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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073
Sponsor	ModernaTX, Inc.
Submission Dates	Individuals 12 through 17 years of age: June 9, 2021; Amendment 191 Individuals 6 through 11 years of age: March 8, 2022; Amendment 364 Individuals 6 months through 5 years of age: April 28, 2022; Amendment 395
Receipt Dates	Individuals 12 through 17 years of age: June 9, 2021; Amendment 191 Individuals 6 through 11 years of age: March 8, 2022; Amendment 364 Individuals 6 months through 5 years of age: April 28, 2022; Amendment 395
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Review Completion Date	June 16, 2022
Established Name/Names Used During Development	Moderna COVID-19 Vaccine/mRNA-1273
Dosage Forms/Strengths and Route of Administration	A suspension for intramuscular injection to be administered as a two-dose primary series: Individuals 12 through 17 years of age: each dose is 0.5 mL (100 mcg of mRNA) Individuals 6 through 11 years of age: each dose is 0.5 mL (50 mcg of mRNA) Individuals 6 months through 5 years of age: each dose is 0.25 mL (25 mcg of mRNA)
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 6 months through 17 years of age

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1 Executive Summary

The Moderna COVID-19 Vaccine (also known as mRNA-1273 and licensed under the trade name Spikevax) is an mRNA vaccine encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein. A two-dose primary series (100 µg each dose, 1 month apart) of the vaccine is approved and also authorized under Emergency Use Authorization (EUA) for use in adults 18 years of age and older for active immunization for prevention of coronavirus disease 2019 (COVID-19) due to SARS-CoV-2. The Sponsor (ModernaTX, Inc) submitted requests to expand the EUA to include use of a two-dose primary series, administered 1 month apart, in three pediatric age groups: 12 through 17 years (abbreviated 12-17 years, submitted June 9, 2021, updated data submitted May 9, 2022); 6 through 11 years (abbreviated 6-11 years, submitted March 8, 2022, updated data submitted May 4, 2022); and 6 months through 5 years (submitted April 18, 2022). In these three age groups, the proposed dose levels for each primary series dose are 100 µg, 50 µg, and 25 µg of mRNA, respectively. Within the 6 months through 5 years cohort, safety and effectiveness were analyzed separately for participants ages 6 through 23 months (abbreviated 6-23 months) and participants 2 through 5 years (abbreviated 2-5 years).

The EUA amendment request includes safety and effectiveness data from two ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trials of the Moderna COVID-19 Vaccine that included approximately 14,000 participants 6 months through 17 years of age enrolled at sites in the United States and Canada, including 10,285 participants who received at least one dose of Moderna COVID-19 Vaccine. Among 3,726 participants 12-17 years of age, 2,486 received mRNA-1273 (100 µg dose) and 1,240 received saline placebo. The median follow-up duration in this adolescent age cohort for mRNA-1273 vaccine recipients was 53 days post-Dose 2 for blinded, placebo-controlled follow-up and 312 days post-Dose 2 including unblinded follow-up. Among 4,002 participants 6-11 years of age, 3,007 received mRNA-1273 (50 µg dose) and 995 received saline placebo. The median duration of follow-up in the 6-11 years age cohort for mRNA-1273 recipients was 51 days post-Dose 2 for blinded, placebo-controlled follow-up and 158 days post-Dose 2 including unblinded follow-up. Among 4,038 participants 2-5 years of age, 3,031 received mRNA-1273 (25 µg dose) and 1,007 received saline placebo. The median duration of follow-up in the 2-5 years age cohort was 71 post-Dose 2 for blinded, placebo-controlled follow-up. Among 2,350 participants 6-23 months of age, 1,761 received mRNA-1273 (25 µg dose) and 589 received saline placebo. The median duration of follow-up in the 6-23 months age cohort was 68 days post-Dose 2 for blinded, placebo-controlled follow-up.

Vaccine effectiveness for all four pediatric age cohorts was inferred by immunobridging based on a comparison of SARS-CoV-2 neutralizing antibody (nAb) responses at 1 month after Dose 2 in participants in each age cohort (12-17 years, 6-11 years, 2-5 years, 6-23 months) to the nAb responses generated by young adults 18-25 years of age, the most clinically relevant subgroup of the adult study population for whom vaccine efficacy (VE) was demonstrated in a clinical endpoint efficacy trial. In the planned immunobridging analyses for each adolescent/pediatric age cohort, the co-primary endpoints for neutralizing antibody responses included the geometric mean titer (GMT) or geometric mean concentration (GMC) and seroresponse rate (SRR), both of which were assessed at 28 days after Dose 2. For each pediatric age cohort, the protocol-specified statistical success criteria were met if the lower bound (LB) of the 95% confidence interval (CI) of the GMT/GMC ratio (pediatric age cohort over young adults) was >0.67 and the GMT/GMC point estimate was >0.8; and if the LB of the 95% CI of the difference in SRR (pediatric age cohort minus young adults) was >−10% and the SRR estimate was >−5%.

Immunobridging success criteria were met for all four pediatric age cohorts. Immunogenicity outcomes were generally consistent across demographic subgroups such as sex, race, and ethnicity. Immune responses at 28 days post-Dose 2 were higher among the small number of participants with evidence of prior SARS-CoV-2 infection at baseline, compared to those among participants with no evidence of prior SARS-CoV-2 infection.

Additionally, descriptive analyses of VE against COVID-19 were assessed in all age cohorts using two COVID-19 case definitions: the same case definition used for the adult efficacy study and a broader Centers for Disease Control and Prevention (CDC) case definition. Using the CDC definition for the protocol-specified VE endpoint of COVID-19 cases starting 14 days after Dose 2, VE was 93.3% (95% CI 47.9, 99.9) for participants 12-17 years of age during an evaluation period when the ancestral strain (with D614G mutation), and then Alpha variant were predominant, 76.8% (95% CI -37.3, 96.6) for participants 6-11 years of age during an evaluation period when the Delta variant was predominant, and 36.8% (95% CI 12.5, 54.0) and 50.6% (95% CI 21.4, 68.6) for participants 2-5 years of age and 6-23 months of age, respectively, during an evaluation period when the Omicron variant was predominant. Estimates of VE for each age cohort were generally consistent with VE estimates from observational studies of a Moderna COVID-19 Vaccine two-dose primary series in adults during the same time periods. No severe cases of COVID-19 were observed among participants 6 months through 17 years in the clinical trials. In all pediatric age cohorts, there were insufficient COVID-19 cases among participants with evidence of prior SARS-CoV-2 infection at baseline to reliably estimate VE for this subgroup.

Across all pediatric age cohorts, including approximately 11,000 mRNA-1273 recipients 6 months through 17 years of age, solicited local and systemic adverse reactions (AR) were mostly mild to moderate in severity, generally of short duration, and occurred more frequently (and with more frequent severe ARs) after Dose 2 than Dose 1. In children 6 months through 11 years of age, rates of solicited local and systemic adverse reactions were generally lower compared to those observed in adolescents and in previous clinical trials with young adults, with the exception of fever which was reported more frequently in the younger age groups compared to adolescents and adults. After any dose, rates of fever were 21-26% among participants 6 months through 5 years of age, and fever >40.0°C was rare and occurred in less than 0.4% of participants in this age cohort. Injection site pain was the most commonly reported solicited adverse reaction (58%-98%) after any dose across all age pediatric age cohorts 6 months through 17 years. Among younger pediatric participants 6-36 months of age, irritability/crying (71-82%) and sleepiness (50%-51%) were frequently reported. Among pediatric participants >36 months of age, fatigue and headache were frequently reported as follows: 62% and 23%, respectively, among participants 37 months through 5 years of age, 73% and 62%, respectively, among participants 6-11 years of age, and 75% and 78%, respectively, among participants 12-17 years of age. Among participants 6-17 years of age, solicited adverse reactions after Dose 1 were generally reported more frequently among participants with evidence of prior SARS-CoV-2 infection compared to participants without evidence of prior infection at baseline. Among participants 6 months through 5 years of age, fever was reported more frequently after both Dose 1 and Dose 2 among participants with evidence of prior SARS-CoV-2 infection compared to participants without evidence of prior SARS-CoV-2 infection, but no differences were observed for other solicited ARs.

Imbalances across all pediatric age cohorts were observed between mRNA-1273 recipients and placebo recipients in the number of unsolicited adverse events (AEs) occurring within 28 days following vaccination; these were mainly attributable to injection site reactions, including injection site lymphadenopathy, and hypersensitivity reactions, which are plausibly related to

vaccine. Among participants 2-11 years, more events of abdominal pain were reported among mRNA-1273 recipients compared to placebo recipients; there is insufficient information to conclude a causal relationship between these events and vaccine. There were no deaths reported among participants 6 months through 17 years. Serious adverse events (SAEs) were infrequent and occurred at similar rates among mRNA-1273 recipients and placebo recipients. Review of SAEs did not reveal any concerning safety signals. There were no notable differences in rates of unsolicited AEs between participants with evidence of prior SARS-CoV-2 infection and those without evidence of prior infection.

Myocarditis/pericarditis, in particular in the first week following Dose 2, is a known risk associated with the Moderna COVID-19 Vaccine, with the highest reported rate in males 18-24 years in routine pharmacovigilance/safety surveillance by the CDC and FDA. There were no confirmed cases of myocarditis or pericarditis among participants 6 months through 17 years in clinical studies with mRNA-1273.

The 174th meeting of the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) was held on June 14-15, 2022, to consider Moderna's requests to expand the authorization of the EUA for the Moderna COVID-19 Vaccine to include use of a 2-dose primary series in the pediatric age groups of 12 through 17 years, 6 through 11 years, and 6 months through 5 years. Following the presentations and committee discussion on the first day, the VRBPAC voted 22-0 in each of two separate votes in favor of determinations that the known and potential benefits of the Moderna COVID-19 Vaccine, when administered as a 2-dose series, outweighed the known and potential risks for use in adolescents 12 through 17 years of age and in children 6 through 11 years of age. Following the presentations and committee discussion on the second day, the VRBPAC voted 21-0 in favor of a determination that the known and potential benefits of the Moderna COVID-19 Vaccine, when administered as a 2-dose series, outweighed the known and potential risks for use in infants and children 6 months through 5 years of age.

Based on the totality of the scientific evidence available at this time to support the conclusion that the Moderna COVID-19 vaccine may be effective, and that the known and potential benefits outweigh the known and potential risks associated with the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 17 years of age, the review team recommends authorization of the Moderna COVID-19 vaccine under EUA for use as a 2-dose primary series, administered 1 month apart, as follows:

- 100 µg each dose for individuals 12 years through 17 years of age;
- 50 µg each dose for individuals 6 years through 11 years of age; and
- 25 µg each dose for individuals 6 months through 5 years of age.

The review team also recommends authorization of a third primary series dose, at the age-appropriate dose level as specified above and administered at least 4 weeks after the second primary series dose, for use in individuals 6 months through 17 years of age with certain kinds of immunocompromise (solid organ transplant recipients or individuals with conditions causing an equivalent level of immunocompromise).

2 Background

2.1 SARS-CoV-2 Virus and COVID-19 Disease

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death. Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported.[1,2] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[3] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15% to 50% of infections.[4,5] However, COVID-19-associated hospitalizations and deaths have occurred in children (see below), and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.[6]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of June 2, 2022, has caused more than 531 million cases of COVID-19, including 6.2 million deaths worldwide.[7] In the US, more than 84 million cases and 1 million deaths have been reported to the CDC. [8,9] Following EUA of the first COVID-19 vaccine in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the US, leading to the Delta variant-associated peak in September of 2021 and the more recent surges in cases attributed to the Omicron variant. As of the week ending March 26, 2022, the Omicron variant (B.1.1.529, also called BA.1) comprised all of the tested strains in the US[10], and sublineages of the Omicron variant (previously BA.2, which replaced BA.1 as the dominant strain, and currently BA.4, and BA.5) are increasingly identified among tested strains.[11]

Of the total COVID-19 cases reported in the US to date, 17.5% occurred among individuals less than 18 years of age.[12] Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network, approximately 8,396 have resulted in hospitalization.[13] As of June 2, 2022, 1,524 deaths from COVID-19 have been reported in the US in individuals less than 18 years of age.[14]

The most common underlying medical conditions among hospitalized children were obesity (31.9%), neurologic disorders (14.8%), and asthma (14.5%). Obesity was associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, or metabolic conditions, or with congenital heart disease.[15] However, a substantial proportion of children hospitalized for COVID-19 have no underlying medical conditions. As in the adult population, COVID-19 in children disproportionally affects underrepresented racial and ethnic groups, with hospitalizations and deaths more frequent among Native American/Alaskan, Hispanic or Latino, and non-Hispanic Black children than among White children.[16,17]

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis.[18,19] While the overall incidence of myocarditis following COVID-19 is low, persons with COVID-19 have a

nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection.[20] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least two affected organs. In severe cases, hypotension and shock can occur. Between May 2020 and October 4, 2021, the CDC received reports of 5,217 cases and 46 deaths that met the definition for MIS-C; the median age of participants was 9 years with half of the cases occurring in children ages 5 to 13 years. Males comprised 60% of cases, and 61% were reported in children who were reported as Hispanic or Black.[21] Up to 66.7% of patients with MIS-C had cardiac involvement, [22] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[23] One study of outcomes in children with MIS-C followed up to 9 months found that while 76% of children with MIS-C required intensive care unit admission and therapy with inotropes or pressors; most symptoms, including cardiovascular manifestations, resolved within 1 to 4 weeks.[24] Limited data are available on long-term outcomes in MIS-C.

