78 (20.6)	110 (29.6)
Grade 1	6 (1.6)	15 (4.1)	39 (10.3)	50 (13.5)
Grade 2	4 (1.1)	7 (1.9)	29 (7.7)	39 (10.5)
Grade 3	1 (0.3)	2 (0.5)	10 (2.6)	19 (5.1)
Grade 4	0	0	0	2 (0.5)
Grade 3 or above	1 (0.3)	2 (0.5)	10 (2.6)	21 (5.7)
Headache – N1	378	369	379	371
Any	109 (28.8)	129 (35.0)	188 (49.6)	226 (60.9)
Grade 1	72 (19.0)	81 (22.0)	87 (23.0)	113 (30.5)
Grade 2	33 (8.7)	42 (11.4)	91 (24.0)	94 (25.3)
Grade 3	4 (1.1)	6 (1.6)	10 (2.6)	19 (5.1)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	6 (1.6)	10 (2.6)	19 (5.1)
Fatigue – N1	378	369	379	371
Any	154 (40.7)	167 (45.3)	216 (57.0)	236 (63.6)
Grade 1	102 (27.0)	97 (26.3)	93 (24.5)	93 (25.1)
Grade 2	48 (12.7)	60 (16.3)	97 (25.6)	107 (28.8)
Grade 3	4 (1.1)	10 (2.7)	26 (6.9)	36 (9.7)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	10 (2.7)	26 (6.9)	36 (9.7)
Myalgia – N1	378	369	379	371
Any	40 (10.6)	58 (15.7)	89 (23.5)	112 (30.2)
Grade 1	27 (7.1)	34 (9.2)	53 (14.0)	47 (12.7)
Grade 2	13 (3.4)	18 (4.9)	29 (7.7)	52 (14.0)
Grade 3	0	6 (1.6)	7 (1.8)	13 (3.5)
Grade 4	0	0	0	0
Grade 3 or above	0	6 (1.6)	7 (1.8)	13 (3.5)
Arthralgia – N1	378	369	379	371
Any	27 (7.1)	39 (10.6)	43 (11.3)	68 (18.3)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Grade 1	21 (5.6)	28 (7.6)	28 (7.4)	40 (10.8)
Grade 2	6 (1.6)	7 (1.9)	13 (3.4)	24 (6.5)
Grade 3	0	4 (1.1)	2 (0.5)	4 (1.1)
Grade 4	0	0	0	0
Grade 3 or above	0	4 (1.1)	2 (0.5)	4 (1.1)
Nausea/vomiting – N1	378	369	379	371
Any	36 (9.5)	26 (7.0)	79 (20.8)	113 (30.5)
Grade 1	33 (8.7)	21 (5.7)	59 (15.6)	90 (24.3)
Grade 2	3 (0.8)	4 (1.1)	18 (4.7)	20 (5.4)
Grade 3	0	1 (0.3)	2 (0.5)	3 (0.8)
Grade 4	0	0	0	0
Grade 3 or above	0	1 (0.3)	2 (0.5)	3 (0.8)
Chills – N1	378	369	379	371
Any	33 (8.7)	40 (10.8)	77 (20.3)	135 (36.4)
Grade 1	23 (6.1)	29 (7.9)	39 (10.3)	65 (17.5)
Grade 2	10 (2.6)	10 (2.7)	37 (9.8)	68 (18.3)
Grade 3	0	1 (0.3)	1 (0.3)	2 (0.5)
Grade 4	0	0	0	0
Grade 3 or above	0	1 (0.3)	1 (0.3)	2 (0.5)

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Toxicity grade for fever is defined as: grade 1=38.0-38.4°C; grade 2=38.5-38.9°C; grade 3=39.0-40.0°C; grade 4=>40.0°C. Toxicity grade for other solicited systemic adverse reactions is defined as: grade 1=no interference with activity (or, for nausea/vomiting: 1-2 episodes/24 hours); grade 2=some interference with activity (or, for nausea/vomiting: >2 episodes/24 hours); grade 3=prevents daily activity; grade 4=emergency room visit or hospitalization.
Source: Study P204 Table 14.3.1.1.1.1 and Table 14.3.1.1.2.1

2.5.6.1.2.2.2 Summary of Solicited Systemic Adverse Reactions in Part 2

In Part 2 of the study, solicited systemic ARs were more common in the mRNA-1273 group than in the placebo group and were more common after dose 2 compared with dose 1 in the mRNA-1273 group (Table 26). After any dose, the most common solicited systemic ARs were fatigue (2194 [73.0%] participants) and headache (1862 [62.0%] participants). In the placebo group, the most common solicited systemic ARs were fatigue (469 [47.2%] participants) and headache (434 [43.7%] participants). The majority of solicited systemic ARs were grade 1 to grade 2 in severity; however, there was a higher occurrence of grade 3 solicited systemic reactions in the mRNA-1273 group than in the placebo group. The most common grade 3

solicited systemic ARs in the mRNA-1273 group after any dose were fatigue (214 [7.1%] participants), headache (133 [4.4%] participants), and fever ≥39.0-39.9°C (127 [4.2%] participants). The most common grade 3 solicited systemic ARs in the placebo group were fatigue (15 [1.5%] participants) and headache (12 [1.2%] participants). In the placebo group, a grade 4 systemic AR of fever was erroneously reported in 1 (0.1%) participant; however, this was a data entry error in the daily eDiary. The participant's actual temperature was 100.0°F (grade 0). There were no grade 4 solicited systemic ARs in the mRNA-1273 group.

The majority of the solicited local ARs in participants in the mRNA-1273 group in Part 2 occurred within the first 1 to 2 days after each dose (Study P204 Table 14.3.1.3.3.2) and persisted for a median of 2 days (Study P204 Table 14.3.1.4.1.2 and Table 14.3.1.4.2.2).

Solicited systemic ARs in Part 2 that persisted beyond 7 days after an injection are also reported as unsolicited TEAEs. In the mRNA-1273 group, solicited systemic ARs persisting beyond 7 days after dose 1 were fever (1 [< 0.1%] participants), headache (44 [1.5%] participants), fatigue (23 [0.8%] participants), myalgia (7 [0.2%] participants), arthralgia (6 [0.2%] participants), nausea/vomiting (7 [0.2%] participants), and chills (5 [0.2%] participants) (Study P204 Table 14.3.1.6.2.1). Solicited systemic ARs persisting beyond 7 days after dose 2 in this group were fever (3 [0.1%] participants), headache (31 [1.0%] participants), fatigue (33 [1.1%] participants), myalgia (7 [0.2%] participants), arthralgia (9 [0.3%] participants), nausea/vomiting (4 [0.1%] participants), and chills (7 [0.2%] participants) (Study P204 Table 14.3.1.6.2.2). In the placebo group, solicited systemic ARs persisting beyond 7 days after dose 1 were headache (15 [1.5%] participants), fatigue (12 [1.2%] participants), myalgia (2 [0.2%] participants), arthralgia (3 [0.3%] participants), nausea/vomiting (3 [0.3%] participants), and chills (3 [0.3%] participants) (Study P204 Table 14.3.1.6.2.1). Solicited systemic ARs persisting beyond 7 days after dose 2 in the placebo group were headache (13 [1.3%] participants), fatigue (8 [0.8%] participants), myalgia (4 [0.4%] participants), arthralgia (3 [0.3%] participants), nausea/vomiting (3 [0.3%] participants), and chills (2 [0.2%] participants) (Study P204 Table 14.3.1.6.2.2).

In the mRNA-1273 group, 12 (0.4%) participants reported solicited systemic ARs with onset after 7 days after dose 1 (Study P204 Table 14.3.1.23.1.1.2). In this group, 3 (0.1%) participants reported solicited systemic ARs with onset after 7 days after dose 2 (Study P204 Table 14.3.1.23.1.2.2). The ARs reported after any dose were fever (4 [0.1%] participants), headache (6 [0.2%] participants), fatigue (3 [< 0.1%] participants), myalgia (1 [< 0.1%] participants), nausea/vomiting (1 [< 0.1%] participants), and chills (1 [< 0.1%] participants) (Study P204 Table 14.3.1.23.1.3.2).

In Part 2 of the study, fever occurred more frequently after any dose in the mRNA-1273 group (778 [25.9%] participants) than in placebo group (36 [3.6%] participants) (Study P204 Table 14.3.1.1.3.2.1). An event of grade 4 fever was erroneously reported in 1 (0.1%) participant in the placebo group. As stated above, this event was due to a data entry error, and the actual temperature was 100.0°F (grade 0). No grade 4 fevers were reported in the mRNA-1273 group. The toxicity grades for fever can be found in the **Table 26** footnotes.

The median onset of the of the solicited systemic AR of fever in the mRNA-1273 group after any dose was 2 days (Study P204 Table 14.3.1.5.3.2) with a median duration of 1 day (Study P204 Table 14.3.1.4.3.2). In the placebo group the median onset of fever was 3 days (Study P204 Table 14.3.1.5.3.2) with a median duration of 1 day (Study P204 Table 14.3.1.4.3.2).

Fevers persisting after 7 days post any dose were reported in 4 (0.1%) participants in the mRNA-1273 group. There were no reports of fever persisting after 7 days post any dose in the placebo group.

Table 26: Summary of Solicited Systemic Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	**Placebo (N=994) n (%)**	**mRNA-1273 50 µg (N=2986) n (%)**	**Placebo (N=968) n (%)**
Solicited systemic adverse reactions – N1	3005	994	2986	968
Any solicited systemic adverse reactions	1743 (58.0)	519 (52.2)	2332 (78.1)	485 (50.1)
95% CI	56.2, 59.8	49.1, 55.4	76.6, 79.6	46.9, 53.3
Grade 1	1104 (36.7)	348 (35.0)	828 (27.7)	323 (33.4)
Grade 2	586 (19.5)	158 (15.9)	1143 (38.3)	148 (15.3)
Grade 3	53 (1.8)	12 (1.2)	361 (12.1)	14 (1.4)
Grade 4	0	1 (0.1)[a]	0	0
Grade 3 or above	53 (1.8)	13 (1.3)	361 (12.1)	14 (1.4)
Fever – N1	3004	994	2986	968
Any	102 (3.4)	15 (1.5)	719 (24.1)	21 (2.2)
Grade 1	57 (1.9)	10 (1.0)	385 (12.9)	14 (1.4)
Grade 2	28 (0.9)	2 (0.2)	222 (7.4)	5 (0.5)
Grade 3	17 (0.6)	2 (0.2)	112 (3.8)	2 (0.2)
Grade 4	0	1 (0.1)[a]	0	0
Grade 3 or above	17 (0.6)	3 (0.3)	112 (3.8)	2 (0.2)
Headache – N1	3002	993	2983	967

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	**Placebo (N=994) n (%)**	**mRNA-1273 50 µg (N=2986) n (%)**	**Placebo (N=968) n (%)**
Any	938 (31.2)	306 (30.8)	1617 (54.2)	275 (28.4)
Grade 1	672 (22.4)	227 (22.9)	759 (25.4)	187 (19.3)
Grade 2	248 (8.3)	75 (7.6)	740 (24.8)	80 (8.3)
Grade 3	18 (0.6)	4 (0.4)	118 (4.0)	8 (0.8)
Grade 4	0	0	0	0
Grade 3 or above	18 (0.6)	4 (0.4)	118 (4.0)	8 (0.8)
Fatigue – N1	3002	993	2983	967
Any	1299 (43.3)	334 (33.6)	1921 (64.4)	334 (34.5)
Grade 1	853 (28.4)	215 (21.7)	800 (26.8)	226 (23.4)
Grade 2	415 (13.8)	111 (11.2)	932 (31.2)	100 (10.3)
Grade 3	31 (1.0)	8 (0.8)	189 (6.3)	8 (0.8)
Grade 4	0	0	0	0
Grade 3 or above	31 (1.0)	8 (0.8)	189 (6.3)	8 (0.8)
Myalgia – N1	3002	993	2983	967
Any	438 (14.6)	96 (9.7)	841 (28.2)	105 (10.9)
Grade 1	315 (10.5)	73 (7.4)	426 (14.3)	75 (7.8)
Grade 2	112 (3.7)	22 (2.2)	344 (11.5)	29 (3.0)
Grade 3	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Grade 4	0	0	0	0
Grade 3 or above	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Arthralgia – N1	3002	993	2983	967
Any	260 (8.7)	75 (7.6)	480 (16.1)	84 (8.7)
Grade 1	213 (7.1)	65 (6.5)	307 (10.3)	71 (7.3)
Grade 2	44 (1.5)	9 (0.9)	148 (5.0)	13 (1.3)
Grade 3	3 (<0.1)	1 (0.1)	25 (0.8)	0
Grade 4	0	0	0	0
Grade 3 or above	3 (<0.1)	1 (0.1)	25 (0.8)	0
Nausea/vomiting – N1	3002	993	2983	967
Any	325 (10.8)	107 (10.8)	713 (23.9)	96 (9.9)
Grade 1	274 (9.1)	93 (9.4)	527 (17.7)	77 (8.0)
Grade 2	46 (1.5)	14 (1.4)	167 (5.6)	19 (2.0)
Grade 3	5 (0.2)	0	19 (0.6)	0
Grade 4	0	0	0	0
Grade 3 or above	5 (0.2)	0	19 (0.6)	0
Chills – N1	3002	993	2983	967
Any	309 (10.3)	67 (6.7)	904 (30.3)	74 (7.7)
Grade 1	242 (8.1)	54 (5.4)	508 (17.0)	61 (6.3)
Grade 2	64 (2.1)	13 (1.3)	377 (12.6)	13 (1.3)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	Placebo (N=994) n (%)	mRNA-1273 50 µg (N=2986) n (%)	Placebo (N=968) n (%)
Grade 3	3 (<0.1)	0	19 (0.6)	0
Grade 4	0	0	0	0
Grade 3 or above	3 (<0.1)	0	19 (0.6)	0

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.

Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Toxicity grade for fever is defined as: grade 1=38.0-38.4°C; grade 2=38.5-38.9°C; grade 3=39.0-40.0°C; grade 4=>40.0°C. Toxicity grade for other solicited systemic adverse reactions is defined as: grade 1=no interference with activity (or, for nausea/vomiting: 1-2 episodes/24 hours); grade 2=some interference with activity (or, for nausea/vomiting: >2 episodes/24 hours); grade 3=prevents daily activity; grade 4=requires emergency room visit or hospitalization.