In addition to directly experiencing COVID-19 and the sequelae of infection themselves, during the first 15 months of the COVID-19 pandemic, more than 140,000 children under 18 years of age in the US experienced a COVID-19-associated death of a parent or custodial caregiver.[25] Other impacts of COVID-19 on children and adolescents include social isolation due to disruption of school, sports, and social group gatherings. Published studies have highlighted increases in symptoms of depression and anxiety[26,27] and increased rates of suicide-related behaviors among children and adolescents during the pandemic.[28]

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1 Spikevax and Moderna COVID-19 Vaccine

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains nucleoside-modified mRNA that encodes for the full-length spike protein of SARS-CoV-2 encapsulated in lipid particles. The primary immunization series consists of 2 intramuscular doses administered 1 month apart, with each 0.5 mL dose of the approved formulation containing 100 µg mRNA. During clinical development it was called mRNA-1273.

Under EUA, the vaccine is called the Moderna COVID-19 Vaccine. The vaccine is authorized for use under EUA as: a two-dose primary series for individuals 18 years of age and older; a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions.

Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.2 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as: a two-dose primary series for individuals 12 years of age and older; a third primary series dose for individuals 12 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 12 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a second booster dose administered at least 4 months after a first booster dose with any FDA authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions. A different presentation of Pfizer-BioNTech COVID-19 Vaccine is authorized under EUA for use in children 5-11 years of age as: a two-dose primary series; a third primary series dose in individuals with certain kinds of immunocompromise; and a single homologous booster dose administered at least 5 months after completion of a primary series. Safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). Safety and effectiveness data supporting emergency use authorization of the Janssen COVID-19 Vaccine are detailed in the decision memorandum on the FDA website.

2.2.4 Therapies for COVID-19

The antiviral remdesivir is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. Additionally, the immune modulator baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric

patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

2.3 Post-Licensure/Post-Authorization Experience with Spikevax and Moderna COVID-19 Vaccine

2.3.1 Observational Studies and Vaccine Effectiveness against Clinically Relevant Variants (e.g., Delta and Omicron)

The emergence of the highly transmissible Omicron variant (B.1.1.529) of SARS-CoV-2 in December 2021 resulted in several waves of COVID-19 cases in many parts of the world and, in the US, coincided with a rapid increase in COVID-19-associated hospitalizations among all age groups.[29] Observational studies have indicated reduced and more rapidly waning effectiveness against symptomatic infection caused by the Omicron variant. Observed estimates of mRNA-1273 vaccine effectiveness against symptomatic disease in adults due to the Omicron variant was 44% (95% CI, 35-52%) 2-12 weeks since completion of the two-dose primary series, and decreases to 24% (95% CI, 16-30) at 12-25 weeks post primary series. In comparison, observed estimates of mRNA-1273 vaccine effectiveness against disease cause by Delta variant was 80% (95% CI, 68-88) at 2-12 weeks and declines to 69% (95% 60-76) at 12-25 weeks.[30] Vaccine effectiveness against the Alpha variant was 92% (95% CI, 88-95) starting one week after completion of the primary series.[31]

Recent estimates of primary series vaccine effectiveness against serious outcomes have been lower during the Omicron predominant period as compared to the Delta predominant period across adult age groups. When evaluating COVID-19 mRNA vaccines authorized or approved for use in the US, including BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and mRNA-1273,

vaccine effectiveness of two doses in adults to prevent COVID-19 hospital admission was 85% (95% CI 82 to 88%) in the Alpha period, 85% (95% CI: 83 to 87%) in the Delta period, and 65% (95% CI:51 to 75%) in the Omicron period.[32]

Although mRNA-1273 has been authorized for use in individuals 6-17 years in several non-US countries, data on vaccine effectiveness with mRNA-1273 in this age group is limited; however, effectiveness estimates for a primary series of the mRNA vaccine authorized for use these age groups in the US (Pfizer-BioNTech COVID-19 Vaccine) have been lower for symptomatic SARS-CoV-2 infection and COVID-19-related acute care visits and hospitalization during the Omicron-dominant period as compared to previous Alpha- and Delta-dominant periods.[33] Additional updated data on vaccine effectiveness was presented by CDC during the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting.

2.3.2 Post-EUA and Post-Licensure Safety Surveillance

As of May 13, 2022, more than 210 million doses of the Moderna COVID-19 Vaccine have been administered in the US.[34] The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following the Moderna COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of May 13, 2022, VAERS received 446,806 AE reports following Moderna COVID-19 vaccination, of which 375,210 were US reports. Among the US reports, 109 reports were in children <6 years of age, 159 reports were in children 6 through 11 years of age, and 7,935 reports were in children 12 through 17 years of age. The top ten most frequently reported MedDRA Preferred Terms (PTs) included:

- 10 most frequent PTs among all ages: headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, injection site pain.
- 10 most frequent PTs in in persons ≤17 years of age: product administered to patient of inappropriate age, pyrexia, interchange of vaccine products, pain in extremity, headache, product storage error, fatigue, myocarditis, wrong product administered, inappropriate schedule of product administration

Note that a report may have one or more PTs. An additional query of VAERS for US reports for all ages by dose number retrieved the following: 180,948 reports after Dose 1; 104,724 reports after Dose 2; and 34,632 reports after dose 3 (data as of May 13, 2022).

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis and pericarditis are existing safety concerns that have been added to the product Fact Sheets and package insert. Review of passive surveillance AE reports and the Sponsor's periodic safety reports does not indicate new safety concerns. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

Anaphylaxis
Post-authorization surveillance for the Moderna COVID-19 Vaccine has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[35,36] Anaphylaxis is an important identified risk in the pharmacovigilance plan (PVP) and included in the label (Section 4 Contraindications, Section 5 Warnings and Precautions, Section 5.1 Management of Acute Allergic Reactions, Section 6 Overall Safety Summary, Section 6.2 Post Authorization Experience).

As of May 13, 2022, there have been a total of 2,031 worldwide reports of anaphylactic/ anaphylactoid reactions among all ages, including 1,517 serious reports, of which 14 were death reports (based on an automated search of the VAERS database, which includes the limitations of passive surveillance described earlier). Among all ages, there have been a total of 984 US reports of anaphylactic/anaphylactoid reaction, including 490 serious reports and 10 death reports. Six of the 10 US death reports were attributed to anaphylaxis post vaccination, and the remaining 4 reports had confounding factors, such as co-morbidities and concurrent conditions, onset of symptoms inconsistent with anaphylaxis due to vaccination, and/or limited information which precluded further assessment. There has been 1 report of anaphylaxis post vaccination among US reports for individuals ≤17 years of age. This was a non-serious report in a 17-year-old male with full recovery. There have been no US reports of anaphylactic/ anaphylactoid reactions among individuals 6 months through 11 years of age. The estimated crude reporting rate for anaphylaxis among individuals of all ages in the US is 4.6 reports per million doses administered at this time based on the above VAERS data.

Myocarditis and pericarditis
Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis associated with the Moderna COVID-19 Vaccine, particularly within 7 days following administration of the second dose of the two-dose primary series. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among adult males under 40 years of age than among females and older males and have been highest in males 18-24 years of age (40.0 cases per million doses following Dose 2 administration among males aged 18-24 years and 18.3 cases per million doses following Dose 2 among males aged 25-29 years as per CDC presentation to the Advisory Committee on Immunization Practices on February 4, 2022).

Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the label (Section 5 Warnings and Precautions, Section 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience). The Sponsor is conducting additional post-authorization/postmarketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

As of May 6, 2022, CDC has identified 3 males, ages 15, 15 and 16 years, who met the CDC case definition for myocarditis. All 3 had events were reported after Dose 2, and all 3 patients

were hospitalized and subsequently discharged home. There have been no confirmed cases in children less than 15 years of age. This vaccine is not currently authorized for use in individuals less than 18 years of age in the US, thus, these vaccination reports represent unauthorized use (i.e., off-label use) of the vaccine in this age group.

The Moderna COVID-19 Vaccine is authorized in individuals 6 years of age and older in other countries. The Sponsor's review of post authorization data through April 15, 2022, found no reports of myocarditis or pericarditis after receipt of Spikevax in children less than 12 years of age. There were 151 reports of myocarditis and pericarditis in adolescents 12 to 17 years of age, none of which were fatal. The majority (88.1%) of cases were reported in males, with the median age of 16 years (range 12-17 years). Fifty-seven percent of cases occurred in males aged 16 to 17 years, of which 68% reported the outcome as resolved or resolving. Events of myocarditis and pericarditis continue to primarily occur in young adult males within 7 days after the second dose of vaccine. Using the CDC myocarditis working definition, there were a total of 12 confirmed cases, 45 probable cases, and 84 cases considered unassessable. Additionally, 8 cases were classified as acute pericarditis, and 2 cases classified as not a case.

2.4 EUA Amendment Request for the Moderna COVID-19 Vaccine for Use in Children 6 Months through 17 Years of Age

The Sponsor submitted requests to amend the EUA for the two-dose primary series of Moderna COVID-19 Vaccine to include use in three pediatric age groups: 12 through 17 years (12-17 years), submitted June 9, 2021; 6 through 11 (6-11 years), submitted March 8, 2022); and 6 months through 5 years (6 months-5 years), submitted April 18, 2022. In these three age groups, the proposed dose levels for each primary series dose are 100 µg, 50 µg, 25 µg of mRNA, respectively. These requests were accompanied by clinical trial data evaluating the safety and effectiveness of the vaccine as follows:

12 through 17 years of age (Study P203): The initial EUA amendment submission included safety data from a total of 2,486 mRNA-1273 recipients vaccinated with two doses of 100 µg mRNA, 1,087 (44%) of whom had ≥2 months of blinded follow-up after Dose 2. Updated data including additional safety follow-up through a later data cut was submitted on May 9, 2022. In this updated analysis, 2,376 mRNA-1273 recipients (95.6%) have been followed for at least 6 months since Dose 2, including both the blinded and open-label phases. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody GMT and SRR 1 month after Dose 2) between adolescents 12 through 17 years of age (n=340) and young adults 18 through 25 years of age who participated in the pivotal study in adults (Study P301). Efficacy against COVID-19 was also assessed with descriptive analyses.

6 years through 11 years of age (Study P204): The initial EUA amendment submission included safety data from a total of 3,007 mRNA-1273 recipients vaccinated with two doses of 50 µg mRNA, 1066 (35.5%) of whom had >2 months of blinded follow-up after Dose 2. Updated data including additional safety follow-up through a later data cut was submitted on May 4, 2022. In this updated analysis, the median duration of follow up including both the blinded and open-label phases was 158 days post Dose 2. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody GMT and SRR 1 month after Dose 2) between children 6-11 years of age (n=320) and young adults 18 through 25 years of age from study P301. Efficacy against COVID-19 was also assessed with descriptive analyses.

6 months through 5 years of age, split into two age subgroups (Study P204):

- **2 through 5 years of age:** Safety data from a total of 3,031 mRNA-1273 recipients vaccinated with two doses of 25 µg mRNA; the median duration of blinded follow-up after Dose 2 was 71 days. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody GMCs and SRRs 1 month after Dose 2) between children 2-5 years of age (n=264) and young adults 18 through 25 years of age from study P301. Efficacy against COVID-19 was also assessed with descriptive analyses.
- **6 months through 23 months of age:** Safety data from a total of 1,761 mRNA-1273 recipients vaccinated with two doses of 25 µg mRNA; the median duration of blinded follow-up after Dose 2 was 68 days. Vaccine effectiveness was inferred by immunobridging based on a comparison of immunogenicity endpoints (SARS-CoV-2 neutralizing antibody GMCs and SRRs 1 month after Dose 2) between children 6-23 months of age (n=230) and young adults 18 through 25 years of age from Study P301. Efficacy against COVID-19 was also assessed with descriptive analyses.

2.4.1 Regulatory Considerations for Adolescent EUA

In spring and summer 2021, after the Sponsor's submission of the EUA amendment requesting use of a two-dose series of the vaccine in adolescents 12-17 years of age, a number of published reports suggested there was a potential increased risk of myocarditis/pericarditis in young males following vaccination with the second dose of either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna).[37,38,39,40,41,42] By the fall of 2021, FDA reviewed results from seven surveillance systems which suggested an estimated two- to seven-fold increased risk of myocarditis/pericarditis following mRNA-1273 vaccination as compared to BNT162b2 in passive surveillance systems in the United Kingdom, Europe, Canada and Canadian province, Ontario and in a Nordic observational study.[43] An active surveillance study conducted by the US CDC Vaccine Safety Datalink (VSD), employing a direct head-to-head comparison of mRNA-1273 and BNT162b2, also indicated that myocarditis/pericarditis rates following vaccination with mRNA-1273 were more than two times higher than with BNT162b2 after Dose 2 in young males (relative risk [RR]: 2.26, 95% CI: 1.09, 4.63).[44] There are significant limitations in results generated by these comparisons but the reported differences in myocarditis/pericarditis risk between the two mRNA vaccines across multiple data sources were concerning, and FDA's assessment was that the totality of evidence available at the time, and availability of BNT162b2 for use in adolescents, did not support EUA of mRNA-1273 for use in adolescents.

Results from subsequent analyses conducted by the CDC and FDA in the fall of 2021 indicated only a small difference in myocarditis/pericarditis risk between mRNA-1273 and BNT162b2. Results from the Vaccine Adverse Event Reporting System (VAERS) passive surveillance system suggested a 30% higher risk for mRNA-1273 in young males.[45] A comparison using the FDA Biologics Effectiveness and Safety (BEST) system reported a smaller 20% increase in myocarditis/pericarditis rates among mRNA-1273 recipients as compared to BNT162b2 recipients, a finding that was not statistically significant (RR: 1.21, 95% CI: 0.56, 2.60).[46] At the time, the preponderance of evidence from seven sources continued to indicate a higher magnitude of myocarditis/pericarditis risk following vaccination with the second dose of mRNA-1273 as compared to BNT162b2 in young males.

As of May 2022, more data and cases of myocarditis/pericarditis following mRNA vaccination accumulated in surveillance systems globally and in the US since 2021. Head-to-head comparisons from the Canadian and Ontario-Canada enhanced passive surveillance systems

indicated an approximately five-fold[47] to seven-fold for young males[48] increased risk for mRNA-1273 compared to BNT162b2. International observational studies conducted in the United Kingdom,[49] Denmark,[50] Nordic countries,[51] Italy,[52] and France[53] suggested a three- to seven-fold differential risk for mRNA-1273 relative to BNT162b2 after Dose 2.

As of May of 2022, more robust results from new analyses run in US surveillance systems show slight decreases in the risk differential between mRNA vaccines. Specifically, comparisons in VAERS indicated only a 7% increased risk of mRNA-1273 relative to BNT162b2 in young males.[54] The most recent direct comparisons from both the CDC VSD and FDA BEST reported a non-statistically significant increase of 50% (RR =1.50, 95% CI: 0.86-2.61)[55] and 25% (RR =1.25, 95% CI: 0.80-1.94)[56], respectively, following vaccination of young males with Dose 2 of mRNA-1273 compared with BNT162b2. Additionally, accrued data from CDC and other sources on myocarditis outcomes continued to strengthen the evidence that most cases of mRNA vaccine-associated myocarditis, including in pediatric age groups, are characterized by rapid resolution of symptoms following conservative management, with no impact on quality of life reported by most patients who were contacted for follow-up at 90 days or more after reporting vaccine-associated myocarditis.[57,58]

In conclusion, several international passive and active surveillance data sources suggest a higher myocarditis/pericarditis risk mRNA-1273 relative to BNT162b2, and this pattern has persisted for more than a year. However, these data have limitations and uncertainties, especially for passive surveillance sources as compared to active surveillance results. More recent results from April and May 2022 analyses from three US surveillance systems do not support a difference in myocarditis/pericarditis risk for mRNA-1273 as compared to BNT162b2 or suggest a small difference because of uncertainties and broad CIs. FDA is considering the totality of this surveillance information on the risk of myocarditis/pericarditis along with other information in determining if the potential benefits for mRNA-1273 outweigh the potential risks of COVID-19.

3 EUA Requirements, Guidance and Considerations Pertaining to COVID-19 Vaccines

3.1 US Requirements to Support Issuance of an EUA for a Biological Product

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

- The chemical, biological, radiological, or nuclear agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

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

3.2 FDA Guidance for Industry Related to COVID-19 Vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit-risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" March 2022, originally issued October 2020).[59] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in children 6 months through 17 years of age. The timing, design, and appropriate endpoints for pediatric studies are discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent COVID-19" from June 2020.[60]

3.3 Regulatory Considerations for Clinical Development of COVID-19 Vaccines in Children

The Vaccines and Related Biological Products Advisory Committee convened on June 10, 2021, to discuss, in general, the data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

Effectiveness
Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to a young adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (GMT and SRR) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric versus young adult populations.

Safety
The size of the safety database sufficient to assess risks of COVID-19 vaccines for EUA in pediatric age groups would generally be the same as for other preventive vaccines for infectious diseases, provided that no specific safety concern is identified that could reasonably be evaluated in pre-authorization clinical trials. These safety data would include characterization of common adverse reactions (reactogenicity, including injection site and systemic adverse reactions), and less common but medically important adverse reactions. Depending on prior

experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure and have at least 6 months of follow-up evaluations after completion of the vaccination regimen. Since COVID-19 vaccines represent a new class of vaccines, with many of the lead candidates based on new platform technologies, an appropriate overall pediatric safety database would approach the upper end of this range, with adequate representation across all pediatric age groups, in particular younger age groups (e.g., <12 years) that are less physiologically similar to adults. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well-controlled studies to support licensure. If another COVID-19 vaccine is licensed or authorized for use in the age group(s) enrolled in the trial, recommended by public health authorities, and widely available such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control.

Within the overall pre-licensure safety database, solicited reactogenicity could be adequately characterized among several hundred trial participants in each relevant age group. Additionally, safety evaluation in all trial participants would include collection of all AEs through at least 1 month after each study vaccination and collection of serious and other medically attended AEs for the duration of the trial. Although longer-term follow-up (through 1 year or longer post-vaccination) of trial participants would be important to ongoing assessment of both benefits and risks, completion of such longer-term follow-up would not be a prerequisite to licensure unless warranted by a specific safety concern. Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials.

4 FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

Moderna submitted requests to amend this EUA to include the use of a two-dose primary series of their COVID-19 vaccine (mRNA-1273) in adolescents 12 through 17 years of age (100 µg each dose, 28 days apart), in children 6 through 11 years of age (50 µg each dose, 28 days apart), and in young children 6 months through 5 years of age (25 µg each dose, 28 days apart). Data to support the EUA amendment requests are from three ongoing clinical studies summarized below in Table 1. Study mRNA-1273-P301 is an ongoing Phase 3 safety, immunogenicity, and efficacy study that was used to support EUA of the Moderna COVID-19 Vaccine and approval of Spikevax in individuals 18 years of age and older. Data from young adult participants (18 through 25 years of age) in this study were used for comparison purposes to demonstrate vaccine effectiveness in adolescents (12 through 17 years), children (6 through 11 years), and young children (6 months through 5 years, further broken down into those 6 month to 2 years and 2 years through 5 years of age) via immunobridging analyses which required demonstration of non-inferiority of neutralizing antibody GMTs and SRRs in each pediatric age group compared to young adults. Study mRNA-1273-P203 is an ongoing multi-center, randomized, blinded, Phase 2/3 placebo-controlled study to evaluate safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents 12 through 17 years of age.

Study mRNA-1273- P204 is an ongoing Phase 2/3 study in children 6 months through 11 years of age with three parts: Part 1 is the open-label, dose-escalation, age de-escalation phase; Part 2 is the randomized, observer-blind, placebo-controlled expansion phase within each of three

age subgroups; and Part 3 will evaluate an open-label lower dose regimen in children 6 through 11 years of age (including a pre-planned third dose). Data from Part 1 and Part 2 only are included to support this EUA amendment.

Table 1. Ongoing Clinical Studies Used to Support Emergency Use Authorization of the Moderna COVID-19 Vaccine in Children and Adolescents

Study Number	Description	mRNA-1273 N	Placebo (Saline) N
P301	Phase 3, randomized, placebo-controlled, study to evaluate safety, efficacy, and immunogenicity of mRNA-1273 in adults 18 years of age and older	**100 µg:** 18-25 years immunobridging comparator group: 878	N/A
P203	Phase 2/3 randomized, placebo-controlled study to evaluate safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents ages 12-17 years	**100 µg:** 12-17 years: 2486	12-17 years: 1240
P204	Phase 2/3, three-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy children 6 months to less than 12 years	**50 µg:** 6-11 years[a]: 3007 **25 µg:** 2-5 years[a]: 3031 6-23 months[a]: 1761	6-11 years[a]: 995 2-5 years[a]: 1007 6-23 months[a]: 589

a. Numbers of participants in the randomized, observer-blind, placebo-controlled phase of Study P204. Additional participants were dosed during the open-label, dose-escalation phase of the study.
N/A=Not applicable.

4.2 Study P301: Adults 18 Years of Age and Older

Study P301 is the Phase 3 study to evaluate the efficacy, safety and immunogenicity of the Moderna COVID-19 Vaccine in adults 18 years of age and older. Results of this study supported EUA of the vaccine and its subsequent approval under the trade name Spikevax. The study took place in 99 sites in the United States. In Part A (blinded phase), participants (N=30,351) were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine or placebo on Day 1 and Day 29. The primary endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline. Sera for analysis of neutralizing antibody titers was collected from participants at Day 0 (pre-vaccination) and at Day 57 (28 days post-Dose 2). Additional details regarding the study design and participant follow-up in Study P301 may be found in the approval memoranda for Spikevax on the FDA website.

4.3 Study P203: Adolescents 12 Years through 17 Years of Age

Participants 12-17 years of age began enrollment into Study P203 on December 9, 2020. Data snapshot was triggered on May 8, 2021, based on availability of immunogenicity data from participants in the study; the median study follow-up duration at the time of the data cutoff was of 53 days after Dose 2.

4.3.1 Study Design

Study P203 is an ongoing randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 administered as two doses 28 days apart in healthy adolescents ages 12-17 years. Participants (N=3,732) were randomized 2:1 to

receive intramuscular injections of either 100 µg of mRNA-1273 vaccine or placebo on Day 1 and Day 29.

Vaccine effectiveness was inferred from an immunobridging evaluation comparing immune responses of adolescents in Study P203 to those of young adults 18-25 years of age from Study P301 (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). Immunobridging success required demonstration of non-inferiority (in adolescents compared to young adults) of two separate measures of immunogenicity as measured by vaccination-specific pseudovirus neutralizing antibody (PsVNA) ID50 titer: GMT and SRR.

Immunogenicity endpoints for adolescents 12 through 17 years of age
Co-primary endpoint 1: GMT: the ratio (adolescents to young adults) of the GMT at Day 57 evaluated against a non-inferiority margin of 1.5 (LB of the 95% CI of the GMT ratio >0.67) AND a point estimate of GMT >0.8 (minimum threshold).

Co-primary endpoint 2: SRR: the difference in the SRRs (adolescents minus young adults) was evaluated against a non-inferiority margin of 10% (LB of the 95% CI >-10%) AND a point estimate of difference in SRRs >-5%. For the PsVNA ID50 assay, seroresponse was defined as a change from below lower limit of quantification (LLOQ) to greater than or equal to the LLOQ, or at least a 3.3-fold rise in participants ≥LLOQ at baseline.

Evaluation of immunogenicity
In post-vaccination virology samples from participants 12-17 years and the comparator group of participants 18-25 years, the immunogenicity of mRNA-1273 was assessed using the pseudotype virus neutralization assay validated at Duke University. The assay measures neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein. (D614G form of the USA-WA1/2020 Wuhan strain). Neutralization is measured as the serum dilution at which the relative luminescence unit (RLU) value is reduced by 50% (ID50) and 80% (ID80) relative to mean RLU value in virus-control wells. The assay was validated using both convalescent serum samples and clinical samples from individuals who received the mRNA-1273 vaccine. The validation results met the pre-established acceptance criteria and support the suitability of the assay to accurately quantify neutralizing antibodies in human serum samples.

Evaluation of efficacy
Supplementary to the immunobridging analysis, adolescents were followed for potential cases of COVID-19 to assess efficacy of the vaccine against laboratory-confirmed COVID-19 in participants 12-17 years of age. Analyses of vaccine efficacy to prevent asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection regardless of symptoms were also conducted. COVID-19 case definitions for Study P203 may be found in Appendix B. Efficacy against COVID-19 was assessed with descriptive analyses.

Evaluation of safety
The primary safety objective was to describe the safety of mRNA-1273 after one or two doses. All participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose in an e-diary. Unsolicited AEs were collected from Day 1 to 28 after the last dose. Medically attended adverse events (MAAEs), SAEs, and adverse events of special interest (AESIs) of MIS-C were reported from Dose 1 to the end of the study. This EUA amendment includes blinded data through the data cutoff of May 8, 2021, or the date of a participant's unblinding (whichever is earlier) as well as additional open-label follow up through a data cutoff of January 31, 2022.

Events of confirmed symptomatic SARS-CoV-2 infection were captured as a MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Following authorization of an alternative COVID-19 vaccine for this age group on May 10, 2021, participants in the study were permitted to unblind to study treatment. Crossover vaccination with mRNA-1273 of participants initially randomized to placebo began in October 2021.