[a.] The reported event of grade 4 fever in the placebo group was due to an error in data entry in the daily eDiary. The actual temperature was 100.0°F (grade 0).

Sources: Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1

2.5.6.1.2.3 Analysis of Solicited Adverse Reactions in Participants 6 to < 12 Years of Age Compared with 18 to 25 Years of Age

Solicited ARs from 6- to < 12-year-old participants in the mRNA-1273 group (50 µg) in Part 2 of Study P204 (referred to as Study P204 participants in the following analyses of solicited ARs) were compared with solicited ARs reported from 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301 (referred to as Study P301 participants in the following analyses of solicited ARs).

2.5.6.1.2.3.1 Analysis of Solicited Local Adverse Reactions in Participants 6 to < 12 Years of Age Compared with 18 to 25 Years of Age

Solicited local ARs within 7 days of any dose of mRNA-1273 were reported at a similar frequency in Study P204 participants (98.6%) (Study P204 Table 14.3.1.1.3.2.1) as in Study P301 participants (94.1%). In participants in both studies the majority of solicited local ARs were grade 1 or 2 (Study P204 Table 14.3.1.1.3.2.1). Grade 3 solicited local ARs were reported in 5.5% of Study P204 participants and no grade 4 ARs were reported in this group (Study P204 Table 14.3.1.1.3.2.1). In contrast, grade 3 ARs were more frequent in Study P301 participants (11.4%). The most common solicited local AR was pain in both the Study P204 (98.4%) and Study P301 (89.4% after both dose 1 and dose 2) participants (Study P204 Table 14.3.1.1.3.2.1).

2.5.6.1.2.3.2 Analysis of Solicited Systemic Adverse Reactions in Participants 6 to < 12 Years of Age Compared with 18 to 25 Years of Age

Solicited systemic ARs within 7 days of any dose of mRNA-1273 were reported at consistent rates in Study P204 participants (86.5%) (Study P204 Table 14.3.1.1.3.2.1) and in Study P301 participants (89.1%). The majority of solicited systemic ARs after any dose were grade 1 or 2 for both Study P204 participants (Study P204 Table 14.3.1.1.3.2.1) and Study P301 participants. Grade 3 solicited systemic ARs were less frequent in Study P204 participants (13.3%) (Study P204 Table 14.3.1.1.3.2.1) than in Study P301 participants (23.5%). The most common solicited systemic ARs in Study P204 participants were fatigue (43.4% after dose 1 and 64.4% after dose 2) and headache (31.2% after dose 1 and 54.2% after dose 2) (Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1). The most common solicited systemic ARs in Study P301 participants were also fatigue (45.9% after dose 1 and 69.2% after dose 2) and headache (42.8% after dose 1 and 70.1% after dose 2).

The solicited systemic AR of fever was more common in Study P204 participants (3.4% after dose 1 and 24.1% after dose 2) (Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1) than in Study P301 participants (1.7% after dose 1 and 18.2% after dose 2). Grade 3 fever was also more frequent in Study P204 participants (0.6% after dose 1 and 3.8% after dose 2) (Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1) than in Study P301 participants (0 after dose 1 and 1.2% after dose 2).

2.5.6.1.3 Unsolicited Adverse Events

Unsolicited AEs after any dose were collected during the 28 days after each IP dose (ie, the day of injection and 27 subsequent days). An event was considered an AE if it was an untoward medical occurrence associated with the use of IP in humans, whether or not considered related to the IP. Adverse events leading to discontinuation from IP and/or study participation, SAEs, AESIs, MAAEs, and pregnancies were collected from Day 1 through the entire study period or until last day of study participation. Any solicited ARs (local or systemic) that persisted beyond 7 days after dosing were also collected as unsolicited AEs and will be presented here as well as in the sections discussing ARs.

An MAAE was defined as an AE that leads to an unscheduled visit to a health care provider. This would include visits to a study site for unscheduled assessments and visits to health care providers external to the study site.

Refer to the Study P204 protocol amendment 5 in Module 5.3.5.1 for additional details on the collection of unsolicited AEs at site visits and by weekly safety phone calls. More details on the adaptation of the safety call script in P204 can be found in Section 2.5.6.

2.5.6.1.3.1 Summary of Unsolicited Adverse Events in Part 1

Overall, 116 (30.5%) participants in the 50 µg group of Part 1 reported at least 1 unsolicited TEAE (Table 27). Serious unsolicited TEAEs within 28 days of any dose were reported for 2 (0.5%) participants in this group (see Section 2.5.6.1.4.1.1). These SAEs included an event of palpitations and an event of foreign body ingestion. These events are discussed more in depth in Section 2.5.6.1.4.1.1, along with any serious events occurring outside the 28-day window. Medically-attended AEs were experienced by 45 (11.8%) participants in the 50 µg group. One (0.3%) participant in the 50 µg group was discontinued from the study vaccine due to a TEAE of urticaria papular and no participants were discontinued from the study as a result of TEAEs (Study P204 Table 14.3.1.15.1). No participants in the 50 µg group reported severe TEAEs.

In the 50 µg group, 41 (10.8%) participants reported at least 1 TEAE determined by the investigator to be related to IP. Of these participants, none reported serious TEAEs considered by the investigator to be related to study IP, 4 (1.1%) reported MAAEs, none were discontinued from the study, and none experienced severe TEAEs.

Incidence of participants experiencing unsolicited AEs in the 50 µg and the 100 µg groups were not notably different.

No participants in either dose group reported TEAEs of MIS-C, myocarditis, or pericarditis. The single severe unsolicited TEAE reported in the 100 µg group is discussed in Section 2.5.6.1.3.2.

Table 27: Summary of Unsolicited Adverse Events up to 28 Days After Any Dose (Part 1 – Safety Set)

Category	mRNA-1273 50 µg (N = 380) n (%)	mRNA-1273 100 µg (N = 371) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination		
All	116 (30.5)	96 (25.9)
Serious	2[a] (0.5)	0
Fatal	0	0
Medically-Attended	45 (11.8)	47 (12.7)
Leading to discontinuation from study vaccine	1 (0.3)	0
Leading to discontinuation from participation in the study	0	0
Severe	0	1 (0.3)
Unsolicited TEAEs related to study vaccination		
All	41 (10.8)	42 (11.3)
Serious	0	0
Fatal	0	0
Medically-attended	4 (1.1)	7 (1.9)

Category	mRNA-1273 50 µg (N = 380) n (%)	mRNA-1273 100 µg (N = 371) n (%)
Leading to discontinuation from study vaccine	1[b] (0.3)	0
Leading to discontinuation from participation in the study	0	0
Severe	0	1 (0.3)

Abbreviations: PT = preferred term; SAE = serious adverse event; TEAE= treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
a. One participant experienced the SAE of body ingestion and another participant the SAE of palpitations (Note: Subsequent to the data snapshot, the event of palpitations was downgraded to nonserious and the onset was changed to > 28 days after dose 2).
b. Adverse event of urticaria papular (Section 2.5.6.1.4.3).
Source: Study P204 Table 14.3.1.7.1.1

2.5.6.1.3.2 Most Common Unsolicited Adverse Events in Part 1

Treatment-emergent AEs reported in greater than 1% of participants in the 50 µg group of Part 1 had the PTs injection site erythema (4.5%), upper respiratory infection (3.2%), oropharyngeal pain (3.4%), nasal congestion (2.9%), cough (2.1%), headache (1.6%), nasopharyngitis (1.3%), urinary tract infection (1.3%), rhinorrhoea (1.3%), otitis externa (1.3%), injection site lymphadenopathy (1.3%), fatigue (1.3%), and vomiting (1.1%) (Table 28). While the overall percentage of participants in the 50 µg group reporting unsolicited AEs is slightly higher than the percentage in the 100 µg group, the percentages of participants reporting TEAEs were not notably different between the groups.

There were no severe TEAEs reported in the 50 µg group (Table 28). A single severe TEAE was reported within the 28 of any dose in the 100 µg group with the PT injection site erythema. The event had an onset 8 days after the first dose. The participant continued on the study and the TEAE resolved in 6 days.

A summary of unsolicited TEAEs by system organ class (SOC) and PT for the 100 µg is presented in Table 28.

Table 28: Summary of Unsolicited Adverse Events Reported in ≥ 1% in Any Treatment Group up to 28 Days after Any Dose Classified by MedDRA Primary System Organ Class and Preferred Term, Any and Severe (Part 1 – Safety Set)

System Organ Class Preferred Term	mRNA-1273 50 µg (N=380)		mRNA-1273 100 µg (N=371)	
	Any n (%)	Severe n (%)	Any n (%)	Severe n (%)
Number of participants reporting unsolicited adverse events	116 (30.5)	0	96 (25.9)	1 (0.3)
Number of unsolicited adverse events	204	0	165	1
Infections and infestations	39 (10.3)	0	30 (8.1)	0
Upper respiratory tract infection	12 (3.2)	0	12 (3.2)	0
Nasopharyngitis	5 (1.3)	0	3 (0.8)	0
Otitis externa	5 (1.3)	0	3 (0.8)	0
Immune system disorders	3 (0.8)	0	4 (1.1)	0
Nervous system disorders	7 (1.8)	0	5 (1.3)	0
Headache	6 (1.6)	0	4 (1.1)	0
Respiratory, thoracic and mediastinal disorders	28 (7.4)	0	21 (5.7)	0
Nasal congestion	11 (2.9)	0	10 (2.7)	0
Oropharyngeal pain	13 (3.4)	0	3 (0.8)	0
Cough	8 (2.1)	0	7 (1.9)	0
Rhinorrhoea	5 (1.3)	0	7 (1.9)	0
Gastrointestinal disorders	10 (2.6)	0	5 (1.3)	0
Vomiting	4 (1.1)	0	0	0
Skin and subcutaneous tissue disorders	5 (1.3)	0	8 (2.2)	0
Musculoskeletal and connective tissue disorders	4 (1.1)	0	3 (0.8)	0
General disorders and administration site conditions	36 (9.5)	0	44 (11.9)	1 (0.3)
Injection site erythema	17 (4.5)	0	12 (3.2)	1 (0.3)
Pyrexia	3 (0.8)	0	8 (2.2)	0
Injection site rash	3 (0.8)	0	7 (1.9)	0
Injection site lymphadenopathy	5 (1.3)	0	4 (1.1)	0
Fatigue	5 (1.3)	0	3 (0.8)	0
Injection site induration	3 (0.8)	0	5 (1.3)	0
Injury, poisoning and procedural complications	11 (2.9)	0	3 (0.8)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities.
Note: Percentages are based on the number of safety participants. MedDRA version 23.0.
Source: Study P204 Table 14.3.1.8.1.1 and Table 14.3.1.17.1

2.5.6.1.3.3 Summary of Unsolicited Adverse Events in Part 2

In the mRNA-1273 group, 716 (23.8%) participants reported at least 1 unsolicited TEAE versus 194 (19.5%) in the placebo group (Table 29). These events fall mainly under the SOC of general

disorders and administration site conditions. Serious unsolicited TEAEs within 28 days of any dose were reported for 2 (< 0.1%) participants in the mRNA-1273 group. These events are discussed in more depth in Section 2.5.6.1.4.1.2 along with SAEs that occurred outside 28 days post any dose. These SAEs had the PTs appendicitis and cellulitis orbital. Medically-attended AEs were reported in 256 (8.5%) of participants in the mRNA-1273 group. AESIs are discussed in Section 2.5.6.1.4.4.1.1. A total of 2 (< 0.1%) participants in the mRNA-1273 group were discontinued from the study vaccine due to a TEAE. One participant was discontinued from study vaccine due to an event of rash and the other participant was discontinued from study vaccine due to 2 TEAEs of urticaria and wheezing. No participants in the mRNA-1273 group were discontinued from the study as a result of TEAEs.

Of the participants reporting TEAEs, 294 (9.8%) participants in the mRNA-1273 group of Part 2 reported TEAEs that were determined by the investigator to be related to IP. Of these participants, none reported serious TEAEs, 31 (1.0%) reported MAAEs, none was discontinued from study vaccine or the study (Table 29).

While no participants in the placebo group experienced severe TEAEs, 9 (0.3%) of participants in the mRNA-1273 group experienced a severe TEAE; of the 9 participants, 6 (0.2%) experienced severe TEAEs that were considered related to study IP Severe TEAEs are further discussed in Section 2.5.6.1.3.4.

A summary of TEAEs in the placebo group can also be found in Table 29.

Table 29: Summary of Unsolicited Adverse Events up to 28 Days After Any Dose (Part 2 – Safety Set)

Category	mRNA-1273 50 µg (N = 3007) n (%)	Placebo (N = 995) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination		
All	716 (23.8)	194 (19.5)
Serious	2[a] (<0.1)	0
Fatal	0	0
Medically-Attended	256 (8.5)	100 (10.1)
Leading to discontinuation from study vaccine	2 (<0.1)	0
Leading to discontinuation from participation in the study	0	0
Severe	9 (0.3)	0
Special interest of MIS-C	0	0
Unsolicited TEAEs related to study vaccination		
All	294 (9.8)	37 (3.7)
Serious	0	0

Category	mRNA-1273 50 µg (N = 3007) n (%)	Placebo (N = 995) n (%)
Fatal	0	0
Medically-attended	31 (1.0)	3 (0.3)
Leading to discontinuation from study vaccine	0	0
Leading to discontinuation from participation in the study	0	0
Severe	6 (0.2)	0
Special interest of MIS-C	0	0

Abbreviations: MIS-C=multisystem inflammatory syndrome in children; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
a. Two participants experienced SAEs with the PTs appendicitis and cellulitis orbital.
Source: Study P204 Table 14.3.1.7.1.2

2.5.6.1.3.4 Most Common Unsolicited Adverse Events in Part 2

TEAEs from Part 2 reported greater than 1% of participants in the mRNA-1273 group included the PTs injection site erythema (2.8%), upper respiratory tract infection (2.3%), headache (2.3%), oropharyngeal pain (2.0%), cough (1.8%), rhinorrhoea (1.7%), nasal congestion (1.6%), injection site lymphadenopathy (1.4%), injection site pain (1.2%), and fatigue (1.1%). In comparison, TEAEs reported in greater than 1% of the placebo group by PT were oropharyngeal pain (2.2%), nasal congestion (2.2%), COVID-19 (2.1%), upper respiratory tract infection (1.9%), headache (1.8%), rhinorrhoea (1.8%), cough (2.1%), and fatigue (1.2%) (Table 30).

TEAEs experienced in the mRNA-1273 group are similar in nature and incidence as those in the placebo group with the exception of an increase in the incidence of injection site conditions in the mRNA-1273 group.

A total of 10 severe TEAEs were reported in 9 (0.3%) participants. Unsolicited severe TEAEs reported in the mRNA-1273 group of Part 2 had the PTs fatigue (< 0.1%), injection site pain (< 0.1%), cellulitis orbital (< 0.1%), nasal congestion (< 0.1%), rhinorrhoea (< 0.1%), oropharyngeal pain (< 0.1%), vomiting (< 0.1%), urticaria (< 0.1%), and foot fracture (<0.1%) (Study P204 Table 14.3.1.17.2.1). All of these severe TEAEs were reported in one participant except for fatigue and injection site pain, which were each reported in 2 participants. The events of fatigue (2 events), injection site pain (2 events), vomiting, and urticaria were considered related to study IP. There were no severe TEAEs reported in the placebo group (Table 30).

Table 30: Summary of Unsolicited Adverse Events Reported in ≥ 1% in Any Treatment Group up to 28 Days After Any Dose Classified by MedDRA Primary System Organ Class and Preferred Term, Any and Severe (Part 2 – Safety Set)

System Organ Class Preferred Term	mRNA-1273 50 µg (N=3007)		Placebo (N=995)	
	Any n (%)	Severe n (%)	Any n (%)	Severe n (%)
Number of participants reporting unsolicited adverse events	716 (23.8)	9 (0.3)	194 (19.5)	0
Number of unsolicited adverse events	1183	10	317	0
Infections and infestations	209 (7.0)	1 (<0.1)	76 (7.6)	0
Upper respiratory tract infection	70 (2.3)	0	19 (1.9)	0
COVID-19	12 (0.4)	0	21 (2.1)	0
Nervous system disorders	12 (0.4)	0	21 (2.1)	0
Headache	69 (2.3)	0	21 (2.1)	0
Respiratory, thoracic and mediastinal disorders	61 (2.0)	0	18 (1.8)	0
Oropharyngeal pain	142 (4.7)	0	58 (5.8)	0
Cough	59 (2.0)	0	22 (2.2)	0
Nasal congestion	54 (1.8)	0	21 (2.1)	0
Rhinorrhoea	47 (1.6)	1 (<0.1)	22 (2.2)	0
Gastrointestinal disorders	50 (1.7)	1 (<0.1)[a]	18 (1.8)	0
Skin and subcutaneous tissue disorders	66 (2.2)	1 (<0.1)[b]	16 (1.6)	0
Musculoskeletal and connective tissue disorders	54 (1.8)	0	6 (0.6)	0
General disorders and administration site conditions	34 (1.1)	0	12 (1.2)	0
Injection site erythema	270 (9.0)	0	35 (3.5)	0
Injection site lymphadenopathy	83 (2.8)	0	0	0
Fatigue	43 (1.4)	2 (<0.1)	4 (0.4)	0
Injection site pain	34 (1.1)	2 (<0.1)	12 (1.2)	0
Injury, poisoning and procedural complications	35 (1.2)	1 (<0.1)[c]	10 (1.0)	0

Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Percentages are based on the number of safety participants. MedDRA version 23.0.

a. Event with preferred term of Vomiting that started on study Day 1 and ended on study Day 9

b. Event with preferred term of urticaria and verbatim term of Worsening of Hives that started 18 days after last vaccination and resolved 6 days later. that started 8 d1

c. Event with the preferred term foot fracture

Source: Study P204 Table 14.3.1.8.1.2 and Table 14.3.1.17.2.1

2.5.6.1.4 Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

2.5.6.1.4.1 Serious Adverse Events

2.5.6.1.4.1.1 Serious Adverse Events in Part 1

In the 50 µg group within the 28-day window post any dose, 1 participant had an SAE of grade 1 palpitations after dose 2, and 1 participant had an SAE of foreign body ingestion that led to inpatient hospitalization (Table 31). Both of the events were also considered MAAEs, and neither of the events was considered related to mRNA-1273 by the investigator. The foreign body ingestion resolved after 3 days' duration. The event of palpitations occurred in a child with a history of palpitations. Electrocardiogram and echocardiogram results were normal, and the child was pending ambulatory Holter monitoring. While the event was initially reported as an SAE that was assessed as not related to study IP, after the date of the data snapshot it was subsequently downgraded to nonserious and the onset was changed to > 28 days after dose 2. Narratives for both these participants are available in Module 5.3.5.1.

No SAEs were reported in the 100 µg group within the 28-day window after dose (Table 31).

For SAEs with onset after 28 days, in the 50 µg group, 1 participant had an SAE of grade 2 optic disc drusen, which occurred 151 days after dose 2 and was ongoing at the time of the data snapshot. The event was considered not related to mRNA-1273 (Study P204 Listing 16.2.7.1.2). In addition, 2 other participants experienced SAEs of grade 3 appendicitis 97 and 72 days, respectively, after dose 2 (further discussed in Section 2.5.6.1.4.4.1.2). Both of the SAEs led to inpatient hospitalization, both recovered, and both were considered not related to mRNA-1273 by the investigator.

In the 100 µg group, 1 participant had an SAE of grade 2 systemic viral infection of unknown etiology that required inpatient hospitalization 101 days after dose 2 (Study P204 Table 14.3.1.13.2.1). The event was also an MAAE and was considered not related to mRNA-1273 by the investigator. The event resolved after 6 days.

Narratives are available for these participants in Module 5.3.5.1.

Table 31: Summary of Serious Adverse Events up to 28 Days After Any Dose (Part 1 – Safety Set)

System Organ Class Preferred Term	**mRNA-1273** **50 µg** **(N = 380)**	**mRNA-1273** **100 µg** **(N = 371)**

	n (%)	n (%)
Number of participants reporting unsolicited serious adverse events	2 (0.5)	0
Number of unsolicited serious adverse events	2	0
Number of related serious adverse events	0	0
Cardiac disorders	1 (0.3)	0
Palpitations	1[a] (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	0
Foreign body ingestion	1 (0.3)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities.
Note: Percentages are based on the number of safety participants. MedDRA version 23.0.
a. The event of palpitations was initially reported as a SAE, but after the date of the data snapshot it was subsequently downgraded to nonserious and the onset was changed to > 28 days after dose 2.
Source: Study P204 Table 14.3.1.13.1.1.

2.5.6.1.4.1.2 Serious Adverse Events in Part 2

In Part 2 of the study, 1 participant had an SAE that occurred within the 28-day window after dose 1 (grade 2 appendicitis) (further discussed in Section 2.5.6.1.4.4.1.3), and 1 participant had an SAE that occurred within the 28-day window after dose 2 (grade 3 cellulitis orbital) in the mRNA-1273 50 µg group (Table 32). Both of the events led to hospitalization and were also considered MAAEs. Both events resolved, and neither of the events was considered related to mRNA-1273 by the investigator.

No participants in the placebo group experienced SAEs during the study (Table 32).

Narratives are available for these participants in Module 5.3.5.1.

Table 32: Summary of Serious Adverse Events up to 28 Days After Any Dose (Part 2 – Safety Set)

System Organ Class Preferred Term	**mRNA-1273 50 µg (N=3007) n (%)**	**Placebo (N=995) n (%)**
Number of participants reporting unsolicited serious adverse events	2 (<0.1)	0
Number of unsolicited serious adverse events	2	0
Infections and infestations	2 (<0.1)	0
Appendicitis	1 (<0.1)	0
Cellulitis orbital	1 (<0.1)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities.
Note: Percentages are based on the number of safety participants. MedDRA version 23.0
Source: Study P204 Table 14.3.1.13.1.2.

2.5.6.1.4.2 Deaths

No deaths have been reported in the study as of the data snapshot (Study P204 Tables 14.3.1.13.1.1 and 14.3.1.13.1.2; Listing 16.2.11.1 and 16.2.11.2).

2.5.6.1.4.3 Discontinuation from Investigational Product or Study Participation

2.5.6.1.4.3.1 Discontinuation from Investigational Product or Study Participation in Part 1

One participant in the 50 µg group, An 11-year-old female with history of seasonal allergies and facial maculopapular rash, had a nonserious, moderate AE of urticaria papular (verbatim term: delayed skin reaction, urticarial and papular rash on left arm, elbows, feet and hands) leading to discontinuation from study vaccine (Study P204 Table 14.3.1.15.1). The event started on Day 9 following dose 1 and was reported as related to study IP. The participant recovered within 6 days of the onset of the event (Study P204 Listing 16.2.7.1.2). A narrative for this participant is available in Module 5.3.5.1.

2.5.6.1.4.3.2 Discontinuation from Investigational Product or Study Participation in Part 2

Two participants in the mRNA-1273 50 µg group had AEs leading to discontinuation from study vaccine, including wheezing, rash, and urticaria (Study P204 Table 14.3.1.15.2).

One participant, a 9-year-old male with history of seasonal allergies, was discontinued from study vaccine due to nonserious events of moderate urticaria (verbatim term: hives all over the body) and mild wheezing (verbatim term: wheezing). A narrative for this participant can be found in Module 5.3.5.1. The urticaria started on Day 24 following dose 1 and the wheezing on Day 29 following dose 1. The relationship of study IP to the event of urticaria was unknown at the time of data snapshot, while the event of wheezing was reported as unrelated to study IP. The participant recovered from the wheezing 3 days after the onset of the event. The event of urticaria was still resolving and the participant was continuing in the study at the time of the data snapshot (Study P204 Listing 16.2.7.1.2).

The other participant, a 10-year-old male with history of chronic kidney disease, experienced a nonserious, mild AE of rash (verbatim term: generalized rash all over body) on Day 10 following

dose 1, which led to withdrawal of the study IP. The participant was continuing follow-up in the study at the time of data snapshot. The event was considered to be resolved on Day 18 (Study P204 Listing 16.2.7.1.2). A narrative for this participant can be found in Module 5.3.5.1.

No participant in the placebo group had an AE leading to discontinuation from study vaccine. In Table 9, 1 participant in the placebo group is listed as having discontinued from study vaccine. A discussion of this participant can be found in Section 2.5.5.1.2.

2.5.6.1.4.4 Other Safety Data

2.5.6.1.4.4.1 Evaluation of Safety Reports of "Suspected COVID-19," "Asymptomatic COVID-19," and "COVID-19"

As noted above (Section 2.5.5.2.2.3.1), the COVID-19 case definitions ("P301 case definition" or "CDC case definition") for efficacy endpoints require the following: (i) Positive RT-PCR (central or local laboratory) (Table 18) and (ii) Eligible symptoms reported on the "SARS-CoV-2 or COVID-19 Symptom Assessment Page" eCRF. The definition of SARS-CoV-2 infection required at least 1 confirmatory laboratory result (bAb level against SARS-CoV-2 nucleocapsid protein positive [as measured by Roche Elecsys] post-baseline OR positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits) for participants with negative SARS-CoV-2 status at baseline.

In Study P204, the sites and investigators are instructed to record only confirmed COVID-19 cases as AEs (Section 7.4.4 of protocol). In some cases, investigators may have completed the "Adverse Event" eCRF page to record suspected COVID-19 or COVID-19 symptoms. However, without sufficient information regarding results of laboratory testing for SARS-CoV-2 (ie, nature of the test, confirmation that test performed in a Clinical Laboratory Improvement Amendments [CLIA]-certified laboratory) and/or without provision of eligible systemic or respiratory symptoms supporting the case definition of COVID-19, these cases could not be counted as an efficacy endpoint. Accordingly, entries bearing the term "COVID" may have been captured in the safety database but may not have met the requirements for inclusion in the efficacy case count. Symptoms related to COVID-19 in the absence of confirmatory laboratory results (central or local) were reported under terms such as "COVID-19" or "suspected COVID-19" or "asymptomatic COVID-19" (Table 40, Table 41, Table 42, Table 43, Table 44).

"Suspected COVID-19" infection was reported as an AE in 9 participants (all in Part 2, 7 participants [0.2%] in the mRNA-1273 group and 2 participants [0.2%] in the placebo group) (Study P204 Table 14.3.1.8.1.2). At the time of the data snapshot (06 October 2021), 7 had a

negative RT-PCR test at a subsequent illness visit and 2 had test results pending, which were subsequently logged as negative after the data snapshot on 07 October 2021. Therefore, none of these 9 cases occurring in the mRNA-1273 and placebo groups was considered a case of COVID-19 for the efficacy analysis.

Listings of adverse events reported as "asymptomatic COVID-19" and "COVID-19" are provided in Appendix 1.

An AE of "asymptomatic COVID-19" was reported on the AE eCRF for participants in cases where: (i) a scheduled study test (eg, Day 1, Day 29, Day 43, or Day 57) was positive, or (ii) where a positive test (performed because of exposure or school testing, for example) was reported to the study investigator, but where confirmatory test results (central or local) were not available to the study site. Many of these events were related to Day 1 or baseline positive results, prior to any administration of mRNA-1273 or placebo. In some cases, laboratory results were unavailable, were not reported, or were not the required RT-PCR or Elecsys testing required for efficacy analysis (for example, antigen testing only).

As shown in Appendix 1, there were AEs reported as "COVID-19" without further specification of symptoms or confirmatory laboratory results. Queries are outstanding on these events. These events were more common in the placebo group than in the mRNA-1273 group.

All cases of "COVID-19," "suspected COVID-19," and "asymptomatic COVID-19" were nonserious and mild to moderate in severity. No cases met the protocol-defined case definition for "severe COVID-19."