Table 2. Analysis Populations, Study P203

Population	Description
Randomization Set	All randomized participants, regardless of treatment status.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of Investigational Product (IP).
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing who: • have baseline (Day 1) SARS-CoV-2 status available, and • have baseline and at least one post-dose antibody assessment for the analysis endpoint.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing who received planned doses of study vaccination per schedule, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, complied with immunogenicity testing schedule, and had no major protocol deviations that impact key or critical data. Participants seropositive at baseline were excluded. The PP Immunogenicity Subset was used for analyses of immunogenicity unless otherwise specified.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, complied with the timing of Dose 2, had no immunologic and virologic evidence of prior COVID-19 at baseline, and had no major protocol deviations that impact key or critical efficacy data.
Modified Intent-to-treat Set (mITT)	All participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (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 Set	All participants in the mITT Set excluding those who received the wrong treatment.
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

4.3.2 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 3 (immunogenicity populations), Table 4 (efficacy populations) and Table 3Table 5 (safety population).

For immunobridging, a random sample of 374 participants from P203 and 340 young adult participants from P301 who received mRNA-1273 were selected for inclusion in the Immunogenicity Subset. No placebo recipients were included in the Immunogenicity Subset. The Per-protocol (PP) Immunogenicity Subset, used for the primary immunogenicity analyses, consisted of 340 adolescent participants and 305 younger adult participants. The majority exclusions from the PP Immunogenicity Subset were due to participants having a positive baseline SARS-CoV-2 status and were similar between the adolescent and young adult groups.

Table 3. Disposition of Participants 12 Through 17 Years of Age (Study P203) and 18 Through 25 Years of Age (Study P301), Immunogenicity Populations

Disposition	12-17 Years mRNA-1273 100 µg	18-25 Years mRNA-1273 100 µg
Randomized	N=2489	N=878
Immunogenicity Subset[a]	N=374	N=340
PP Immunogenicity Subset[b]	N=340	N=305
Excluded from PP Immunogenicity Subset[c], n (%)	34 (9.1)	35 (10.3)
Reason for exclusion, n (%)		
Positive baseline SARS-CoV-2 status	26 (7.0)	17 (5.0)
Did not receive Dose 2 per schedule	0	16 (4.7)
Received Dose 2 out of window	8 (2.1)	2 (0.6)

Source: P203, Table 1.2.3.1

a. The Immunogenicity Subset consists of participants in the Full Analysis Set (FAS) who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.

b. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.

c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.

In the populations used to assess the efficacy endpoints, dispositions were overall similar between the mRNA-1273 and placebo groups. There was a slightly higher percentage of participants in the placebo arm who were excluded from the PP Set for Efficacy due to discontinuation of study treatment prior to Dose 2, likely due to eligibility to receive alternate COVID-19 vaccine.

Table 4. Disposition of Participants 12 Through 17 Years of Age, Study P203, Efficacy Population

Disposition	mRNA-1273 100 µg	Placebo	Total
Randomized	N=2489	N=1243	N=3732
Full Analysis Set[a]	N=2486	N=1240	N=3726
mITT Set[b]	N=2167	N=1075	N=3242
mITT1 Set for Efficacy[c]	N=2163	N=1073	N=3236
Excluded from mITT1 Set for Efficacy, n (%)	326 (13.1)	170 (13.7)	496 (13.3)
Reason for exclusion, n (%)	--	--	--
Randomized but not dosed	3 (0.1)	3 (0.2)	6 (0.2)
Positive or missing baseline SARS-CoV-2 status	319 (12.8)	165 (13.3)	484 (13.0)
Received incorrect vaccination	4 (0.2)	2 (0.2)	6 (0.2)
PP Set for Efficacy[d], n (%)	N=2139	N=1042	N=3181
Excluded from PP Set for Efficacy	350 (14.1)	201 (16.2)	551 (14.8)
Reason for exclusion, n (%)	--	--	--
Randomized but not dosed	3 (0.1)	3 (0.2)	6 (0.2)
Positive or missing baseline SARS-CoV-2 status	319 (12.8)	165 (13.3)	484 (13.0)
Discontinued study treatment or participation without receiving Dose 2	2 (<0.1)	13 (1.0)	15 (0.4)
Not received Dose 2 and passed window of +14 days	1 (<0.1)	0	1 (<0.1)
Received incorrect vaccination	4 (0.2)	2 (0.2)	6 (0.2)
Received Dose 2 out of window	21 (0.8)	18 (1.4)	39 (1.0)

Source: P203, Ad-hoc Table 1.1, Ad-hoc Table 1.2

a. The FAS consists of all randomized participants who received at least one dose of IP. Numbers are based on planned treatment group.

b. The mITT Set consists of all participants in the FAS who had 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) before the first dose of IP, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.
c. The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (i.e., at least one dose received in Part A was not as randomized). Numbers are based on planned treatment group.
Percentages are based on the number of participants randomized.
d. The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of second dose of injection; had a negative
RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group. Percentages are based on the number of participants randomized.

The disposition of participants from P203 who contributed to the assessment of safety are shown in Table 5. There was a higher rate of study discontinuation in the placebo group (15.1%) than the mRNA-1273 group (2.3%); the majority discontinuations were withdrawals by the participant due to eligibility for an alternative COVID-19 vaccine. One participant (<0.1%) in the mRNA-1273 group discontinued the study due to an AE (discussed in Section 4.3.6).

Table 5. Disposition of Participants 12 Through 17 Years of Age, Study P203, Safety Population

Disposition	mRNA-1273 100 µg	Placebo
Randomized	N=2489	N=1243
Completed one dose, n (%)	2486 (99.9)	1240 (99.8)
Completed two doses, n (%)	2480 (99.6)	1222 (98.3)
Discontinued from study, n (%)	57 (2.3)	188 (15.1)
Reason for discontinuation, n (%)	--	--
Adverse event[a]	1 (<0.1)	0
Withdrawal by participant	27 (1.1)	102 (8.2)
Lost to follow-up	3 (0.1)	6 (0.5)
Protocol deviation	8 (0.3)	14 (1.1)
Physician decision	1 (<0.1)	0
Death	0	0
Other	17 (0.7)	66 (5.3)
Safety Set[b]	N=2486	N=1240
Solicited Safety Set[c]	N=2485	N=1240
First Injection Solicited Safety Set, n (%)	2482 (99.8)	1238 (99.8)
Second Injection Solicited Safety Set, n (%)	2478 (99.7)	1220 (98.4)

Source: P203, Table 1.1, Table 14.1.1.1.5.4
a. Only one discontinuation due to AE included in disposition analysis due to coding. One additional discontinuation due to AE noted in analysis for unsolicited AEs leading to study discontinuation.
b. The Safety Set consists of all randomized participants who received any dose.
c. The Solicited Safety Set consists of all participants who were randomized and received any dose and contributed any solicited AR data (i.e., had at least 1 postbaseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.

Follow-up duration for participants 12 through 17 years of age

Participants 12-17 years of age began enrollment into Study P203 on December 9, 2020. As of the initial May 8, 2021, data cutoff, a total of 3,726 adolescents (2,486 in the mRNA-1273 group and 1,240 in the placebo group) were enrolled and contributed to the safety population (Table 6). The median follow-up time after Dose 2 was 53 days and similar between the mRNA-1273 and placebo groups. A total of 1,087 mRNA-1273 recipients (801 of whom were 12-15 years of age and 286 of whom were 16-17 years of age) had ≥2 months of blinded follow-up after Dose 2. There was a higher percentage of participants in the mRNA-1273 group with ≥2 months of follow-up post Dose 2 (43.7%) as compared with the placebo group (38.2%). This difference was driven by the 16 to 17-year-old age group, in which many placebo recipients withdrew from the study due to eligibility to obtain an alternative COVID-19 vaccine under EUA.

Table 6. Follow-Up Duration, Participants 12 Through 17 Years of Age, Safety Set, May 8, 2021, Data Cutoff

Length of Follow-Up	mRNA-1273 100 µg N=2486	Placebo N=1240	Total N=3726
Blinded follow-up			
≥28 days post-Dose 2, n (%)	2452 (98.6%)	1173 (94.6%)	3625 (97.3%)
≥56 days post-Dose 2, n (%)	1087 (43.7%)	474 (38.2%)	1561 (41.9%)
Median follow-up post-Dose 2, days (min, max)	53 (0, 121)	51 (0, 121)	53 (0, 121)

Source: P203, Table 1.4

A later data cutoff, of January 31, 2022, was used to provide longer-term safety follow-up from the ongoing trial. This follow-up included blinded data collection through May 31, 2021, and open-label data collection (as a result of unblinding and crossover of original placebo recipients) through January 31, 2022. The median duration of blinded follow-up was 136 days post Dose 2 for mRNA-1273 recipients and 78 days post Dose 2 for placebo recipients. For participants in the original mRNA-1273 group, the median total duration of follow-up including both blinded and open-label phases was 312 days post Dose 2. In this group, 2,376 participants (95.6%) were followed for at least 6 months since Dose 2.

4.3.3 Demographics and Other Baseline Characteristics

The PP Immunogenicity Subset, which contributed to the co-primary endpoints for the study, consisted of 340 vaccinated adolescent participants from Study P203 and 305 vaccinated younger adult participants from Study P301 (Table 7). In the adolescent population, 29.7% were 16-17 years of age and 70.3% were 12-15 years of age. Compared to the younger adult population, the adolescent population in the immunogenicity subset was less racially and ethnically diverse and had a lower percentage of participants who were obese at baseline.

Table 7. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age (Study P203) and 18 Through 25 Years of Age (Study P301), Per-Protocol Immunogenicity Subset

Characteristic	12-17 Years mRNA-1273 100 µg N=340	18-25 Years mRNA-1273 100 µg N=305
Sex, n (%)	--	--
Female	162 (47.6)	157 (51.5)
Male	178 (52.4)	148 (48.5)
Age	--	--
12 to <16 years, n (%)	239 (70.3)	--
16 to <18 years, n (%)	101 (29.7)	--
Median age, years	14	23
Race, n (%)	--	--
American Indian or Alaska Native	0	3 (1.0)
Asian	15 (4.4)	30 (9.8)
Black or African American	4 (1.2)	34 (11.1)
Native Hawaiian or Other Pacific Islander	--	2 (0.7)
White	285 (83.8)	211 (69.2)
Other	7 (2.1)	8 (2.6)
Multiracial	19 (5.6)	14 (4.6)
Not reported	6 (1.8)	3 (1.0)
Unknown	4 (1.2)	0

Characteristic	12-17 Years mRNA-1273 100 µg N=340	18-25 Years mRNA-1273 100 µg N=305
Ethnicity, n (%)	--	--
Hispanic or Latino	26 (7.6)	81 (26.6)
Not Hispanic or Latino	304 (89.4)	222 (72.8)
Not reported	9 (2.6)	0
Unknown	1 (0.3)	2 (0.7)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	267 (78.5)	147 (48.2)
Communities of Color	69 (20.3)	158 (51.8)
Missing	4 (1.2)	0
Body Mass Index, n (%)	--	--
<30 kg/m^2	316 (92.9)	233 (76.4)
≥30 kg/m^2	24 (7.1)	71 (23.3)

Source: P203, Table 1.3.2
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.

The demographic characteristics of the PP Set for Efficacy in participants 12-17 years of age (N=2,139 vaccine group, N=1,042 placebo group) are similar to the baseline characteristics of safety population (Table 8). Demographic characteristics were similar between the mRNA-1273 and placebo groups.

Table 8. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age (Study P203), Safety Set

Characteristic	mRNA-1273 100 µg N=2486	Placebo N=1240
Sex, n (%)	--	--
Female	1203 (48.4)	608 (49.0)
Male	1283 (51.6)	632 (51.0)
Age, n (%)	--	--
12 to <16 years	1838 (73.9)	929 (74.9)
16 to <18 years	648 (26.1)	311 (25.1)
Median age, years	14	14
Race, n (%)	--	--
American Indian or Alaska Native	12 (0.5)	7 (0.6)
Asian	142 (5.7)	79 (6.4)
Black or African American	83 (3.3)	42 (3.4)
Native Hawaiian or Other Pacific Islander	2 (<0.1)	0
White	2085 (83.9)	1041 (84.0)
Other	27 (1.1)	9 (0.9)
Multiracial	118 (4.7)	50 (4.0)
Not reported	11 (0.4)	11 (0.9)
Unknown	6 (0.2)	1 (<0.1)
Ethnicity, n (%)	--	--
Hispanic or Latino	280 (11.3)	152 (12.3)
Not Hispanic or Latino	2188 (88.0)	1076 (86.8)
Not reported	17 (0.7)	10 (0.8)
Unknown	1 (<0.1)	2 (0.2)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	1857 (74.7)	912 (73.5)
Communities of Color	625 (25.1)	325 (26.2)
Missing	4 (0.2)	3 (0.2)

Characteristic	mRNA-1273 100 µg N=2486	Placebo N=1240
Body Mass Index, n (%)	--	--
<30 kg/m^2	2316 (93.2)	1146 (92.4)
≥30 kg/m^2	170 (6.8)	94 (7.6)
Missing BMI	0	0
Positive baseline SARS-CoV-2 status[b], n (%)	147 (5.9)	69 (5.6)
Negative baseline SARS-CoV-2 status[c], n (%)	2167 (87.2)	1075 (86.7)
Missing baseline SARS-CoV-2 status, n (%)	172 (6.9)	96 (7.7)

Source: P203, Table 1.3, 14.1.3.2.4
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. 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.
c. Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.