2.5.6.1.4.4.1 Analyses of Adverse Events of Special Interest

A priority list of AESIs relevant to development of COVID-19 vaccines, developed by the Brighton Collaboration, was included in the Study P204 protocol (Law 2020). The investigator was asked to report events listed in Table 33 even if the event occurred in the setting of a SARS-CoV-2 infection. Section 2.5.6.1.4.4.2 discusses events of clinical interest related to hypersensitivity, Section 2.5.6.1.4.4.3 summarizes events of clinical interest of potential cardiac etiology. Section 2.5.6.1.4.4.4 includes additional analyses for myocarditis and pericarditis.

AEs considered AESIs in Study P204 are listed in Table 33.

Narratives are available for these participants in Module 5.3.5.1.

Table 33: Adverse Events of Special Interest

Adverse Event	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48 hours; OR o Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR o Urine volume ≤0.5 mL/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria o 3-fold elevation above the upper normal limit for ALT or AST OR o > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme

Adverse Event	Additional Notes
	• Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 ×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barre Syndrome o Acute disseminated encephalomyelitis o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per protocol. • Follow reporting procedures in protocol Section 7.4.5
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

2.5.6.1.4.4.1.2 Adverse Events of Special Interest in Part 1

AESI were assessed as those occurring (i) within 28 days of any injection and (ii) across the study duration. Results are presented first for the 50 µg dose group and then for the 100 µg dose group.

50 µg dose group:

Events of appendicitis were reported in 2 (0.5%) participants, both occurred beyond 28 days from any injection. One event occurred in a 7-year-old male participant on Study Day 125. The participant was hospitalized and underwent appendectomy. No additional treatment for appendicitis was reported, he was discharged 4 days after onset, and was considered subsequently recovered. The second event occurred in a 10-year-old PPD male on Study Day 100. The participant was hospitalized and underwent open surgery for appendicitis. No additional treatment for appendicitis was reported. The participant subsequently recovered and was discharged from the hospital 3 days after the onset of the event. Neither event was considered related to study IP by the investigator. Narratives for both of these participants can be found in Module 5.3.5.1. The delayed time to onset of these 2 events make them unlikely to have a causal relationship to vaccination.

An event of non-cardiac chest pain (mild) was reported as an AESI in 1 participant, occurring 72 days after dose 2. This event also does not meet AESI criteria as per protocol, but the event was marked as an AESI in the eCRF by the investigator. All AESIs were not considered related to study IP, except the event of non-cardiac chest pain.

Although palpitations were not considered AESI based on definitions above, an investigator reported an event of palpitations as an AESI (eCRF) occurring within 28 days. This event is further discussed in Section 2.5.6.1.4.4.3.1.

100 µg group:

No reports of AESIs occurring within 28 days of any dose. Beyond 28 days after any dose, 2 (0.5%) participants were reported with AESIs – neither was considered related to IP: (i) one mild event of bullous impetigo reported in a 6-year-old male on study day 79, or 48 days after the most recent dose and (ii) one event of ageusia reported in a 11-year-old female 28 days after the most recent dose, with contemporaneous nasal congestion. A narrative for this participant is available Module 5.3.5.1.

2.5.6.1.4.4.1.3 Adverse Events of Special Interest in Part 2

mRNA-1273 group:

Only one AESI was reported in 1 (< 0.1%) participant in this group and it occurred within 28 days of any dose: the event of appendicitis was reported in a 7-year-old female randomized to the mRNA-1273 (50 µg) group. The event occurred on Study Day 26; the child was hospitalized

and underwent appendectomy. No additional treatment for appendicitis was reported. The participant subsequently recovered and was discharged from the hospital 1 day after the onset of the event. The event was not considered related to study IP by the investigator. A narrative for this participant can be found in Module 5.3.5.1. There were no unusual features of the event of appendicitis and the participant went on to receive the second dose of mRNA-1273 without any additional events reported

Placebo group:

Only 2 AESIs were reported: ageusia and anosmia (verbatim terms COVID-19 associated anosmia and ageusia) were reported in a single (0.1%) 8-year-old male participant, occurring 11days after dose 1 (Study P204 Listing 16.2.7.1.2). This event met the "CDC case definition" and "P301 case definition" of COVID-19 (Section 2.5.5.2.2.3.3). The event was not considered related to study IP by the investigator.

2.5.6.1.4.4.2 Events of Clinical Interest Based on the MedDRA SMQs of Hypersensitivity

All unsolicited TEAEs within the narrow and the narrow and broad hypersensitivity standard Medical Dictionary for Regulatory Activities (Version 23) queries (SMQs) were summarized for Part 1 and Part 2 of the study. Hypersensitivity SMQs represent a strategy for searching a safety database for events or symptoms that might indicate potential events of hypersensitivity or anaphylaxis, but do not necessarily represent identification of actual cases of hypersensitivity or anaphylaxis.

2.5.6.1.4.4.2.1 Events of Clinical Interest Based on the MedDRA SMQs of Hypersensitivity in Part 1

This section summarizes participants reporting events within the narrow hypersensitivity SMQ and the combined narrow and broad hypersensitivity SMQ events in Part 1 of study P204 for both 50 ug and 100 ug groups. Events are considered that occurred within 48 hours (more consistent with possible acute hypersensitivity) and those occurring beyond 48 hours of any dose.

No events of anaphylaxis were reported in Part 1.

In total, 54 participants experienced a total of 61 events of potential hypersensitivity reactions (Study P204 Table 14.3.1.22.3.2.2.1). The 54 participants included 23 (6.1%) in the 50 µg mRNA-1273 group and 31 (8.4%) in the 100 µg group (Table 34).

In the 50 µg group the most commonly reported PT within the hypersensitivity SMQs using the narrow and broad standard were seasonal allergy (6 [1.6%] participants), injection site rash (3 [0.8%] participants), urticaria (3 [0.8%] participants), and vaccination site rash (2 [0.5%] participants).

In the 100 µg group in Part 1, the most commonly reported PT within the hypersensitivity SMQs using the narrow and broad standard were injection site rash (7 [1.9%] participants), seasonal allergy (5 [1.3%] participants), and sneezing (5 [1.3%] participants).

In Part 1, only 2 events were reported on the day of or day after dose administration. These events were seasonal allergies and urticaria. The event of urticaria with the verbatim term of "several coalesced hives on both sides of face" occurred in an 8-year-old female and started the day after the second dose. The event was reported as mild, related and reported as resolved the next day. This participant had no other AEs reported during the study.

Beyond 48 hours of any dose, 2 events were reported with PTs of bronchial hyperreactivity and wheezing. The event of bronchial hyperreactivity (verbatim term Exacerbation of reactive airway disease) was reported in a 11-year-old male participant with history of reactive airways, 45 days after the second dose. The event was considered related, mild and reported as resolved 2 days after it started. The event of wheezing was reported in a 11-year-old male with past medical history of mild intermittent asthma, 28 days after the second dose and reported as moderate and not related. The event resolved 4 days after it started.

Table 34: Events of Clinical Interest After Any Dose Based on the MedDRA SMQs of Hypersensitivity Narrow and Broad Scope in Part 1 (Part 1 – Safety Set)

Preferred Term	mRNA-1273 50 µg (N=380) n (%)	mRNA-1273 100 µg (N=371) n (%)
Number of Subjects Reporting Hypersensitivity	**23 (6.1)**	**31 (8.4)**
Number of Subjects Reporting Related Hypersensitivity	**8 (0.2)**	**14 (0.4)**
Number of Events of Hypersensitivity	**24**	**37**
Seasonal allergy	6 (1.6)	5 (1.3)
Injection site rash	3 (0.8)	7 (1.9)
Sneezing	2 (0.5)	5 (1.3)
Urticaria	3 (0.8)	2 (0.5)
Vaccination site rash	2 (0.5)	2 (0.5)
Dermatitis contact	1 (0.3)	2 (0.5)
Asthma	0	2 (0.5)
Pruritus	1 (0.3)	1 (0.3)
Rhinitis allergic	1 (0.3)	1 (0.3)

Preferred Term	mRNA-1273 50 µg (N=380) n (%)	mRNA-1273 100 µg (N=371) n (%)
Bronchial hyperreactivity	1 (0.3)	0
Bullous impetigo	0	1 (0.3)
Conjunctivitis	0	1 (0.3)
Conjunctivitis allergic	1 (0.3)	0
Dermatitis	0	1 (0.3)
Hypersensitivity	0	1 (0.3)
Rash	0	1 (0.3)
Rash macular	0	1 (0.3)
Rash maculo-papular	1 (0.3)	0
Rash pruritic	0	1 (0.3)
Stomatitis	0	1 (0.3)
Urticaria papular	1 (0.3)	0
Wheezing	1 (0.3)	0

Note: Percentages are based on the number of safety subjects. Hypersensitivity is identified through selected narrow and broad SMQ.
Source: Study P204 Table 14.3.1.22.3.2.2.1 and Listing 16.2.7.19.2.1

2.5.6.1.4.4.2.2 Events of Clinical Interest Based on the MedDRA SMQs of Hypersensitivity in Part 2

No events of anaphylaxis were reported in Part 2.

The number of participants reporting events within the narrow hypersensitivity SMQ and the combined narrow and broad hypersensitivity SMQ was 98 (3.3%) in the mRNA-1273 group, reporting a total of 112 events, and 14 (1.4%) participants in the placebo group, reporting a total of 16 events (Table 35). In the mRNA-1273 group in Part 2, the most commonly reported PTs within hypersensitivity SMQs were injection site rash (22 [0.7%] participants), urticaria (10 [0.3%] participants), rash (10 [0.3%] participants), and seasonal allergy (9 [0.3%] participants). In the placebo group, the most commonly reported hypersensitivity SMQs were seasonal allergy (5 [0.5%] participants) and injection site hypersensitivity (3 [0.3%] participants).

In total, 58 (1.9%) participants in the mRNA-1273 group reported events with PTs included in the narrow and broad hypersensitivity SMQs that were considered related to study IP. In contrast, 2 (0.2%) participants in the placebo group reported related events in the hypersensitivity SMQs.

In the mRNA group, most frequently reported SOCs were general disorders and administration site conditions and of Skin and subcutaneous tissue disorders.

Of these 116 events within the narrow and broad hypersensitivity SMQ reported in the mRNA-1273 group, 58 TEAEs (50%) were assessed by the Investigator as related to IP (Study P204 Table 14.3.1.22.2.2.2 and Listing 16.2.7.1.2).

Of the related events, the most frequent PTs were injections site reaction (injection site rash, injection site hypersensitivity, injection site urticaria or vaccination site rash). The other related PTs were mainly in the SOC of Skin and subcutaneous tissue disorders with the most frequent PTs of Urticaria. None of these events of urticaria started the day of vaccination (Study P204 Table 14.3.1.22.2.2.2 and Listing 16.2.7.1.2).

In Part 2, 13 events were reported in the mRNA-1273 group on the day of or day after dose administration. Of these, 8 of these events were in the SOC of Skin and subcutaneous tissue disorders, 1 in the SOC of General disorders and administration site conditions, 1 the SOC of Eye disorders, 2 in the SOC of Respiratory, thoracic and mediastinal disorders (asthma and sneezing), 1 in the SOC of vascular disorders (PT flushing).

The episode of asthma occurred the same day of the second dose and was reported as not related. This episode occurred in a child with history of asthma and multiple allergies (dairy, meat, dust and pollen) who was already on albuterol. No other AEs were reported at the same time for this participant (Study P204 Table 14.3.1.22.2.2.2 and Listing 16.2.7.1.2).

The event of flushing occurred within 15 minutes of dosing and lasted less than 30 min. It was reported as mild and related to the IP. No other AEs were reported at that time for this participant (Study P204 Table 14.3.1.22.2.2.2 and Listing 16.2.7.1.2).

Only one participant had more than one event reported the same day or the day after any dosing within the hypersensitivity SMQ with the PTs of rash pruritic (Verbatim terms: Pruritic Non-Urticarial Papular Rash Left Posterior Shoulder and Linear Pruritic non urticarial rash left forearm) (Study P204 Table 14.3.1.22.2.2.2 and Listing 16.2.7.1.2).

Two events reported in the hypersensitivity SMQ are further described here: (i) an event of bronchospasm (verbatim viral induced bronchospasm) was reported in a 11-year-old male with history of asthma 8 days after the second dose. It was reported as related, moderate, and resolved the same day it started, and (ii) an event of periorbital swelling was reported in a 9-year-old male 2 days after receiving the first dose. The event was reported as related, mild and resolved on study day 4.

In general, while events of potential hypersensitivity reactions were reported more frequently in participants receiving mRNA-1273 than placebo, none of the events is clinically concerning for

anaphylaxis or a severe episode of hypersensitivity. Adverse reaction of rash and injection site reactions including pruritis, rash, swelling and erythema, are currently listed on the mRNA-1273 product label.

Table 35: Events of Clinical Interest After Any Dose Based on the MedDRA SMQs of Hypersensitivity Narrow and Broad Scope in Part 1 (Part 2 – Safety Set)

Preferred Term	mRNA-1273 50 µg (N=3007) n (%)	Placebo (N=995) n (%)
Number of Subjects Reporting Hypersensitivity	**98 (3.3)**	**14 (1.4)**
Number of Subjects Reporting Related Hypersensitivity	**58 (1.9)**	**2 (0.2)**
Number of Events of Hypersensitivity	**112**	**16**
Injection site rash	22 (0.7)	0
Seasonal allergy	9 (0.3)	5 (0.5)
Urticaria	10 (0.3)	2 (0.2)
Rash	10 (0.3)	3 (0.3)
Injection site hypersensitivity	7 (0.2)	0
Asthma	5 (0.2)	2 (0.2)
Rash maculo-papular	4 (0.1)	0
Sneezing	3 (<0.1)	2 (0.2)
Dermatitis	4 (0.1)	0
Dermatitis contact	3 (<0.1)	0
Pruritus	3 (<0.1)	0
Injection site urticaria	3 (<0.1)	0
Wheezing	2 (<0.1)	0
Eczema	2 (<0.1)	0
Rash erythematous	2 (<0.1)	0
Rash pruritic	2 (<0.1)	0
Rhinitis allergic	1 (<0.1)	0
Auricular swelling	1 (<0.1)	0
Bronchial hyperreactivity	0	0
Bronchospasm	1 (<0.1)	0
Ear swelling	1 (<0.1)	0
Eczema nummular	1 (<0.1)	0
Erythema	1 (<0.1)	0
Eye swelling	1 (<0.1)	0
Flushing	1 (<0.1)	0
Hypersensitivity	1 (<0.1)	0
Lip oedema	1 (<0.1)	0
Periorbital oedema	1 (<0.1)	0
Periorbital swelling	1 (<0.1)	0
Rash macular	1 (<0.1)	0

Preferred Term	mRNA-1273 50 µg (N=3007) n (%)	Placebo (N=995) n (%)
Respiratory distress	1 (<0.1)	0
Urticaria contact	1 (<0.1)	0
Vessel puncture site rash	1 (<0.1)	0
Conjunctivitis	0	1 (0.1)

Note: Percentages are based on the number of safety subjects. Hypersensitivity is identified through selected narrow and broad SMQ.
Source: Study P204 Table 14.3.1.22.3.2.2.2 and Listing 16.2.7.19.2.2

2.5.6.1.4.4.3 Cases of Clinical Interest Based on MedDRA Cardiomyopathy SMQs

Enhanced collection of unsolicited AE: To advise participants and investigators of the potential risk for myocarditis and pericarditis, the informed consent form and the Investigator Brochure associated with study P204 were updated on 28 July 2021, prior to start of Part 2. In addition, Investigators were advised of the CDC working case definitions for myocarditis and pericarditis (Gargano et al 2021). The safety call script –used on Day 8 and D36 (7 days after dose 1 and after dose 2) and in subsequent safety calls - was revised to specifically solicit symptoms of myocarditis and pericarditis. Sites were instructed to ask the caregiver the following question: "Has your child experienced any of the following symptoms since we last spoke? Chest pain, pressure or discomfort; Shortness of breath, fast breathing at rest, or any pain with breathing; Fast-beating, fluttering or pounding heart." If the answer was yes, the sites were to advise the caretaker to seek medical evaluation and report outcome back to the site. Additionally, source documents were queried for clinical information relevant to AE and included in case descriptions. The active solicitation for these events likely enhanced reporting frequency.

Approaches to interrogate the safety database: With this enhanced approach to collecting AE, all unsolicited and solicited TEAEs in the full safety database across (Parts 1 and 2, participants 6 to <12 years receiving at least 1 study dose, n=4756 participants) were interrogated for events or symptoms that might indicate potential events of clinical interest, but do not necessarily represent identification of actual cases of cardiac etiology. Two overlapping approaches were used to interrogate all TEAEs using:

(i) the narrow and the narrow and broad cardiomyopathy standard MedDRA SMQs,

(ii) an algorithm generated using MedDRA terms v.23.0 included in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al. 2021; See Appendix 2).

In the sections below, events identified using the Cardiomyopathy SMQ and then the MedDRA 'myocarditis/pericarditis algorithm' are provided. Since some of the PT in these 2 strategies overlap, any events captured in the Cardiomyopathy SMQ are presented first and only those not previously captured in that SMQ are then summarized in the 'myocarditis/pericarditis algorithm' section. As above, results are presented first for Part 1 and then for Part 2. Any participants reporting more than one of the PT captured in these 2 approaches are identified as such, to identify occurrences more suggestive of potential cases of myocarditis or pericarditis.

2.5.6.1.4.4.3.1 Events of Clinical Interest Based on MedDRA Cardiomyopathy SMQs in Part 1

No AEs of myocarditis or pericarditis were reported in Part 1.

There were 8 participants in total in Part 1 who reported events included within the cardiomyopathy SMQ, both narrow and broad (Study P204 Table 14.3.1.22.3.15.2.1). Three events were reported in 3 (0.8%) participants in the 50 µg group and 5 events were reported in 5 (1.3%) participants in the 100 µg group with PTs included in the narrow and broad scope cardiomyopathy SMQs (Table 36). These events and participants are described in brief here (first for the 50 µg and then for the 100 µg dose group) and more fully in individual narratives in Module 5.3.5.1.

50 µg group:

In the 50 µg group, there were 2 (0.5%) events of dyspnoea and 1 (0.3%) event of palpitations reported within the cardiomyopathy SMQ.

The 2 dyspnoea events occurred in 2 participants: one 11-year-old male participant with concurrent events of cough, oropharyngeal pain (sore throat), nasal congestion and URTI and occurring 16 days after dose 1; and the other participant, 11-year-old female with concurrent history of asthma and occurring 23 days after dose 2. Each of these events occurred with concurrent conditions (ie, URTI in one and asthma in the other) and these likely provide a more plausible explanation for each event of dyspnoea.

The participant with the palpitations event, a 7-year-old female, had relevant medical history of (i) concurrent seasonal allergies and (ii) history of previous palpitations for more than one year. The palpitations were reported occurring 35 days post-dose 2. Following the data snapshot, this event was actually confirmed as occurring 31 days post-dose 2; also after the snapshot, the investigator downgraded the palpitation event to nonserious. The timing of this event together

with the relevant medical history do not suggest this event was indicative of myocarditis or pericarditis.

Regarding relatedness, in the 50 µg group, all events in this category were considered not related to the study IP, likely because of the mitigating factors. Additionally, all events were considered nonserious and mild to moderate in severity.

100 µg group:

In the 100 µg group there were 2 events of dyspnoea (0.5%), 2 events of palpitations (0.5%) and 1 event chest pain (0.3%) reported within the cardiomyopathy SMQ.

Two dyspnoea events were reported in 2 participants: (i) one participant, an 8-year-old male, with dyspnoea (mild, considered not-related) occurring 92 days post-dose 2 presented with concurrent events of headache, cough, nasal congestion, oropharyngeal pain and rhinorrhea, and (ii) a 9-year-old reported nonserious, mild dyspnoea 2 days post-dose 2, together with nonserious, mild chest discomfort and musculoskeletal discomfort (back pain), all of which resolved within 'a few hours' according to the parents. This event of chest discomfort – not a PT in the Cardiomyopathy SMQ – was identified as part of an additional algorithm generated to enrich identification of potential signals of myocarditis or pericarditis (Gargano et al. 2021). The child had a relevant history of asthma for which he was receiving albuterol and Pulmicort. The investigator assessed the events of chest discomfort, back discomfort, and dyspnoea to be not related to the IP. The late occurrence of the first event together with the constellation of concurrent symptoms is more suggestive of a respiratory tract infection; the second event occurring in a child with known asthma and resolving on the same day of occurrence is also not suggestive of possible myocarditis or pericarditis.

The 2 palpitation events were reported in 2 participants: (i) one participant (11-year-old female with history of tree nut allergy) reported palpitations on the day of dose 2; parent reported that child experienced anxiety "like she could not catch her breath upon returning home" and also noted that home "O2 sat" was normal and "pulse was normal"; per the parent, the subject "felt her heart skipped a few beats for a brief time". No chest pain, syncope or near syncope, fever, chills or chest wall pain were reported. Symptoms resolved the same day; the investigator considered the event related, likely because of the occurrence on the day of dosing; (ii) One other participant, a 10-year-old female, reported palpitation on exertion, occurred 6 days after dose 2 and resolving on the same day. The first event of palpitations may well have been related to an anxiety-related reaction triggered by the administration of a parenteral injection given the parental description; the second event appears related to the exertion, given the transient nature of the event and lack of any associated symptoms.

One event of chest pain (moderate) was reported in a 9-year-old male occurring 17 days after dose 2 and resolving the same day. The child had a history of attention deficit hyperactivity disorder (ADHD) for which he received the concomitant medication of Methylphenidate hydrochloride (the label notes potential chest pain and chest discomfort and additionally notes that exertional chest pain may occur). The chest pain was described as general pain and discomfort and occurred while training for boxing according to the parent. Report of the chest pain led to evaluation including an ECG and a chest x-ray, both of which were 'normal'. The investigator considered the event related. The 'normal' cardiac evaluation together with an onset of 17 days with resolution the same day in a child receiving Methylphenidate hydrochloride, are not consistent with the presentation of myocarditis or pericarditis previously described (Gargano et al 2021a).

In the 100 µg group, investigators considered 3 of the 5 events related and 2 of the events not related to study IP. All events were nonserious and mild or moderate. All events were reported as resolved. Narratives can be found in Module 5.3.5.1.

Table 36: Summary of PTs within the MedDRA Cardiomyopathy SMQs – Narrow and Broad Scope (Part 1 – Safety Set)

Preferred Term	mRNA-1273 50 µg (N=380) n (%)	mRNA-1273 100 µg (N=371) n (%)
Number of Events	3	5
Number of Subjects Reporting Events	3 (0.8)	5 (1.3)
Dyspnoea	2 (0.5)	2 (0.5)
Palpitations	1 (0.3)	2 (0.5)
Chest pain	0	1 (0.3)

Source: Study P204 Table 14.3.1.22.3.15.2.1

2.5.6.1.4.4.3.2 Events of Clinical Interest Based on the MedDRA Cardiomyopathy SMQs in Part 2

No AEs of myocarditis or pericarditis were reported in Part 2.

In Part 2, with a 3:1 randomization rate (mRNA-1273:placebo), there were a total of 9 participants who reported 11 events within the cardiomyopathy SMQ, both narrow and broad: 8 (0.3%) participants in the mRNA-1273 group and 1 (0.1%) participant in the placebo group. The 8 participants in the mRNA-1273 group reported 10 events and the 1 participant in the placebo group reported 1 event (Table 37). These events and participants are described here in brief (first for the mRNA-1273 and then the placebo group) and more fully in individual narratives in

Module 5.3.5.1. In the mRNA-1273 group, there were 3 events of chest pain (<0.1%), 7 events of dyspnoea (0.2%), and 1 event of syncope (< 0.1%). In the placebo group, there was 1 reported event of dyspnoea (0.1%).

mRNA-1273 group:

The 3 events of chest pain were reported in 3 participants in the mRNA-1273 group: 1 post-dose 1 and 2 post-dose 2. (1) One report of chest pain in an 8-year-old female occurred 7 days post-dose 1 and was resolved 3 days later. She had a medical history of asthma for which her concomitant medications included albuterol (labelled in part with chest pain, chest discomfort, tachycardia and palpitations). Of note, this participant received dose 2 of mRNA-1273 with no additional AEs reported; (2) a second report of chest pain in an 11-year-old male occurred 2 days post-dose 2 was described as 2 brief discrete episodes of "chest pain," occurring a "couple of days apart" with each episode lasting only seconds in duration. This child had a medical history of seasonal allergies, asthma and anxiety. Per the investigator the participant located the discomfort to his right midsternal border at the costochondral junctions; no associated diaphoresis, dyspnoea, radiation or pallor were described. The participant had a history of anxiety and was described as clearly anxious on examination; otherwise, physical examination and ECG were reported as unremarkable. The Investigator assessed this event as 'possibly musculoskeletal in origin (eg, costochondritis) and more likely related to a hypervigilant state secondary to anxiety'; (3) a third report of chest pain in a 7-year-old male occurred 2 days post-dose 2, with events resolving within 4 days. The chest pain was described as intermittent, and shortness of breath was also described. The child had no relevant medical history. Per the investigator the participant was evaluated in the emergency department where he was considered to be in good health with no respiratory or cardiac issues identified. Electrocardiogram and echocardiogram were performed and excluded cardiac origin for the chest pain and dyspnoea. The event was considered to be related to the IP by the investigator. This event is also listed but not described, below, under the dyspnea PT.

Six events of dyspnoea were reported in 5 participants, with 4 reports after the first dose and 2 after the second dose. One of these 7 events of dyspnoea have been described above in the 3 events of chest pain (a 7-year-old male with intermittent chest pain and shortness of breath). Four additional participants, reporting 5 events, are described here:

(i) A 6-year-old female with a medical history of seasonal allergies experienced difficulty breathing due to seasonal allergies occurring 6 days post-dose 1 which resolved the same day. Concomitant medications included albuterol and loratadine. The events were considered not related by the investigator,

(ii) A 9-year-old male with a medical history of seasonal allergies and ADHD reported 2 events of dyspnoea both occurring 13 days post-dose 1, together with fatigue, oropharyngeal pain and cough. The events were reported as "difficulty breathing" (moderate) and once as "shortness of breath" (mild), and both occurred and both resolved on the same day. Concomitant medications included diphenhydramine hydrochloride, fluticasone propionate, risperidone, atomoxetine, and cetirizine hydrochloride. The events were considered not related by the investigator, compatible with possible respiratory tract infection as the cause of the dyspnoea given the fatigue, oropharyngeal pain and cough.

(iii) A 9-year-old female with no relevant medical history, reported dyspnoea one day post-dose 2 which resolved the next day. Concurrent symptoms included headache and a urinary tract infection. The concurrent occurrence of headache and urinary tract infection may have resulted in feeling of malaise, which could increase the perception of subjective symptoms such as dyspnoea.

(iv) A 9-year-old female with unknown medical history, reported dyspnoea 21 days post-dose 1 which resolved in 3 days. The participant also experienced concurrent rhinorrhea and cough. The constellation of dyspnoea, rhinorrhea and cough are more compatible with possible respiratory tract infection than potential myocarditis or pericarditis. The event was considered not related to the IP.

(v) The 7-year-old male described above with intermittent chest pain and dyspnoea is noted here for completeness. As noted above, ED evaluation identified no respiratory or cardiac issues.

One event of syncope was reported in a 10-year-old female with medical history of asthma, who experienced syncope on the day of dose 1 and which resolved the same day. No other information was provided. The event was considered not related to the IP by the investigator.

Placebo group:

A 9-year-old female with unknown medical history reported dyspnoea occurring 21 days post-dose 1 which resolved 3 days later. She had concurrent events of rhinorrhea and cough suggesting a possible upper respiratory infection as the cause of the dyspnoea. The event was considered not related to the IP.

Summary: All events in Part 2 were nonserious with 9 considered mild and 2 considered moderate - the latter 2 in the mRNA group. The median TTO was 7 days (range: 1 to 22 days).

Nine of the 11 events were considered not related to the IP by the investigator and 2 events were considered related to the IP by the investigator. All events were reported as recovered/ resolved.