4.3.4 Vaccine Effectiveness

Immunogenicity
Vaccine effectiveness in the adolescent population was inferred through immunobridging to the young adult data in Study P301 using the co-primary endpoints of GMT ratio and difference in SRRs at 28 days post-Dose 2.

Results for the co-primary endpoint of GMT ratio (adolescents to young adults) are displayed in Table 9, below. GMTs were measured by PsVNA assay (see Section 4.3.1 for further details on assay) at one month after Dose 2 (Day 57) in subjects in the immunogenicity subset. The GMT ratio was 1.1 (95% CI 0.9, 1.2) which met the pre-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >0.8.

Table 9. Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 12 Through 17 Years of Age, Study P203, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

12-17 Years 100 µg GMT (95% CI) N1=340	18-25 Years 100 µg GMT (95% CI) N1=296	GMT Ratio (12-17 Years/18-25 Years) (95% CI)	Met Success Criterion[a]
1401.7 (1276.3,1539.4)	1301.3 (1177.0, 1438.8)	1.1 (0.9, 1.2)	Yes

Source: P203, Table 2.1.1.3.1
N1=number of participants with non-missing data at baseline and the corresponding timepoint.
Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available. The ULOQ for selected P301 participants tested previously was different. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 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.
a. Co-primary endpoint 1: GMT at Day 57. Success criteria: the lower bound of the 95% CI of the GMT ratio rules out 0.67 (lower bound >0.67) using a noninferiority margin of 0.67, and the GMR point estimate >0.8.

Results for the co-primary endpoint of difference in SRRs between adolescents and young adults are displayed in Table 10, below. The difference in SRRs was 0.2% (95% CI -1.8, 2.4) which met the pre-specified success criterion of a LL of the 95% CI greater than -10% and a SRR difference point estimate of -5%.

Post-hoc analyses: conventional seroresponse ≥4-fold rise definition
In the study protocol, seroresponse at the participant level was defined as a change in ID50 titer ≥LLOQ if the baseline titer was <LLOQ, or ≥3.3-fold rise in titer from baseline, if the baseline titer was ≥LLOQ. During review of this amendment, CBER raised concerns that the Sponsor's

seroresponse definition may not be sufficient to demonstrate vaccine effect. For instance, a change to ≥LLOQ from <LLOQ may simply result from assay variability, while a ≥3.3-fold rise in titer from baseline may only rule out differences due to assay variability and not necessarily indicate a meaningful immunologic response to vaccination. The proportion of participants who achieved seroresponse was re-analyzed based on a more conventional seroresponse definition that included a ≥4-fold rise in titer from baseline; if the baseline titer was <LLOQ, then it was set to LLOQ for the analysis. Use of the conventional seroresponse definition that included a ≥4-fold rise, did not change the number of responders in each group, the overall results, nor the corresponding 95% CI. In the P203 immunogenicity subset, there were 4 adolescents who failed to meet the seroresponse definition because all 4 had baseline and post-vaccination ID50 titers <LLOQ.

Table 10. Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 12 Through 17 Years of Age, Study P203, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

12-17 Years 100 µg Seroresponse[a] n (%) (95% CI)[b] N1=340	18-25 Years 100 µg Seroresponse[a] n (%) (95% CI)[b] N1=296	Difference in Seroresponse Rate% ([12-17y]−[18-25y]) (95% CI)[c]	Met Success Criterion?[d]
336 (98.8) (97.0, 99.7)	292 (98.6) (96.6, 99.6)	0.2 (-1.8, 2.4)	Yes

Source: P203, Table 2.1.2.3.1, 2.1.2.3.6
N1=number of participants with non-missing data at baseline and the corresponding timepoint.
a. Seroresponse due to vaccination-specific pseudovirus neutralizing antibody ID50 titer at a participant level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ. The numbers and percentages remain unchanged when using the seroresponse definition of at least 4-fold rise from baseline, where baseline titers <LLOQ are set to LLOQ for the analysis. Percentages are based on N1
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
d. Co-primary endpoint 2: Seroresponse rate at Day 57. Success criteria: the lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e., lower bound >−10%) using a noninferiority margin of 10%, and the seroresponse rate difference point estimate >−5%

The GMTs and SRRs for SARS CoV-2 neutralizing titers at Day 57 were similar between adolescents and young adults, and did not vary by demographic subgroup, though the small number of participants in some subgroups resulted in wide CIs and limit the interpretation of the results. In the small number of participants who had positive SARS-CoV-2 status at baseline, there was a more robust immune response observed Day 57 compared to participants who were seronegative at baseline.

Table 11. Subgroup Analyses of Co-Primary Immunogenicity Endpoints of Geometric Mean SARS-CoV-2 Neutralizing Titers and Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 12 Through 17 Years of Age, Study P203, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

Characteristic	12-17 Years mRNA-1273 100 µg GMT (95% CI) P203	18-25 Years mRNA-1273 100 µg GMT (95% CI) P301	GMT Ratio (95% CI) P203 vs P301	12-17 Years mRNA-1273 100 µg Seroresponse[e] n (%) (95% CI[f]) P203	18-25 Years mRNA-1273 100 µg Seroresponse[e] n (%) (95% CI[f]) P301	Difference in Seroresponse Rates % (95% CI[g]) P203 vs P301
Age						
12-15 years	n=239 1391.0 (1243.8, 1555.6)	n=296 1301.3 (1176.9, 1438.9)	**1.1** **(0.9, 1.2)**	N1=239 235 (98.3) (95.8, 99.5)	N1=296 292 (98.6) (96.6, 99.6)	**-0.3** **(-3.0, 2.0)**
16-17 years	n=101 1427.3 (1201.7, 1695.3)	n=296 1301.3 (1176.9, 1438.9)	**1.1** **(0.9, 1.3)**	N1=101 101 (100) (96.4, 100.0)	N1=296 292 (98.6) (96.6, 99.6)	**1.4** **(-2.3, 3.4)**
Sex						
Male	n=178 1493.5 (1321.5, 1687.8)	n=143 1352.3 (1179.8, 1550.0)	**1.1** **(0.9, 1.3)**	N1=178 177 (99.4) (96.9, 100.0)	N1=143 141 (98.6) (95.0, 99.8)	**0.8** **(-1.9, 4.5)**
Female	n=162 1307.31 (1132.6, 1508.9)	n=153 1255.4 (1083.1, 1455.0)	**1.0** **(0.8, 1.3)**	N1=162 159 (98.1) (94.7, 99.6)	N1=153 151 (98.7) (95.4, 99.8)	**-0.5** **(-4.2, 3.0)**
Race						
Black or African American	n=4 1159.6 (463.3, 2902.2)	n=29 1479.0 (1052.0, 2079.4)	**0.8** **(0.3, 2.1)**	N1=4 4 (100) (39.8, 100.0)	N1=29 29 (100) (88.1, 100.0)	**0** **(NA, NA)**
White	n=285 1385.2 (1248.3, 1537.1)	n=207 1314.6 (1163.5, 1485.3)	**1.1** **(0.9, 1.2)**	N1=285 281 (98.6) (96.4, 99.6)	N1=207 204 (98.6) (95.8, 99.7)	**0.0** **(-2.3, 2.9)**
Other	n=51 1519.6 (1212.0, 1905.3)	n=60 1181.1 (958.8, 1455.0)	**1.3** **(0.9, 1.8)**	N1=51 51 (100) (93.0, 100.0)	N1=60 59 (98.3) (91.1, 100.0)	**1.7** **(-5.5, 8.9)**
Ethnicity						
Hispanic or Latino	n=26 1260.2 (899.1, 1766.4)	n=79 1505.9 (1240.7, 1827.7)	**0.8** **(0.6, 1.2)**	N1=26 25 (96.2) (80.4, 99.9)	N1=79 78 (98.7) (93.1, 100.0)	**-2.6** **(-17.8, 3.7)**
Not Hispanic or Latino	n=304 1422.5 (1287.1, 1572.1)	n=215 1235.1 (1096.7, 1391.0)	**1.2** **(1.0, 1.3)**	N1=304 301 (99.0) (97.1, 99.8)	N1=215 212 (98.6) (96.0, 99.7)	**0.4** **(-1.7, 3.1)**

Characteristic	12-17 Years mRNA-1273 100 µg GMT (95% CI) P203	18-25 Years mRNA-1273 100 µg GMT (95% CI) P301	GMT Ratio (95% CI) P203 vs P301	12-17 Years mRNA-1273 100 µg Seroresponse[e] n (%) (95% CI[f]) P203	18-25 Years mRNA-1273 100 µg Seroresponse[e] n (%) (95% CI[f]) P301	Difference in Seroresponse Rates % (95% CI[g]) P203 vs P301
Race and Ethnicity[a]						
White non-Hispanic	n=267 1415.5 (1271.8, 1575.5)	n=145 1220.1 (1055.1, 1410.8)	**1.1** **(1.0, 1.4)**	N1=267 264 (98.9) (96.8, 99.8)	N1=145 143 (98.6) (95.1, 99.8)	**0.3** **(-2.1, 3.9)**
Communities of Color	n=69 1350.5 (1099.5, 1658.7)	n=151 1384.4 (1204.8, 1590.9)	**1.0** **(0.8, 1.3)**	N1=69 68 (98.6) (92.2, 100.0)	N1=151 149 (98.7) (95.3, 99.8)	**-0.1** **(-6.5, 3.5)**
High risk conditions						
Body Mass Index: <30 kg/m^2	n=316 1378.5 (1263.9, 1503.5)	n=227 1221.8 (1102.9, 1353.6)	**1.1** **(1.0, 1.3)**	N1=316 313 (99.1) (97.3, 99.8)	N1=227 225 (99.1) (96.9, 99.9)	**-0.1** **(-2.0, 2.3)**
Body Mass Index: ≥30 kg/m^2	n=24 1745.9 (1032.4, 2952.5)	n=68 1622.0 (1187.1, 2216.1)	**1.1** **(0.6, 2.0)**	N1=24 23 (95.8) (78.9, 99.9)	N1=68 66 (97.1) (89.8, 99.6)	**-1.2** **(-17.6, 6.9)**
Baseline SARS-CoV-2 status						
Baseline SARS-CoV-2 positive[b,c]	n=27 2866.6 (1690.3, 4861.4)	n=15 1216.2 (596.0, 2481.9)	**2.4** **(1.0, 5.8)**	N1=27 27 (100) (87.2, 100.0)	N1=15 13 (86.7) (59.5, 98.3)	**13.3** **(-0.5, 38.2)**
Baseline SARS-CoV-2 negative[b,d]	n=347 1413.1 (1284.9, 1554.2)	n=300 1263.3 (1140.5, 1399.5)	**1.1** **(1.0, 1.3)**	N1=347 343 (98.8) (97.1, 99.7)	N1=300 296 (98.7) (96.6, 99.6)	**0.2** **(-1.8, 2.4)**

Source: P203, Table 2.1.1.3.2, Table 2.1.1.3.3, Table 2.1.1.3.4, Table 2.1.2.3.2, Table 2.1.2.3.3, Table 2.1.2.3.4
n=number of participants with non-missing data at the corresponding timepoint.
N1=number of participants with non-missing data at baseline and the corresponding timepoint.
Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available. The ULOQ for selected P301 participants tested previously was different. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 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.
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. Results by baseline SARS-CoV-2 status were based on the Immunogenicity Subset, which included for 12-17 years N=374 and for 18-25 years N=340. Total Ns include participants for whom baseline SARS-CoV-2 status are missing.
c. 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.
d. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
e. Seroresponse due to vaccination specific to pseudovirus neutralizing antibody ID50 titer at a participant level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
f. 95% CI is calculated using the Clopper-Pearson method.
g. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Clinical efficacy

VE was descriptively analyzed as a secondary endpoint in the study, with the data cutoff date of May 8, 2021. The study evaluated the first occurrence of symptomatic COVID-19 in participants without evidence of previous SARS-CoV-2 at baseline, using two different case definitions—the P301 COVID-19 definition (same definition as used in the adult efficacy study) and the broader CDC case definition. In participants 12-17 years, the observed VE against the P301-defined COVID-19 starting 14 days after Dose 2 was 100% (95% CI 28.9, non-evaluable), with 4 cases in the placebo arm and no cases in the vaccine arm. Using the CDC case definition, the observed VE was 93.3% (95% CI 47.9, 99.9) with 7 cases in the placebo arm and 1 case in the vaccine arm. These results appear to be consistent with the VE observed from the adult efficacy study (P301); however, the small number of COVID-19 cases, especially using the P301 definition, resulted in large CIs.

During the time period in which COVID-19 cases were accrued in the study, the ancestral strain (with D614G mutation), and then the Alpha variant were the predominant circulating SARS-CoV-2 strains in the US.