Of the 11 events identified in the cardiomyopathy SMQ for Part 2, 2 participants reported more than one PT concurrently and are noted here again: (i) the 7-year-old male who reported intermittent chest pain and dyspnoea 2 days post-dose 2, and (ii) the 9-year-old PPD male reported the PT of dyspnoea twice (once as shortness of breath and once as difficulty breathing). Both participants are described above and neither participant had presentations suggestive of myocarditis or pericarditis.

Table 37: Summary of PTs Reported by Subjects within the MedDRA Cardiomyopathy SMQs (Part 2 – Safety Set)

Preferred Term	mRNA-1273 50 µg (N=3007) n (%)	Placebo (N=995) n (%)
Number of Events	10	1
Number of Subjects Reporting Events	8 (0.3)	1 (0.1)
Dyspnoea	5 (0.2)	1 (0.1)
Chest pain	3 (< 0.1)	0
Syncope	1 (< 0.1)	0

Source: Study P204 Table 14.3.1.22.3.15.2.2

2.5.6.1.4.4.4 Additional Analysis of Myocarditis and Pericarditis

As noted above and to increase the sensitivity of identifying potential cases of myocarditis or pericarditis not rising to full clinical identification, an additional analysis was conducted based on an algorithm created using MedDRA terms v.23.0 (given that reporting of adverse events for the current ongoing clinical trials is based on v. 23.0 of the MedDRA dictionary) and following the flow of events included in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al 2021). Three PTs, not already captured in the Cardiomyopathy SMQ above, were identified in the safety database using this algorithm: angina pectoris, chest discomfort and musculoskeletal chest pain. The algorithm is described in Appendix 2.

In this ad-hoc analysis, reviewing only those PT not captured in the Cardiomyopathy SMQ, one participant reported more than 1 event: one participant reported 1 event of chest discomfort and 1 event of dyspnoea. This participant is described above under the cardiomyopathy SMQ analysis, based on the report of dyspnoea and is therefore not described here (Section 2.5.6.1.4.4.3.1).

Part 1:

In Part 1, this ad-hoc analysis identified 2 participants with relevant PT, one in the 50 µg group and one in the 100 µg group (Table 38).

One report of chest discomfort was reported in a 9 year-old male in the 100 µg mRNA-1273 group2 days post-dose 2: this child has been fully described in Section 2.5.6.1.4.4.3.1 and will not be described here.

One musculoskeletal chest pain was reported in a 10-year-old male in the 50 µg mRNA-1273 group, occurring 90 days post-dose 2. This participant was evaluated at the emergency department the following day where myocarditis was ruled out based on a normal ECG and a diagnosis of non-cardiac chest pressure related to worsening anxiety was made. The event was considered not related to the IP by the study investigator. The event resolved and was considered mild and nonserious.

Table 38: Summary of PT Reported – Ad-Hoc Summary of Additional PT Reported Under CDC Definition of Myocarditis/Pericarditis – Part 1

	mRNA-1273 50 µg (N=380) n (%)		mRNA-1273 100 µg (N=371) n (%)	
Preferred Term	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
Chest discomfort	0	0	0	1 (0.3)
Musculoskeletal chest pain	0	1 (0.3)	0	0

Source: Study P204 Listing 16.2.7.32.2.1 and Listing 16.2.7.32.2.2

Part 2:

In Part 2, this ad-hoc analysis identified 5 participants with relevant PTs, all in the mRNA-1273 group, 1 with angina pectoris, 2 with chest discomfort and 2 with musculoskeletal chest pain (Table 39).

There was 1 report of angina pectoris in a 10-year-old male in the mRNA-1273 group, occurring on the day of dose 1 and resolving on the same day. His parents reported him feeling “squeezing around the heart”. The participant had an evaluation including measurement of serum troponin, ECG and pediatric transthoracic echocardiogram. All 3 tests were within normal limits and a diagnosis of myocarditis was excluded. Parents confirmed no complaints and the participant received dose 2 of the vaccine as planned with no reports of additional events. The AE resolved and was deemed as not related to IP by the investigator.

There were 2 reports of chest discomfort identified in 2 participants, both in the mRNA-1273 group: (i) a 9-year-old male with a history of anxiety reported an event of chest discomfort on the day of dose 1 which lasted for 2 days. The participant had an ECG 2 days after receiving dose 1 and it was normal. A diagnosis of non-cardiac chest pressure related to worsening anxiety was made. The participant received dose 2 of the vaccine as planned with no other reported events. The event was considered not related; (ii) a 10-years old female reported chest discomfort occurring 5 days post-dose 2, that resolved within 24 hours without any treatment and was considered not related to the IP.

There were 2 reports of musculoskeletal chest pain identified in 2 participants, both in the mRNA-1273 group: (i) an 8-year-old male with concurrent medical history of URTI, fever and concomitant medications of azithromycin, Benadryl and Mucinex, reported musculoskeletal chest pain occurring 13 days post-dose 2 which resolved the following day. The participant was evaluated by the pediatrician who determined that the event was unlikely to be due to cardiac origin, (ii) a second report was a 7-year-old male with medical history of chronic lung disease, retinopathy of prematurity, asthma and PPD who reported musculoskeletal chest pain 22 days post-dose 2. The description of 'musculoskeletal chest pain' is far more likely to be related to the underlying conditions of asthma or chronic lung disease (for example 'chest tightness' that could be interpreted as chest pain in the former), than related to myocarditis or pericarditis.

Table 39: Summary of PT Reported – Ad-Hoc Summary of Additional PT Reported Under CDC Definition of Myocarditis/Pericarditis – Part 2

	mRNA-1273 50 µg (N=3007) n (%)		Placebo (N=995) n (%)	
Preferred Term	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
Angina pectoris	1 (< 0.1)	0	0	0
Chest discomfort	1 (< 0.1)	1 (< 0.1)	0	0
Musculoskeletal chest pain	0	2 (< 0.1)	0	0

Source: Study P204 Listing 16.2.7.32.2.2

Summary: Careful analysis of the safety database of children 6 to <12 years in study P204 for individual AE that together comprise the clinical definition of myocarditis and pericarditis, including chest pain, chest discomfort, angina, dyspnoea, syncope, palpitations, or musculoskeletal chest pain, do not identify previously unreported events of myocarditis or pericarditis.

This analysis did not identify any cases fulfilling the CDC working case definition for cases of acute myocarditis or acute pericarditis.

2.5.7 BENEFITS AND RISKS CONCLUSIONS

2.5.7.1 Therapeutic Context

2.5.7.1.1 Disease or Condition

Since the beginning of the COVID-19 pandemic, hospitalizations and deaths associated with COVID-19 have occurred more frequently in adults (Ayoub et al 2021; CDC 2021c; Hay et al 2020); however, COVID-19 can also lead to severe outcomes in children and adolescents (Kim et al 2020; Havers et al 2021). From the start of the pandemic to May 2021, approximately 2.6 million cases of COVID-19 have been reported among children 5 to < 9 years of age and approximately 3.8 million cases have been reported among children 10 to 14 years of age in 105 countries (Unicef 2021). In the US, an excess of 2670 hospitalizations among children 5 to 17 years of age have been observed through 21 October 2021 with 28.5% requiring intensive care unit interventions and more than 500 deaths observed (CDC 2021c). A large cohort study found that children under 16 years of age with COVID-19 were observed to have a 37 times higher risk of myocarditis than the uninfected age and gender-matched control population (Boehmer et al 2021). Additionally, there is evidence of "long-COVID-19" in children even after mild infection (Dembiński et al 2021). Children and adolescents also can develop a life-threatening hyperinflammatory state 4– 6 weeks after infection with primary COVID-19 termed MIS-C (Vogel et al 2021), often presenting with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021d). More than 5217 cases and 46 deaths meeting case definition of MIS-C have been reported in the US (CDC 2021m).

Changes in social policy, individual behavior, and viral dynamics are moving the burden of disease into younger age groups. Schools have opened at the same time as relaxed mask mandates and an increase in the number of cases caused by the highly transmissible B.1.617.2 Delta variant of SARS-CoV-2 (CDC 2021e). Before the Delta wave of the pandemic, persons 17 years of age and younger comprised the lowest weekly cases and death rates per 100,000 population; however, in the current Delta wave, 12 to 17 years of age have the highest case rates, followed closely by 5 years to 11 years of age (CDC 2021f). The hospitalization rate for children and adolescents has also increased with the spread of the Delta variant; rates rose each week to 1.4 per 100,000 children during the week ending 14 August 2021, which was 4.7 times the rate during the week ending 26 June 2021 and approached the peak hospitalization rate of 1.5 observed during the week ending 09 January 2021 (Delahoy et al 2021).

COVID-19 cases among students may lead to consequences such as school closures and remote learning (CDC 2021l), which can be detrimental to the education and mental health of students (AAP 2021).

2.5.7.2 Benefits

2.5.7.2.1 Overall Benefits of mRNA-1273

Early in 2020, the WHO declared COVID-19 to represent a Public Health Emergency of International Concern, denoting its highest level of public health emergency. More than 243 million SARS-CoV-2 infections have been reported worldwide, and over 4.9 million deaths have been attributed to the virus (Johns Hopkins University 2021).

It is widely acknowledged that the key to controlling this pandemic and mitigating its impacts is primary prevention through vaccination. Efforts to control the pandemic through other public health measures (eg, social distancing, mask wearing) and with the use of therapeutic agents to treat SARS-CoV-2 infections are helpful but not sufficient.

mRNA-1273 is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older under EUA in the US and in individuals 12 years of age and older under various types of approvals worldwide, including the EU, Canada, and Japan. The efficacy of mRNA-1273 to prevent COVID-19 has been demonstrated in adults 18 years and older in the pivotal Study P301. Analysis of the primary efficacy endpoint from the final blinded analysis showed a VE of 93.2% (95% CI: 91.0%, 94.8%, $p < 0.0001$). These results are consistent with the results from the interim and primary analyses conducted in November 2020 in adults ≥18 years of age, confirming persistent, high efficacy over a median observation period of over 5.3 months.

The immunogenicity (effectiveness) and VE of mRNA-1273 in adolescents 12 to < 18 years of age has been demonstrated in Study P203. The coprimary endpoints of Study P203 were met and demonstrated the noninferiority of mRNA-1273 in adolescents compared with young adults in Study P301. The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the 1.5-fold noninferiority criterion (ie, lower bound of the 95% CI for GMR is ≥ 0.67). The difference in adolescent to young adult nAb seroresponse rates at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the 10% noninferiority criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%). VE was 100% (lower bound, 95%CI: 28.9%) using the “P301 case definition” starting 14 days after dose 2, with 4 cases in the placebo group and 0 cases in the vaccine group. Using the “CDC case definition” starting 14 days after dose 1, VE was 92.7% (95% CI: 67.8%, 99.2%) based on accrual of a total of 15 cases (2 cases [3.83 per 1,000 person-years] in mRNA-1273 group and 13 cases [52.47 per 1,000 person-years] in the placebo group. mRNA-1273 is also indicated for use in adolescents 12 years of age and older in Canada, Europe, the United Kingdom,

Switzerland, Japan, Australia, Saudi Arabia, Taiwan, Israel, Singapore, and several other countries.

2.5.7.2.2 Benefits in Children 6 Years to < 12 Years

Vaccine effectiveness in children 6 years to < 12 years of age was inferred by meeting the prespecified success criteria for the primary immunogenicity objective. The primary objective of Study P204 was immunobridging, which was achieved by demonstrating noninferiority of both GMR nAb and the seroresponse rate from children 6 years to < 12 years of age compared with those from young adults (18 to 25 years) in the pivotal P301 study (in which efficacy was demonstrated). In the PP Immunogenicity Subset, baseline nAb GMT (measured by PsVNA ID_{50}) in children 6 years to < 12 years old in Study P204 was below the LLOQ and was 1964.601 (95% CI: 1694.578, 2277.651) at Day 57, 28 days after dose 2; 99.3% of children achieved seroresponse at Day 57. The geometric fold-rise was 209.466 (95% CI: 182.947, 239.829), indicating robust immunogenicity and seroresponse of 50 µg of mRNA-1273 in children ages of 6 years to <12 years. The GMR of nAb titers at Day 57 of children 6 years to <12 years of age (Study P204) compared with young adults (Study P301) was 1.510 (95% CI: 1.263, 1.804), meeting the noninferiority success criterion (ie, lower bound of the 95% CI for GMR ≥ 0.67 and GMR point estimate > 0.8). The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 0.6% (95% CI: -2.8%, 2.8%), meeting the noninferiority success criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%).

Based on the successful immunobridging, the VE of mRNA-1273 in children 6 years to <12 years of age is expected to match the VE observed in the pivotal P301 study in adults, where VE was 94.1%.

Although there were few cases in the PP population (from Day 14 after dose 2), VE in Part 2 in the mITT1 for COVID-19 cases using the "CDC case definition" occurring 14 days or more after dose 1 was 93.0% (95% CI: 75.1%, 98.7%). These results show an early onset of protection after vaccination with mRNA-1273 and were consistent with the high, protective efficacy observed in the pivotal P301 study in adults, where 94.1% VE (95% CI: 89.3%, 96.8%) was observed 14 days after dose 2 in the final blinded analysis. Additionally, VE in Part 2 of the mITT1 for asymptomatic SARS-CoV-2 infections occurring 14 days or more after dose 1 was 65.0% (95% CI: 16.1%, 85.3%). These results were comparable to the 63.0% (95% CI: 56.6%, 68.5%) VE against asymptomatic infection observed in the pivotal P301 study. The VE in Part 2 of the mITT1 for SARS-CoV-2 infections (regardless of symptoms) occurring 14 days or more after dose 1 was 80.1% (95% CI: 61.5%, 90.0%). These results were consistent with the 82.0% (95%

CI 79.5%, 84.2%) VE against SARS-CoV-2 infection (regardless of symptoms) observed in Study P301.

In summary, immunobridging was successfully demonstrated in children 6 years to < 12 years of age by to young adults (18 to 25 years of age). It would be expected based on the successful immunobridging as well as early efficacy demonstrated that children 6 years to < 12 years of age would be protected from COVID-19 and subsequent sequelae.