Table 12. Vaccine Efficacy, First Occurrence COVID-19 Starting 14 Days After Dose 2, Participants 12 Through 17 Years of Age, Study P203, Per-Protocol Set for Efficacy

Endpoint	mRNA-1273 100 µg N=2,139 Cases (%) Person-years[a] Incidence Rate per 1,000 person-years (95% CI)[b]	Placebo N=1,042 Cases (%) Person-years[a] Incidence Rate per 1,000 person-years (95% CI) [b]	Vaccine Efficacy (95% CI)[c]
P301 definition	0 516.0 0 (NE, 7.1)	4 (0.4) 242.1 16.5 (4.5, 42.3)	100.0% (28.9, NE)
CDC definition	1 (<0.1) 515.7 1.9 (0, 10.8)	7 (0.7) 241.5 29.0 (11.7, 59.7)	93.3% (47.9, 99.9)

Source: P203, Table 2.7.1.1, 2.8.1.1
Abbreviation: NE=non-evaluable.
a. Person-years is defined as the total years from randomization date to the first date of COVID-19, last date of study participation, efficayc data cutoff/extraction date, or unblinding point, whichever is earlier
b. Incidence rate is defined as the number of subjects with an event divided by the number of subjects 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. Vaccine efficacy (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.

For additional discussion of clinical efficacy below, the broader CDC definition of COVID-19 will be used instead of the P301 definition to increase the number of cases and the precision of the estimate.

Subgroup analyses of vaccine efficacy

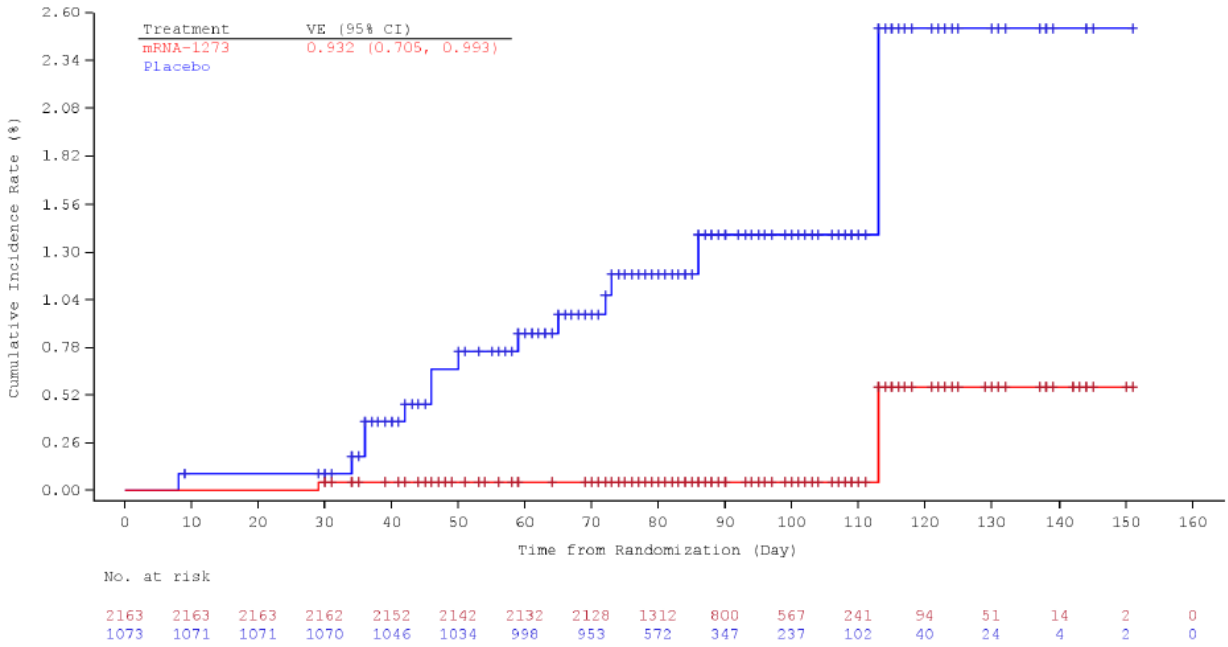
Vaccine efficacy by subgroup was not evaluated given the small number of cases in both arms. The majority of COVID-19 cases occurred in participants who identified as White and non-Hispanic and non-obese, reflective of the overall study population. There were no cases of COVID-19, by either case definition, in subjects who were SARS-CoV-2 seropositive at baseline.

Cumulative incidence curves

The cumulative incidence curve for COVID-19 based on the CDC case definition starting after randomization (same day as Dose 1), in the mITT1 set (Figure 1), shows that cases of COVID-

19 remained similarly low in both the mRNA-1273 and placebo groups until approximately 7 days after Dose 2, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the mRNA-1273 group.

Figure 1. Cumulative Incidence Curves (Vaccine vs Placebo) for COVID-19 (CDC Case Definition) Starting After Randomization, Participants 12 Through 17 Years of Age, Study P203, mITT1 Set



Source: P203, Figure 2.2.1.2

Severe COVID-19 cases

There were no reports of severe COVID-19 cases in participants 12-17 years of age.

Additional efficacy analyses

Additional analyses of the efficacy endpoint were conducted to evaluate VE against COVID-19, based on the CDC case definition, by time period (Table 13). VE for the prevention of COVID-19 starting any time after Dose 1 was 93.2% (95% CI 70.5, 99.3). Although these data suggest some protection against COVID-19 following one dose, very few cases occurred between Dose 1 and Dose 2, and the follow-up time after one dose was limited in study participants. These data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 13. COVID-19 Cases (CDC Case Definition) From Randomization by Time Period, Participants 12 Through 17 Years of Age, Study P203, mITT1 Set

First COVID-19[d] Occurrence	mRNA-1273 100 µg Cases /N Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo Cases /N Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	VE[c] (95% CI)
Any time after (≥) Dose 1	2/2163 522.4 3.8 (0.5, 13.8)	14/1073 247.7 56.5 (30.9, 94.8)	93.2% (70.5, 99.3)
Any time after (≥) Dose 1 to before (<) Dose 2	0/2163 179.3 0.0 (NE, 20.6)	2/1073 89.6 22.3 (2.7, 80.6)	100% (-166.2, NE)
Any time after (≥) Dose 2	2/2160 521.9 3.8 (0.5, 13.8)	12/1058 246.0 48.8 (25.2, 85.2)	92.1% (64.7, 99.1)

Source: P203, Table 2.8.3.1, adolescent-cber-tables-12-17-yr.docx, Table 16, P203 dataset
a. Person-years is defined as the total years from randomization date to the first date of secondary definition of COVID-19, the last date of study participation, efficacy data cutoff/extraction date, or unblinding point within the respective time period, whichever is earlier.
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. Vaccine efficacy is 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.
d. COVID-19 (secondary case definition) is at least 1 symptom from a pre-specified list of COVID-19 symptoms derived from the CDC case definition (systemic symptoms: fever [temperature >38ºC/≥100.4ºF] or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea) and a positive nasopharyngeal swab or saliva sample for SARS-CoV-2 by RT-PCR.

SARS-CoV-2 infection, regardless of symptoms

Efficacy was also evaluated against SARS-CoV-2 infection, regardless of symptoms, which includes both COVID-19 cases as well as cases of asymptomatic infection. Asymptomatic SARS-CoV-2 infection is defined as absence of COVID-19 symptoms and either of the following: (a) bAb levels against SARS-CoV-2 nucleocapsid (N) protein (as measured by *Roche Elecsys*) negative at Day 1 and becoming positive starting at Day 57 or later or (b) positive RT-PCR test at scheduled or unscheduled/illness visits. Per protocol, all participants in Study P203 had scheduled assessment of N-serology and RT-PCR testing at the Day 57 visit. Nasal swabs for RT-PCR were also collected from all study subjects at the Day 29 visit, prior to administration of Dose 2. A majority of the study subjects (93.1% of mRNA-1273 recipients and 89.2% of placebo recipients) had Day 57 N-serology results available at the time of the data cutoff for this analysis. Given the limited number of assessment timepoints for RT-PCR and N-serology, it is likely that not all asymptomatic SARS-CoV-2 cases were captured by this analysis.

As shown in Table 14 below, VE against SARS-CoV-2 infections, regardless of symptoms, was primarily driven by the larger number of asymptomatic cases compared to COVID-19 cases in the study. Interpretation of these results are limited by the imprecision around the point estimate, as indicated by the wide CIs, especially for the asymptomatic infection endpoint. It is also important to note that these analyses include limited follow-up time during a period when Alpha was the predominant SARS-CoV-2 strain.

Table 14. Incidence of SARS-CoV-2 Infection Starting 14 Days after Dose 2, Participants 12-17 Years of Age, Per-Protocol Set for Efficacy

Infection	mRNA-1273 100 µg N=2139 Cases (%) Person-Years Incidence Rate per 1,000 Person-Years (95% CI)	Placebo N=1042 Cases (%) Person-Years Incidence Rate per 1,000 Person-Years (95% CI)	VE[a] (95% CI)
SARS-CoV-2 infection, regardless of symptom	22 (1.0) 513.3 42.9 (26.9, 64.9)	23 (2.2) 238.0 96.6 (61.3, 145.0)	55.7% (16.8, 76.4)
Asymptomatic SARS-CoV-2 infection	21 (1.0) 513.3 40.9 (25.3, 62.5)	16 (1.5) 238.0 67.2 (38.4, 109.2)	39.2% (-24.7, 69.7)

Source: P203, Table 2.5.1.1, Table 2.6.1.1
a. Vaccine efficacy is 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.

4.3.5 Safety

Overview of adverse events

Safety analyses presented immediately below are derived from blinded period safety data available through the cutoff date of May 8, 2021. Additional safety analyses from longer-term safety follow-up, which included unblinded follow-up through the cutoff date of January 31, 2022, are presented in Section 4.3.6.

Overall, the proportions of MAAEs and SAEs were balanced between vaccine and placebo groups. SAEs were uncommon and no deaths were. The rate of unsolicited AEs, including related unsolicited AEs, was higher in the vaccine group compared to the placebo group. As compared to the placebo group, a greater percentage of adolescent participants in the vaccine group experienced local and systemic solicited adverse reactions (ARs).

Table 15 below summarizes AEs in the safety population.

Table 15. Number and Percentage of Participants Reporting at Least One Safety Event, Participants 12 Through 17 Years of Age, Study P203, Safety Set, Solicited Safety Set, Solicited Safety Set

Event Type	mRNA-1273 100 µg n/N1 (%)	Placebo n/N1 (%)
Solicited adverse reactions	--	--
Immediate[a] unsolicited adverse events after vaccination (any dose)	6/2486 (0.2)	5/1240 (0.4)
Dose 1	3/2486 (0.1)	4/1240 (0.3)
Dose 2	3/2480 (0.1)	1/1222 (<0.1)
Solicited local adverse reaction within 7 days	2431/2485 (97.8)	602/1240 (48.5)
Dose 1	2339/2482 (94.2)	455/1238 (36.8)
Dose 2	2314/2478 (93.4)	398/1220 (32.6)
Grade 3 or 4 solicited local adverse reaction (any dose)	344/2485 (13.8)	4/1240 (0.3)
Solicited systemic adverse reaction within 7 days	2284/2485 (91.9)	830/1240 (66.9)
Dose 1	1701/2482 (68.5)	687/1238 (55.5)
Dose 2	2134/2478 (86.1)	561/1220 (46.0)
Grade 3 or 4 systemic adverse reaction (any dose)	414/2485 (16.7)	58/1240 (4.7)

Event Type	mRNA-1273 100 µg n/N1 (%)	Placebo n/N1 (%)
Unsolicited adverse events	n/N (%)	n/N (%)
Unsolicited adverse event up to 28 days after any injection	510/2486 (20.5)	197/1240 (15.9)
Non-serious unsolicited adverse event	509/2486 (20.5)	196/1240 (15.8)
Related non-serious unsolicited AE	312/2486 (12.6)	72/1240 (5.8)
Severe non-serious unsolicited AE	11/2486 (0.4)	1/1240 (<0.1)
Related severe non-serious unsolicited AE	9/2486 (0.4)	1/1240 (<0.1)
Medically attended adverse events[b]	203/2486 (8.2)	104/1240 (8.4)
Related MAAE	20/2486 (0.8)	6/1240 (0.5)
SAE[b]	6/2486 (0.2)	2/1240 (0.2)
Related SAE	0	0
AESI (MIS-C)[b]	0	0
Deaths[b]	0	0
AE leading to study discontinuation	1	0

Source: P203, Tables 3.1.1.1, 3.1.1.2, 3.1.1.3, 3.2.1.1, 3.2.12.1, Listings 3.4, 4
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; MIS-C=multisystem inflammatory syndrome in children; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
a. Participants were observed for 60 minutes following vaccination.
b. Through data cutoff: May 8, 2021, or the unblinding date, whichever came first.
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

Immediate adverse events
Immediate unsolicited events occurring within 60 minutes of vaccination were infrequent and occurred in 0.2% of mRNA-1273 recipients and 0.4% of placebo recipients. All events were grade 1 or 2. There were no reports of anaphylaxis or syncope immediately following vaccination.