Study P204, Part 2 was conducted at a time when Delta was the predominant circulating COVID-19 variant, and VE in the mITT1 population was directly demonstrated in children 6 years to < 12 years of age.

Observational studies in adults also have demonstrated the effectiveness of mRNA-1273 against variants of concern, including the Delta variant. Specifically, VE for mRNA-1273 was 86.7% (95% CI: 84.3, 88.7%) for Delta infection and 97.6% (95% CI: 92.8%, 99.2%) for Delta hospitalization from 01 March 2021 to 27 July 2021 in a large and closed managed care system in the greater Los Angeles area (Bruxvoort et al 2021a). Combined with the demonstrated efficacy in the mITT population, mRNA-1273 would be expected to provide protection for children against the Delta variant, similar to that observed in adults.

There are additional benefits to vaccinating children beyond the direct medical benefits. Cases of SARS-CoV-2 infection can lead to school closures and educational disruptions. Given the VE observed against SARS-CoV-2 infection (regardless of symptoms), vaccinating children 6 years to < 12 years of age with mRNA-1273 has the potential to help schools remain open for in-person education. Young children attending school represent a type of institutional setting in which the risk of virus transmission is high. If children are not vaccinated, they will remain a large, susceptible group capable of being infected with the virus and transmitting it to others. A mathematical modeling study demonstrated the importance of vaccinating children and adolescents and found that including these populations for vaccination could reduce overall COVID-related mortality across all age groups by 57% and reduce cases of “long COVID” by 75% (Shiri et al 2021).

2.5.7.3 Risks

In P204, the safety analysis set of 4753 participants included 3758 study mRNA-1273 participants and 995 placebo recipients. Overall, the safety data is consistent with events commonly seen in the pediatric population and with the reactogenicity known for the mRNA-1273 vaccine.

In Part 1 of the study, solicited local ARs occurred at similar frequencies after dose 1 and after dose 2 in both the 50 µg and 100 µg groups. The majority of solicited local ARs in both groups occurred in the first 1 to 2 days after any dose and persisted for a median of 3 days. Injection site pain was the most common solicited local AR in Part 1.

Solicited systemic ARs also occurred at a higher frequency in the 100 µg compared to the 50 µg group after both dose 1 and dose 2. The majority of solicited systemic ARs occurred in the first 1 or 2 days and persisted for a median of 2 days. The majority of solicited systemic ARs were grade 1 or 2. Grade 3 or higher solicited systemic ARs were more common in the 100 µg than the 50 µg group which contributed to the choice of 50 µg dose for Part 2 of the study. The most common solicited systemic AR was fatigue.

In Part 2 of the study, solicited local ARs occurred more frequently in the mRNA-1273 group after dose 1 and dose 2 than in the placebo group within the first 1 to 2 days after any dose and generally persisted for a median of 3 days. Injection site pain was the most common solicited local AR. Solicited systemic ARs were also more common in the mRNA-1273 group and were more common after dose 2, within the first 1 to 2 days after each dose and generally persisted for a median duration of 2 or 3 days. The most common solicited systemic ARs were headache, fatigue, myalgia, and chills. The majority of solicited systemic ARs were grade 1 to grade 2 in severity; however, there was a higher occurrence of grade 3 or higher solicited reactions in the mRNA-1273 group. Fever occurred more often in the mRNA-1273 group after any dose.

Solicited ARs from 6- to < 12-year-old participants in the mRNA-1273 group (50 µg) in Part 2 of Study P204 were compared with solicited ARs reported from young adult (18- to 25-year-old) participants in the mRNA-1273 group (100 µg) in Part A of Study P301. In participants 6- to < 12-years-old, solicited local ARs were reported slightly more frequently than in young adult participants in Study P301 while solicited systemic ARs were reported slightly less frequently. Pain was the most common local AR, and fatigue and headache were the most common systemic ARs in both age groups. Grade 3 ARs (local and systemic) were more common in the young adult population from Study P301 than in the 6- to < 12-year-old participants in P204. The systemic AR of fever was reported more frequently in Study P204 participants than in young adults in Study P301. Overall, local and systemic ARs reported in the 2 populations were generally similar.

In Part 2, the most commonly reported unsolicited TEAE in all participants in the 28 days after dose by PT was injection site erythema. Imbalances in unsolicited TEAEs up to 28 days after any dose observed in the mRNA-1273 group were primarily attributable to events related to reactogenicity in the general disorders and administration site conditions SOC, which included

events of injection site lymphadenopathy, injection site erythema, injection site induration, injection site pain, injection site pruritis, injection site hypersensitivity, and injection site urticaria. Overall, imbalances in events of injection site erythema, injection site lymphadenopathy, and injection site reactions were comparable to the TEAEs observed in adults (participants ≥ 18 years of age in Study P301).

There were no reports of anaphylactic reaction assessed as related to IP in participants receiving mRNA-1273.

There were no SAEs assessed by the Investigator as related to study vaccine, no deaths, no pregnancies, and no cases of MIS-C reported as of the data snapshot.

Myocarditis and pericarditis are typically rare events in children. Studies conducted in the pre-COVID era suggest that the incidence in children between 6 years and <12 years old is lower than that observed in young adolescents or infants (Arola et al 2017). The true incidence of myocarditis independent of COVID-19 vaccination is unknown. Myocarditis may be underdiagnosed because it may present with non-cardiac prodromal symptoms in a considerable number of patients. Diagnosis is challenging because symptoms are frequently nonspecific, especially in infants and children, masquerading as respiratory and gastrointestinal infections. Whereas teenagers may suffer from chest pain, palpitations, and rhythm disturbances, smaller children often present with respiratory or gastrointestinal symptoms and newborns with restlessness and poor feeding or symptoms resembling severe bacterial infection (Durani et al 2009). Prior to the emergence of COVID-19, myocarditis, mostly due to other viral infection, was described as the most common cause of heart failure in previously healthy pediatric patients.

Myocarditis leading to hospital admission is relatively uncommon in children. As previously noted, the incidence rises with age. There is no gender difference in risk prior to approximately age 6 years, when the incidence begins to rise somewhat more rapidly among boys. The incidence and differential risk by gender becomes significantly greater starting at approximately the age of 12 years.

COVID-19 is an independent risk factor for myocarditis. The rates of pediatric (age <16 years) myocarditis requiring hospitalization that are attributable to COVID-19 are greater than 36-fold higher than in age matched controls (Boehmer et al 2021). The risk for myocarditis among patients with COVID-19 has been identified to be nearly 16 times as high as the risk among patients without COVID-19, with the association between COVID-19 and myocarditis being most pronounced among children and older adults. Myocarditis is occurring in patients with SARS-CoV-2 infection at rates estimated to be as high as 876 cases per million in the 12- to 17-year-old males (Singer et al 2021). Hospitalization in young adults due to COVID-19 have a

mean length of stay of 5 days, with ~5% of patients requiring mechanical ventilation; death can occur (Barda et al 2021).

In contrast, hospitalization for myocarditis following mRNA COVID-19 vaccination is far less common with a mean length of stay of around 1-2 days with no reported deaths (Rosenblum 2021). VAERS (CDC/ACIP) data indicate that following 86 million doses of mRNA COVID-19 vaccines administered to persons under 30 years of age, a total of 3 deaths associated with myocarditis had been reported. All 3 had a potential infectious etiology (rather than being considered attributable to vaccine) (Oster 2021).

As described earlier no cases of myocarditis/pericarditis were reported in either part of Study P204.

Enhanced surveillance for potential cases of myocarditis and pericarditis was implemented in this study, through additional questions added to the safety call script as well as review of the cardiomyopathy SMQs along with specific medical evaluations for potential cases of myocarditis or pericarditis. This analysis did not identify any cases of either condition in either part of the study.

The frequency of solicited ARs and unsolicited AEs observed in participants 6 years to < 12 years of age were generally consistent with those observed in young adults (18 to 25 years of age) in Study P301. No new safety concerns emerged, and the results demonstrate an acceptable reactogenicity and tolerability profile, as well as no changes in the known safety profile on mRNA-1273.

In the post-authorization period, as of 30 September 2021, 518,902,500 doses of mRNA-1273 had been distributed worldwide. Globally, an estimated 124,399,577 people are considered to be fully vaccinated after receiving a 2-dose primary series of mRNA-1273 (Monthly Safety Report 09), and the data show that mRNA-1273 has an acceptable safety profile.

Rare cases of anaphylaxis, myocarditis, and pericarditis events have been reported during the post-authorization period from regulatory authorities and from spontaneous reports from healthcare professionals and patients.

The post-authorization data 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 and have resolved; however, information is not yet available about potential long-term sequelae.

Safety surveillance via routine and enhanced pharmacovigilance activities, as well as and reporting to health authorities will continue during the post-emergency authorization/conditional approval period for individuals 6 years of age and older according to the regulations and the Risk Management Plan. The Applicant will educate vaccinators and vaccination centers of the authorized dosing to prevent potential dosing errors and will monitor this closely via routine pharmacovigilance.

2.5.7.4 Benefit-Risk Assessment

2.5.7.4.1 Benefit-Risk Context – Medical Need

The benefits and risks of the proposed indication is set within the context of the COVID-19 pandemic. Vaccination with safe and efficacious vaccines targeting SARS-CoV-2 is the essential public health tool for control of the pandemic.

There is an urgent unmet medical need to prevent COVID-19 cases, COVID-related hospitalizations, sequelae from COVID-19 (eg, MIS-C and "long-COVID-19"), and deaths in children. Additionally, decreasing COVID-19 cases in schools is critical to minimize school closures; schools and school-supported programs are fundamental to child development, well-being, academic skills, and mental health. Vaccinating children 6 years to < 12 years-old with mRNA-1273 has the potential to meet this unmet medical need. If children are not vaccinated, they will remain a large, susceptible group capable of being infected with the virus and transmitting it to others.

Since April 2021, when cases of myocarditis and pericarditis were first described following receipt of mRNA COVID-19 vaccines, there have been a number of studies, as well as ongoing pharmacovigilance activities that have characterized these events. It is critical to balance the rare and generally mild events of myocarditis identified after use of the mRNA vaccines against the positive public health impact of these vaccines. A report presented at the Advisory Committee on Immunization Practices meeting on 23 June 2021, estimated that over a 120-day period, 45 to 56 cases of myocarditis per million dose 2 vaccinations were predicted to occur in males 18 to 24 years of age, whereas mRNA COVID-19 vaccination would simultaneously prevent 12,000 COVID-19 cases, 530 hospitalizations, 127 admissions to the intensive care unit, and 3 deaths (Gargano et al 2021b). Based upon extensive review of this and other available evidence, the Applicant concluded that the benefit of mRNA COVID-19 vaccination clearly outweighed the risk of myocarditis in all recommended age groups, including younger male adolescents at heightened risk for myocarditis after vaccination.

2.5.7.4.2 Benefit-Risk Analysis Evaluation

In the clinical development program in adults, the primary dosing series of mRNA-1273 demonstrated 94% efficacy against COVID-19 in the Phase 3 Coronavirus Efficacy (COVE) trial (Study P301 Part A; NCT04470427) in more than 30,000 participants, complemented by nAb and bAb responses in Phase 1 (NCT04283461) and Phase 2 (NCT04405076) studies. The safety profile of the primary series of mRNA-1273 has been well characterized in clinical studies, including P301 Part A which included 15,184 adults exposed to mRNA-1273.

Based on the successful immunobridging, the VE of mRNA-1273 in children 6 years to <12 years of age is expected to match the VE observed in the pivotal P301 study in adults, where VE was 94.1%.

Although there were few cases in the PP population (from Day 14 after dose 2), VE in Part 2 in the mITT1 for COVID-19 cases using the "CDC case definition" occurring 14 days or more after dose 1 was 93.0% (95% CI: 75.1%, 98.7%). These results show an early onset of protection after vaccination with mRNA-1273 and were similar to the high, protective efficacy observed in the pivotal P301 study in adults, where 94.1% VE (95% CI: 89.3%, 96.8%) was observed 14 days after dose 2 in the final blinded analysis. Additionally, VE in Part 2 of the mITT1 for asymptomatic SARS-CoV-2 infections occurring 14 days or more after dose 1 was 65.0% (95% CI: 16.1%, 85.3%). These results were comparable to the 63.0% VE (95% CI: 56.6%, 68.5%) against asymptomatic infection observed in the pivotal P301 study.

Study P204, Part 2 was conducted at a time when the Delta variant was the predominant circulating COVID-19 variant, and VE in the mITT1 population was demonstrated.

Observational data on the effectiveness of mRNA-1273 against variants of concern, including the highly transmittable Delta variant (Bruxvoort et al 2021), also support that mRNA-1273 would be similarly expected to provide protection for children against cases and hospitalizations due to the Delta variant.

In P204, there has been no emergent safety concerns in children 6 years to < 12 years old, and the AE profile of mRNA-1273 consists primarily of grade 1 to grade 2 reactogenicity AE lasting 2 to 3 days. Overall, both local and systemic reactogenicity AE was generally consistent for mRNA-1273 in children 6 years to < 12 years of age and in the young adult (18 to 25 years of age) population in the mRNA-1273-P301 study. Vaccination with mRNA-1273 generally resulted in transient local injection site and systemic reactions. Review of unsolicited AEs did not reveal any new safety signals and no SAEs during the study were assessed by the Investigator as related to mRNA-1273. There were no deaths reported. The overall safety profile

observed in this study was generally consistent with the known safety profile to date observed in other studies of mRNA-1273.

There have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest (Gargano et al 2021a). No events of myocarditis or pericarditis were reported in this clinical trial. As an additional screening tool to identify potential undiagnosed cases of myocarditis and pericarditis, Moderna adopted a more comprehensive analysis of the data collected in clinical trials, the results of which are presented in Section 2.5.6.1.4.4.4. No participants in either part of Study P204 met the criteria for either myocarditis or pericarditis described in the algorithm created following the CDC Working Case Definition for Acute Myocarditis and Acute Pericarditis (Gargano et al 2021a). The great majority of cases with any symptom that is a component of this case definition had more plausible explanations for their symptom, eg, dyspnoea in a patient with a known history of asthma.