Solicited adverse reactions
Solicited local and systemic ARs with onset within 7 days after vaccination are presented in the tables below. Solicited ARs were recorded daily by study participants using e-diaries and included the assessment of local injection site reactions (pain, erythema, swelling and axillary swelling/tenderness) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting and chills). By order of frequency, adverse reactions in participants 12 through 17 years of age following administration of any dose of mRNA-1273 were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%), chills (49.1%), arthralgia (34.6%), axillary swelling/tenderness (34.6%), nausea/vomiting (29.3%), swelling at the injection site (27.7%), erythema at the injection site (25.8%), and fever (13.7%).

Solicited local reactions
Solicited local ARs were reported at higher rates in mRNA-1273 recipients than placebo recipients. The overall rates of local adverse reactions were similar after Dose 1 and Dose 2; however, erythema and swelling were reported more frequently following Dose 2. Injection site pain was the most frequent solicited local adverse reaction in mRNA-1273 recipients of both age groups after any dose. Injection site reactions following any dose were mostly grade 1 or grade 2. Grade 3 or higher local adverse reactions were reported by 13.8% of mRNA-1273 recipients.

Table 16 below provides rates of local ARs by treatment group.

Table 16. Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, Participants 12 Through 17 Years of Age, Study P203, Solicited Safety Set

Event	mRNA-1273 100 µg N=2482 Dose 1 n (%)	Placebo N=1238 Dose 1 n (%)	mRNA-1273 100 µg N=2478 Dose 2 n (%)	Placebo N=1220 Dose 2 n (%)
Local adverse reaction	N1=2482	N1=1238	N1=2478	N1=1220
Any	2339 (94.2)	455 (36.8)	2314 (93.4)	398 (32.6)
Grade 3	170 (6.8)	1 (<0.1)	220 (8.9)	3 (0.2)
Pain[a]	N1=2482	N1=1238	N1=2478	N1=1220
Any	2310 (93.1)	431 (34.8)	2290 (92.4)	370 (30.3)
Grade 3	133 (5.4)	1 (<0.1)	126 (5.1)	3 (0.2)
Erythema (redness)[b]	N1=2482	N1=1238	N1=2478	N1=1220
Any ≥25 mm	334 (13.5)	8 (0.6)	484 (19.5)	11 (0.9)
Grade 3	21 (0.8)	0	72 (2.9)	0
Swelling (hardness)[b]	N1=2482	N1=1238	N1=2478	N1=1220
Any ≥25 mm	403 (16.2)	12 (1.0)	509 (20.5)	12 (1.0)
Grade 3	27 (1.1)	0	56 (2.3)	0
Axillary swelling or tenderness[c,d]	N1=2481	N1=1238	N1=2477	N1=1220
Any	578 (23.3)	101 (8.2)	519 (21.0)	61 (5.0)
Grade 3	10 (0.4)	0	7 (0.3)	0

Source: P203, Tables 3.1.1.1, 3.1.1.2
Abbreviation: AR=adverse reaction.
Notes: Any=Grade 1 or higher. The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.
a. Pain Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.
b. Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis.
c. Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4:requires emergency room visit or hospitalization.
d. Axillary swelling or tenderness: For this event, N1 (number of exposed participants who submitted any data for the event) differed from the N who received mRNA-1273 Dose 1 (N1=2481) and Dose 2 (N1=2477).
No grade 4 solicited local adverse reactions were reported.

Solicited systemic adverse reactions

Solicited systemic ARs were reported at higher rates in mRNA-1273 recipients than placebo recipients. Systemic ARs occurred more frequently after Dose 2 compared to Dose 1. Headache and fatigue were the most frequent solicited systemic adverse reactions in vaccine recipients after any dose. Systemic ARs following any dose were mostly grade 1 or grade 2. Table 17 below provides rates of systemic ARs by treatment group.

Among vaccine recipients, the median day of onset was Day 2 for systemic reactogenicity with the exception of fatigue for which the median onset was Day 1. The overall median duration of systemic reactogenicity was 2 days. A greater percentage of participants reported that symptoms persisted after Day 7 following Dose 1 compared with Dose 2.

Table 17. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 17 Years of Age, Study P203, Solicited Safety Set

Event	mRNA-1273 100 µg N=2482 Dose 1 n (%)	Placebo N=1238 Dose 1 n (%)	mRNA-1273 100 µg N=2478 Dose 2 n (%)	Placebo N=1220 Dose 2 n (%)
Any systemic adverse reaction	N1=2482	N1=1238	N1=2478	N1=1220
Any	1701 (68.5)	687 (55.5)	2134 (86.1)	561 (46.0)
Grade 3	108 (4.4)	36 (2.9)	340 (13.7)	25 (2.0)
Grade 4	0	0	3 (0.1)	1 (<0.1)
Fever[a]	N1=2480	N1=1238	N1=2477	N1=1219
≥38.0°C	63 (2.5)	12 (1.0)	302 (12.2)	12 (1.0)
38.0°C to 38.4°C	36 (1.5)	9 (0.7)	162 (6.5)	6 (0.5)
38.5°C to 38.9°C	18 (0.7)	2 (0.2)	93 (3.8)	4 (0.3)
39°C to 40.0°C	9 (0.4)	1 (<0.1)	46 (1.9)	1 (<0.1)
>40.0°C	0	0	1 (<0.1)	1 (<0.1)
Headache[b]	N1=2480	N1=1238	N1=2478	N1=1220
Any	1106 (44.6)	477 (38.5)	1739 (70.2)	370 (30.3)
Grade 3	56 (2.3)	17 (1.4)	112 (4.5)	14 (1.1)
Grade 4	0	0	1 (<0.1)	0
Fatigue[c]	N1=2481	N1=1238	N1=2478	N1=1220
Any	1188 (47.9)	453 (36.6)	1679 (67.8)	353 (28.9)
Grade 3	33 (1.3)	18 (1.5)	188 (7.6)	10 (0.8)
Grade 4	0	0	0	0
Myalgia[c]	N1=2480	N1=1238	N1=2477	N1=1220
Any	668 (26.9)	205 (16.6)	1154 (46.6)	153 (12.5)
Grade 3	24 (1.0)	10 (0.8)	129 (5.2)	3 (0.2)
Grade 4	0	0	0	0
Arthralgia[c]	N1=2480	N1=1238	N1=2477	N1=1220
Any	371 (15.0)	143 (11.6)	716 (28.9)	113 (9.3)
Grade 3	15 (0.6)	5 (0.4)	57 (2.3)	2 (0.2)
Grade 4	0	0	0	0
Nausea/vomiting[d]	N1=2480	N1=1238	N1=2477	N1=1220
Any	281 (11.3)	110 (8.9)	591 (23.9)	106 (8.7)
Grade 3	2 (<0.1)	0	2 (<0.1)	0
Grade 4	0	0	1 (<0.1)	0
Chills[e]	N1=2480	N1=1238	N1=2477	N1=1220
Any	456 (18.4)	138 (11.1)	1066 (43.0)	97 (8.0)
Grade 3	4 (0.2)	1 (<0.1)	11 (0.4)	0
Grade 4	0	0	0	0
Use of antipyretic or pain medication	N1=2482	N1=1238	N1=2478	N1=1220
Any	748 (30.1)	118 (9.5)	1242 (50.1)	108 (8.9)

Source: P203, Tables 3.1.1.1, 3.1.1.2
Note: Any = grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received at least one dose of IP and contributed any solicited AR data (i.e., had at least 1 postbaseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) dose and contributed any solicited AR data from the time of the first (second) dose through the following 6 days. Medications were collected on the eDiary.
a. Fever is defined as: grade 1 = 38 to 38.4°C; grade 2 = 38.5 to 38.9°C; Grade 3 = 39 to 40°C; grade 4 = greater than 40°C.
b. Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; grade 4 requires emergency room visit or hospitalization.
c. Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; grade 4 requires emergency room visit or hospitalization.
d. Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; grade 4 requires emergency room visit or hospitalization for hypotensive shock.
e. Chills: Grade 3 prevents daily activity and requires medical intervention; grade 4 requires emergency room visit or hospitalization.

Duration of Local Adverse Reactions

Among vaccine recipients, the median day of onset of local reactogenicity was Day 1 and the median duration was 3 days. A greater percentage of participants reported that symptoms persisted after Day 7 following Dose 1 compared to following Dose 2.

Delayed solicited injection site reactions (beginning after Day 7) after any injection were reported by 0.9% of vaccine recipients compared to no placebo recipient. Delayed solicited local reactions, which also include axillary swelling or tenderness, were reported by 0.9% of vaccine recipients after Dose 1 compared to fewer than 0.1% following Dose 2. The most common delayed local reactions were erythema and swelling. Delayed solicited systemic reactions (beginning following Day 7 post-vaccination) were reported infrequently by vaccine recipients, with 0.6% of participants reporting a delayed systemic reaction following Dose 1 compared with 0.1% following Dose 2. The most common delayed systemic reactions were headache and fatigue.

Duration of Systemic Adverse Reactions

Among vaccine recipients, the median day of onset was Day 2 for systemic reactogenicity with the exception of fatigue for which the median onset was Day 1. The overall median duration of systemic reactogenicity was 2 days. A greater percentage of participants reported that symptoms persisted after Day 7 following Dose 1 compared with Dose 2.

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing mRNA-1273 and placebo groups by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the demographic subgroups, although some race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Solicited local and systemic reactions after vaccination among mRNA-1273 recipients by SARS-CoV-2 status at baseline are shown in Table 18. After Dose 1, the frequencies of solicited local ARs were similar between the two groups, except for axillary swelling or tenderness, which was higher among those with positive (39.5%) than with negative (22.5%) SARS-CoV2 status at baseline. Solicited systemic ARs after Dose 1 were more frequently reported among participants with positive than with negative SARS-CoV-2 status at baseline, most notably for the solicited ARs of fever (19.7% vs 1.5%), headache (70.1% vs 43.4%), fatigue (70.1% vs 46.4%), and chills (49.0% vs 16.8%). In general, the frequencies of solicited local and systemic adverse reactions after Dose 2 were similar or slightly lower in the baseline positive participants compared to baseline negative participants.

Table 18. Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose by Baseline SARS-CoV-2 Status, by Maximum Severity, mRNA-1273 Participants 12 Through 7 Years of Age, Study P203, Solicited Safety Set

Event	Baseline SARS-CoV-2 Negative N=2163 Dose 1 n (%)	Baseline SARS-CoV-2 Positive N=147 Dose 1 n (%)	Baseline SARS-CoV-2 Negative N=2162 Dose 2 n (%)	Baseline SARS-CoV-2 Positive N=146 Dose 2 n (%)
Any local adverse reaction	N1=2163	N1=147	N1=2162	N1=146
Any	2047 (94.6)	131 (89.1)	2029 (93.8)	125 (85.6)
Grade 3 or above	143 (6.6)	13 (8.8)	198 (9.2)	10 (6.8)
Pain at injection site	N1=2163	N1=147	N1=2162	N1=146
Any	2023 (93.5)	128 (87.1)	2006 (92.8)	124 (84.9)
Grade 3 or above	113 (5.2)	9 (6.1)	114 (5.3)	7 (4.8)
Erythema (redness)	N1=2163	N1=147	N1=2162	N1=146
Any ≥25mm	308 (14.2)	19 (12.9)	432 (20.0)	18 (12.3)
Grade 3 or above	19 (0.9)	1 (0.7)	62 (2.9)	3 (2.1)
Swelling (hardness)	N1=2163	N1=147	N1=2162	N1=146
Any ≥25mm	360 (16.6)	24 (16.3)	449 (20.8)	22 (15.1)
Grade 3 or above	21 (1.0)	4 (2.7)	50 (2.3)	2 (1.4)
Axillary swelling or tenderness	N1=2162	N1=147	N1=2161	N1=146
Any	487 (22.5)	58 (39.5)	465 (21.5)	25 (17.1)
Grade 3 or above	9 (0.4)	1 (0.7)	7 (0.3)	0
Any systemic adverse reaction	N1=2163	N1=147	N1=2162	N1=146
Any	1462 (67.6)	128 (87.1)	1866 (86.3)	122 (83.6)
Grade 3 or above	82 (3.8)	21 (14.3)	304 (14.1)	15 (10.3)
Fever	N1=2161	N1=147	N1=2161	N1=146
≥38.0°C	33 (1.5)	29 (19.7)	262 (12.1)	20 (13.7)
38.0°C to 38.4°C	20 (0.9)	16 (10.9)	136 (6.3)	13 (8.9)
38.5°C to 38.9°C	9 (0.4)	9 (6.1)	85 (3.9)	5 (3.4)
39°C to 40.0°C	4 (0.2)	4 (2.7)	40 (1.9)	2 (1.4)
>40.0°C	0	0	1 (<0.1)	0
Headache	N1=2161	N1=147	N1=2162	N1=146
Any	938 (43.4)	103 (70.1)	1527 (70.6)	90 (61.6)
Grade 3 or above	44 (2.0)	11 (7.5)	97 (4.5)	7 (4.8)
Fatigue	N1=2162	N1=147	N1=2162	N1=146
Any	1004 (46.4)	103 (70.1)	1470 (68.0)	94 (64.4)
Grade 3 or above	27 (1.2)	4 (2.7)	173 (8.0)	5 (3.4)
Myalgia	N1=2161	N1=147	N1=2161	N1=146
Any	557 (25.8)	63 (42.9)	1017 (47.1)	63 (43.2)
Grade 3 or above	19 (0.9)	3 (2.0)	117 (5.4)	2 (1.4)
Arthralgia	N1=2161	N1=147	N1=2161	N1=146
Any	305 (14.1)	36 (24.5)	633 (29.3)	39 (26.7)
Grade 3 or above	12 (0.6)	2 (1.4)	52 (2.4)	0
Nausea/vomiting	N1=2161	N1=147	N1=2161	N1=146
Any	237 (11.0)	30 (20.4)	522 (24.2)	29 (19.9)
Grade 3 or above	2 (<0.1)	0	2 (<0.1)	1 (0.7)

Event	Baseline SARS-CoV-2 Negative N=2163 Dose 1 n (%)	Baseline SARS-CoV-2 Positive N=147 Dose 1 n (%)	Baseline SARS-CoV-2 Negative N=2162 Dose 2 n (%)	Baseline SARS-CoV-2 Positive N=146 Dose 2 n (%)
Chills	N1=2161	N1=147	N1=2161	N1=146
Any	363 (16.8)	72 (49.0)	934 (43.2)	63 (43.2)
Grade 3 or above	4 (0.2)	0	10 (0.5)	0

Source: P203, Table 3.1.1.7, 3.1.1.8
Note: Any=Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 3=>100 mm. 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 3=prevents daily activity. Toxicity grade for headache, fatigue, myalgia, arthralgia is defined as Grade 1=no interference with activity, Grade 3=prevents daily activity; Toxicity grade for nausea/vomiting is defined as Grade 1=no interference with activity or 1-2 episodes/24 hours; Grade 3=prevents daily activity; Toxicity grade for chills is defined as Grade 1=no interference with activity; Grade 3=prevents daily activity and requires medical intervention

Unsolicited adverse events

Through the May 8, 2021, data cutoff for Study P203, 97.3% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 53 days after Dose 2.