Cumulatively, through 30 September 2021, out of the 332,619 cases reported in the global safety database, there were a total of 2113 cases (0.6% of all case reports) of myocarditis (1439 cases) and pericarditis (674 cases) cases reported in adults >18 years of age. Of the 2113 cases, 2107 were reported as serious. There were 1506 (71.3%) male patients and 565 (26.7%) female patients, with 42 cases (2.0%) that did not provide gender information. The majority of cases involved males between the ages of 18 to 39 years old (1070, 50.7%).

Cumulatively through 30 September 2021, there were 21 reports of myocarditis and pericarditis in patients between 12 to 17 years of age, of whom were 19 males and 2 females. There were 18 reports of myocarditis, 4 were in males after the first dose of mRNA-1273 (TTO 1 to 2 days); 7 after the second dose (TTO from 0 to 3 days) with 6 males and 1 female; and there were 7 after an unknown dose number, 6 males and 1 female (TTO from 0 days to 2 days). There were 3 cases of pericarditis, all 3 were males, 2 after the second dose of mRNA-1273 and 1 with an unknown dose number. Time to onset was between 1 to 2 days.

Analysis conducted on the post-authorization safety data as of 30 September 2021, showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 5 days, with a reported average duration of the events as 10.2 days with a median of 5 days (min 0; max 51). Most events were reported as either resolved or resolving, including 7 events reported as resolved with sequelae.

Review of the post-authorization data also shows no difference in the observed safety profile of mRNA-1273 in the adolescent population when compared to the >18 years old population.

The CDC recently released a study providing insight into COVID-19 infection and the risk of hospitalization due to myocarditis in individuals under the age of 16 (Boehmer et al 2021). A large cohort study found that children under 16 years of age with COVID-19 are at 37 times higher risk of myocarditis than the uninfected age and gender-matched hospitalized control population. Since the introduction of mRNA COVID-19 vaccines in the US in December 2020, an elevated risk for myocarditis among mRNA COVID-19 vaccine recipients was observed, particularly among males 12 to 29 years of age, with 39 to 47 expected cases of myocarditis, pericarditis, and myopericarditis per million second mRNA COVID-19 vaccine doses administered. A study from Israel reported that mRNA COVID-19 vaccination was associated with an elevated risk for myocarditis (risk ratio = 3.24; 95% CI: 1.55, 12.44); in the same study, a separate analysis showed that SARS-CoV-2 infection was a stronger risk factor for myocarditis (risk ratio = 18.28, 95% CI: 3.95, 25.12) (Barda et al 2021). On June 23, 2021, the Advisory Committee on Immunization Practices concluded that the benefits of COVID-19 vaccination clearly outweighed the risks for myocarditis after vaccination. The CDC study (Boehmer et al 2021) supports the recommendation by providing evidence of an elevated risk for myocarditis among persons of all ages with diagnosed COVID-19.

2.5.7.4.3 Risk Management

Based on the analysis of all the safety data available as of 30 September 2021, the Applicant considers cases of myocarditis and pericarditis to be consistent with the known safety profile of mRNA-1273 and appropriate risk minimization and risk communications strategies have already been implemented. The Applicant will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities.

To further characterize the risk of myocarditis and pericarditis, these outcomes will be assessed in several Post-Authorization Safety Studies (PASS) in the US and EU. The previously endorsed PASS studies assessing the risk of multiple AESIs (US PASS protocol mRNA-1273-P903 and EU PASS mRNA-1273-P904) have been expanded to capture any use of mRNA-1273 observed, including subgroups of children and adolescents. Analyses in these studies will quantify the incidence of vaccine associated myocarditis by age, sex, and dose of mRNA-1273, and will utilize both historical cohort and self-controlled risk interval methods to assess absolute and relative risk. Further, new analyses currently in development will characterize the natural history, clinical course, short and long-term outcomes, and risk factors for myocarditis temporally associated with mRNA-1273.

Based on post-marketing data sources from literature, safety database, routine pharmacovigilance and signal management, mRNA-1273 vaccine is considered to be well tolerated and with an acceptable safety profile. Moderna prioritizes the identification and characterization of emergent safety concerns occurring under real world conditions and takes this responsibility especially seriously given the unprecedented number of vaccine doses administered under the Emergency Use Authorization (or Conditional Marketing Approval) and the role that mRNA-1273 (and other COVID-19 vaccines) have as essential contributors to the control of the COVID-19 pandemic.

The post-authorization safety data show that mRNA-1273 vaccine is well tolerated, and the safety profile is similar to that observed during the Applicant's clinical trials. The 3 most common events reported cumulatively for mRNA-1273, by PT were headache (6.3%), pyrexia (6.3%), and fatigue (5.5%). With 518,902,500 doses of mRNA-1273 distributed to 47 countries as of 30 September 2021, the reporting rate of SAEs was 118.6 serious cases per 1 million doses distributed.

Based on the cumulative evidence, the overall benefit-risk evaluation of the mRNA-1273 vaccine remains positive.

The cumulative review of all the post-authorization safety data supports the adequacy of the safety profile of mRNA-1273 as described in the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccine Providers) and EUA Full Prescribing Information.

2.5.7.5 CONCLUSIONS

The data presented in this submission include inferred effectiveness by bridging to efficacy data in the pivotal study P301 as well as direct observation of early efficacy in the mITT1 population and support the extension of the use of mRNA-1273 to children 6 years to < 12 years for the prevention of COVID-19. The observed efficacy against infection with SARS-CoV-2 (with or without symptoms) at a time of primarily delta variant infections also suggests a benefit in the prevention of transmission. Results are generally consistent with the safety profile observed in young adults 18 to 25 years of age. No cases of myocarditis or pericarditis were reported and additional thorough search of the safety database for specific PT did not identify any cases suggestive of these disorders. The immunogenicity, safety, and efficacy data from Study P204, support administration of mRNA1273 as 2 50 µg doses 28 days apart in children 6 years to < 12 years of age. Considering the ongoing public health emergency due to SARSCoV-2, the burden of disease in children 6 years to < 12 years of age, and the effectiveness and safety data from clinical Study P204 presented herein, the Applicant considers that the known and potential benefits of the mRNA-1273 outweigh the known and potential risks for mRNA-1273.

The use of mRNA-1273 in children 6 years to < 12 years of age meet the conditions for EUA. SARSCoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to children infected by this virus. Based on the totality of scientific evidence, it is reasonable to believe that mRNA-1273 may be effective in preventing COVID-19, and the known and potential benefits of mRNA-1273 when used to prevent COVID-19 outweigh the known and potential risks, and there is no adequate, approved, and available alternative to the emergency use or conditional approval of mRNA-1273 to prevent COVID-19.

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Appendix 1 Adverse Events of SARS-CoV-2 Infection and COVID-19 without Confirmatory Laboratory Results

Table 40: Adverse Events of SARS-CoV-2 Infection (Reported as "Asymptomatic COVID-19") in the Part 1 50 µg Group (Safety Set)

Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
80	Negative	None
61	Negative	Asymptomatic SARS-CoV-2 Infection

Table 41: Adverse Events of SARS-CoV-2 Infection (Reported as "Asymptomatic COVID-19") in Part 2 (Safety Set)

Treatment Group	Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
mRNA-1273	1	Positive	
mRNA-1273	8	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	8	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	4	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
Placebo	1	Positive	
mRNA-1273	36	Negative	None
mRNA-1273	20	Negative	None
mRNA-1273	19	Negative	None
mRNA-1273	30	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	8	Negative	None
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	25	Negative	None
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection

Treatment Group	Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
mRNA-1273	29	Negative	COVID-19 CDC Definition
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	33	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	29	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	1	Negative	None
mRNA-1273	34	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	32	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	30	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	29	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	29	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	29	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	31	Negative	None

Table 42: Adverse Events of "COVID-19" in the Part 1 50 µg Group (Safety Set)

Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
98	Negative	None

Table 43: Adverse Events of "COVID-19" in Part 2 (Safety Set)

Treatment Group	Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
mRNA-1273	1	Positive	
mRNA-1273	1	Positive	
Placebo	23	Positive	
Placebo	29	Positive	
Placebo	22	Missing	
mRNA-1273	8	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	39	Negative	Asymptomatic SARS-CoV-2 Infection
mRNA-1273	8	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	8	Negative	None
mRNA-1273	10	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	8	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	2	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	8	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
mRNA-1273	9	Negative	None
mRNA-1273	31	Negative	COVID-19 CDC Definition
mRNA-1273	16	Negative	COVID-19 CDC Definition
mRNA-1273	27	Negative	None
mRNA-1273	11	Negative	None
Placebo	8	Negative	None
Placebo	17	Negative	COVID-19 P301 Definition COVID-19 CDC Definition

Treatment Group	Study Day of AE	Baseline SARS-CoV-2 Status	Efficacy Criteria Met
Placebo	40	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	15	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	15	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	25	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	8	Negative	None
Placebo	6	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	24	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	10	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	28	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	35	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	29	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	34	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	32	Negative	Asymptomatic SARS-CoV-2 Infection
Placebo	40	Negative	None
Placebo	26	Negative	None
Placebo	5	Negative	None
Placebo	17	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	26	Negative	COVID-19 P301 Definition COVID-19 CDC Definition
Placebo	35	Negative	COVID-19 CDC Definition

Appendix 2 CDC Working Case definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring after Receipt of COVID-19 mRNA Vaccines

Table 44: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
	Probable case	**Confirmed case**
Acute myocarditis	Presence of ≥ 1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR**, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥ 1 new finding of • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis[c] • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[c] **AND** • No other identifiable cause of the symptoms and findings	Presence of ≥ 1 new or worsening of the following clinical symptoms:[a] • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥ 1 new finding of • Histopathologic confirmation of myocarditis[b] • cMRI findings consistent with myocarditis[c] in the presence of troponin level above upper limit of normal (any type of troponin) **AND** • No other identifiable cause of the symptoms and findings
Acute pericarditis[d]	Presence of ≥ 2 new or worsening of the following clinical features: • acute chest pain[e] • pericardial rub on exam • new ST-elevation or PR-depression on EKG	

Condition	Definition
	• new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram.

Note: An independent Cardiac Event Adjudication Committee (CEAC) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet Center for Disease Control and Prevention criteria for "probable" or "confirmed" events (Gargano et al 2021a), and provide the assessment to the Applicant. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

a. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

b. Using the Dallas criteria (Aretz et al 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria. https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

d. https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

e. Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Reference: (Gargano et al 2021a).

Appendix 3 Tables, Figures, and Listings Not Referenced in the Document Body

Study Population

Table 14.1.3.8 Subject Demographics and Baseline Characteristics by Age Group

Table 14.1.3.9 Subject Demographics and Baseline Characteristics by Age Group Per-Protocol Set for Efficacy — Subjects with COVID-19(P301 Primary Definition) Starting 14 Days After Second Injection

Efficacy

Table 14.2.1.1.3.5.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group, Dose Level and Baseline SARS-CoV-2 Status in Part 1 Expansion Immunogenicity Subset

Table 14.2.1.1.3.6.1 Subgroup Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers

Table 14.2.1.2.3.6.1 Subgroup Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 by Age Group in Part 1 Expansion — Seroresponse Rate Per-Protocol Immunogenicity Subset

Table 14.2.2.1.2.3.1 Summary of Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD by Age Group and Dose Level in Part 1 Expansion Per-Protocol Immunogenicity Subset

Table 14.2.6.1.1.2.2 Analysis of Incidence Rate of Asymptomatic SARS-CoV-2 Infection Starting 14 Days After Second Injection Based on Different Test Results by Age Group

Table 14.2.7.1.1.3 Subgroup Analysis of Incidence Rate of COVID-19 (P301 Primary Definition) Starting 14 Days After Second Injection by Age Group

Figure 14.2.1.2.6.1 Box Plot (Log Scale) of Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD by Age Group and Dose Level in Part 1 Expansion

Figure 14.2.4.1.1.2 Cumulative Incidence Curve of COVID-19 (P301 Primary Definition) Starting 14 Days After Second Injection by Age Group in Part 2

Figure 14.2.4.2.3.2 Cumulative Incidence Curve of COVID-19 (P301 Primary Definition) Starting After Randomization by Age Group in Part 2

Figure 14.2.5.2.3.2 Cumulative Incidence Curve of CDC Case Definition of COVID-19 Starting After Randomization by Age Group in Part 2

Listing 16.2.6.5.1 Efficacy Endpoints in Part 1

Safety

Table 14.1.8.1.1 Summary of Medications for Pain/Fever after First Vaccination by Age Group in Part 1 First Injection Solicited Safety Set

Table 14.1.8.2.1 Summary of Medications for Pain/Fever after Second Vaccination by Age Group in Part 1 Second Injection Solicited Safety Set

Table 14.3.1.3.1.1 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After First Injection by Onset Day, Age Group and Dose Level in Part 1

Table 14.3.1.3.2.1 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Second Injection by Onset Day, Age Group and Dose Level in Part 1

Table 14.3.1.4.1.1 Summary of Number of Days Reporting Solicited Adverse Reactions After First Injection by Age Group and Dose Level in Part 1

Table 14.3.1.4.2.1 Summary of Number of Days Reporting Solicited Adverse Reactions After Second Injection by Age Group and Dose Level in Part 1

Table 14.3.1.5.1.1 Summary of Onset Day of Solicited Adverse Reactions Within 7 Days After First Injection by Age Group and Dose Level in Part 1

Table 14.3.1.5.2.1 Summary of Onset Day of Solicited Adverse Reactions Within 7 Days After Second Injection by Age Group and Dose Level in Part 1

Table 14.3.1.5.3.1 Summary of Onset Day of Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Dose Level in Part 1

Table 14.3.1.6.3.1 Summary of Subjects with Solicited Adverse Reactions Persisting Beyond 7 Days After Any Injection by Grade, Age Group and Dose Level in Part 1

Table 14.3.1.7.1.4.1 Summary of Unsolicited TEAE up to 28 Days After Any Injection by Age Group, Baseline SARS-CoV-2 Status and Dose Level in Part 1

Table 14.3.1.7.2.1 Summary of Unsolicited TEAE throughout the study by Age Group and Dose Level in Part 1

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