Table 19 below shows rates of unsolicited AEs in the adolescent safety subset that occurred within 28 days of vaccination and at rates of ≥1% in any group. Overall, rates of unsolicited AEs, including events Grade 3 or higher, were slightly higher in vaccine recipients compared to placebo recipients. The proportions of participants with unsolicited AE were 20.5% and 15.9% in the vaccine and placebo groups, respectively. This observed difference was mostly driven by events classified under System Organ Class (SOC) *General disorders and administration site conditions*, the majority of which included injection site adverse reactions, consistent with the overall findings for local reactogenicity reported on the e-Diary by participants. By Preferred Term (PT), *Injection site lymphadenopathy* was most frequently reported unsolicited AE (4.3% of vaccine recipients vs 0.4% of placebo recipients) that was not a protocol-specified injection site reaction captured by the e-diary for this study.

Table 19. Unsolicited Adverse Events Occurring in ≥1% of Any Treatment Group Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Participants 12 Through 17 Years of Age, Study P203, Safety Set

Adverse Event	mRNA-1273 100 µg N=2486 Any	Placebo N=1240 Any	mRNA-1273 100 µg N=2486 Severe	Placebo N=1240 Severe
Unsolicited AEs (Any)	510 (20.5)	197 (15.9)	13 (0.5)	2 (0.2)
System Organ Class Preferred Term				
General disorders and administration site conditions	250 (10.1)	50 (4.0)	9 (0.4)	0
Injection site lymphadenopathy	108 (4.3)	5 (0.4)	1 (<0.1)	0
Fatigue	46 (1.9)	23 (1.9)	1 (<0.1)	0
Injection site erythema	48 (1.9)	3 (0.2)	6 (0.2)	0
Injection site induration	28 (1.1)	3 (0.2)	2 (0.1)	0
Injection site pain	28 (1.1)	8 (0.6)	0	0

Adverse Event	mRNA-1273 100 µg N=2486 Any	Placebo N=1240 Any	mRNA-1273 100 µg N=2486 Severe	Placebo N=1240 Severe
Infections and infestations	76 (3.1)	51 (4.1)	1 (<0.1)	0
COVID-19	5 (0.2)	13 (1.0)	0	0
Nervous system disorders	68 (2.7)	31 (2.5)	0	1 (0.1)
Headache	60 (2.4)	28 (2.3)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	58 (2.3)	32 (2.6)	1 (<0.1)	0
Myalgia	29 (1.2)	14 (1.1)	1 (<0.1)	0
Injury, poisoning and procedural complications	55 (2.2)	31 (2.5)	1 (<0.1)	0
Respiratory, thoracic and mediastinal disorders	34 (1.4)	12 (1.0)	0	0
Gastrointestinal disorders	28 (1.1)	20 (1.6)	1 (<0.1)	0
Skin and subcutaneous tissue disorders	28 (1.1)	7 (0.6)	0	0

Source: P203, Tables 3.2.2.1.2, 3.2.8
COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities;
Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.

During the 28-day follow-up period following any dose, lymphadenopathy-related events that were not necessarily captured in the 7-day e-diary were reported by 5.0% of vaccine recipients and 0.5% of placebo recipients. These events included lymphadenopathy, vaccination-site lymphadenopathy and injection-site lymphadenopathy which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected arm.

Adverse events of clinical interest
FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following Dose 1 through the data cutoff date or unblinding (whichever was earlier). SMQs were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in imbalance between the two treatment groups, and which captured events considered clinically relevant by the FDA, will be discussed.

SMQ *Cardiomyopathy*
For the SMQ *Cardiomyopathy*, which includes PTs that may be related to myocarditis and pericarditis such as *Chest pain*, *Dyspnea*, and *Palpitations*, 12 events were reported in 12 vaccine recipients (0.5%) compared to 3 events in 3 placebo recipients (0.2%). Of the events identified, one was clinically concerning for vaccine-associated myocarditis:

- A 12-year-old male participant reported events of dyspnea and painful respiration with chest pain one day after Dose 2 of mRNA-1273. He reported symptoms of fatigue, fever, chills, headache, myalgia, and oropharyngeal pain on the day of Dose 2 (no information regarding whether any of these symptoms were present prior to vaccination). Per the participant's father, the day after vaccination, the participant woke up feeling pain on the left side of the chest with breathing. He presented to the ER 2.5 hours after onset of symptoms, at which point the chest pain was still present, but resolving. In the ER, he was noted to have normal physical exam and vital signs

obtained showed blood pressure of 130/80 mmHg, heart rate of 125 beats per minute, respiratory rate of 20 breaths per minute, and temperature of 99.8°F. An ECG obtained was interpreted as sinus tachycardia with non-specific T-wave abnormalities. Chest x-ray was read as normal. He was administered ibuprofen and oral dexamethasone and discharged home. Differential diagnoses reported by the ER physician on discharge included reaction to COVID-19 vaccine, viral syndrome, and atypical chest pain. Pain improved and resolved on the same day (hours after onset of the events). The investigator later changed the reported AE term from chest pain to musculoskeletal and connective tissue related event. This event was assessed as related to study vaccine by the investigator. FDA agrees with the investigator's assessment. This event occurred prior to the establishment of the cardiac event adjudication committee for studies conducted by the Sponsor. On retrospective review of the case by the Sponsor, based on the lack of clinical concern for myocarditis by the investigator and the ER physician, and non-specific ECG findings, this case was not considered to meet the CDC criteria for probable or confirmed myocarditis, pericarditis, or myopericarditis.

Including the above case, *Dyspnea* was reported in 4 vaccine recipients (0.2%) and 1 placebo recipient (0.1%). The 3 other *Dyspnea* events in mRNA-1273 participants are briefly described below.

- A 12-year-old female participant reported dyspnea on the day of Dose 1, with concurrent symptoms of chills, headache, fatigue, and rhinorrhea. The event was entered as resolved 45 days later. No further information was reported. In FDA assessment, this event is possibly related to vaccine, although it is also possible that it represents a viral respiratory infection.
- A 13-year-old female participant reported dyspnea approximately 11 hours after receipt of Dose 2, which resolved after 1 hour. No other symptoms were reported around the time of this event. In FDA assessment, this is unlikely to be related given the rapid resolution without intervention and no other associated symptoms.
- A 12-year-old male participant reported dyspnea 9 days after Dose 2, without other concurrent symptoms and which resolved on the same day. Based on the limited amount of information there is insufficient information to conclude on causality, although the event appears to have been mild and transient.

Syncope was reported in 7 mRNA-1273 recipients (0.3%) and 2 placebo recipients (0.2%). One event in an mRNA-1273 recipient occurred one day post Dose 1, which was associated with blood draw. All other events of syncope occurred greater than 28 days following vaccination and the majority were also associated with blood draws. None of these events are considered related to vaccine by FDA.

Palpitations was reported in one vaccine recipient and no placebo recipients. A 14-year-old female participant with no known history of cardiac conditions reported palpitations 1 day after Dose 2. She also reported concurrent symptoms of non-cardiac chest pain, wheezing, vomiting and headache. The participant was evaluated in the ER where an ECG was obtained and read as normal. No further testing was done. Palpitations resolved one day after onset, chest pain resolved 2 days after onset, and wheezing resolved 3 days after onset. FDA agrees with the investigator's assessment that this event was possibly related to vaccine.

For the SMQ *Hypersensitivity*, 49 events were reported in 46 vaccine recipients (1.9%) compared to 17 events in 10 placebo recipients (0.8%). The most frequently reported events in

vaccine recipients (n=33) were classified as PTs under SOCs *General disorders and administration site conditions* and *Skin and subcutaneous tissue disorders* such as *Injection site hypersensitivity*, *Rash*, *Dermatitis* and *Urticaria*. Within 28 days after any vaccination, hypersensitivity events were reported by 1.8% of vaccine recipients (n=44) compared to 0.6% of placebo recipients (n=7). Nineteen events occurred with 7 days of vaccination, and most of them resolved within 1-3 days. All events in vaccine recipients were grade 1 or 2, and none were considered serious. Based on FDA's review, these events are likely related to vaccination due to the temporality with vaccination and clinical plausibility. There were no reports of anaphylaxis related to vaccination.

Serious adverse events
From Dose 1 through data cutoff, SAEs were reported in 6 mRNA-1273 recipients (0.2%) and 2 placebo recipients (0.2%). FDA agrees with the investigator's assessments that none of these events were related to study vaccine.

The following SAEs occurred in adolescent mRNA-1273 recipients:

- Three participants were hospitalized for depression and/or suicidal ideation. Two of the three participants reported treatment with a selective serotonin reuptake inhibitor prior to vaccination. These events occurred on Day 31 following Dose 1 and Days 30 and 35 following Dose 2. Two events were considered resolved and one event was resolving at the time of data cutoff. The rate of these events was similar in the vaccine and placebo arms and is unlikely related to the study product.
- One participant was admitted to the hospital for appendicitis on Day 4 following Dose 1 and underwent an appendectomy. The event was considered resolved on Day 5 following Dose 1 and the patient was discharged from the hospital. On Day 7 the participant experienced an SAE of diarrhea, vomiting and fever requiring readmission to the hospital. This event resolved on Day 8 following Dose 1.
- One participant experienced drug induced-liver injury on Day 14 following Dose 1. The participant reported medication use with trimethoprim/sulfamethoxazole for a Bartholin's gland cyst that was diagnosed on Day 8. On Days 12-17 the participant experienced a diffuse rash followed by fever, fatigue, myalgia, nausea and vomiting. On Day 18, the participant was admitted to the hospital. Laboratory abnormalities included elevated levels of alanine aminotransferase [251 U/L (ref range:5-50], aspartate aminotransferase [224 (10-35)] and alkaline phosphatase [395 (0-186)]. A complete cell count showed decreased total white blood cells [2.40 × 10^3/μL (4.50-11.0)] with an 6% eosinophils and decreased platelets [128 × 10^3/μL (150-400)]. The event was considered resolved on Day 35 following Dose 1. The second dose was not administered due to the physician decision to discontinue the participant from the study and further dosing. The participant was diagnosed with hepatitis, most-likely drug-induced liver injury secondary to trimethoprim/sulfamethoxazole which is a plausible explanation for the event given known risks of trimethoprim/sulfamethoxazole.
- One participant was admitted to the hospital for surgical repair of pectus excavatum. The event occurred on Day 31 following Dose 2 and was considered resolved on Day 32.

The SAEs that occurred in placebo recipients include a participant with a history of renal stones hospitalized for hydronephrosis/obstructive nephropathy 5 days after Dose 1 that resolved and another participant hospitalized for a suicide attempt 2 months after Dose 2.

Deaths
There were no deaths among Study P203 participants through the data cutoff.

AEs leading to study withdrawal
One mRNA-1273 recipient and no placebo recipients were discontinued from the study due to an AE. The vaccine recipient experienced grade 2 right eye swelling on day 4 following Dose 2. The event was not considered related to the vaccine by the investigator and was resolving at the time of the study withdrawal. Based on the limited information and lack of alternative etiology, in FDA assessment, this event may represent possible hypersensitivity reaction related to vaccine.

One mRNA-1273 recipient was discontinued from the study vaccine due to an AE of COVID-19 infection which occurred on day 10 following Dose 1. In the eCRF, it was noted that a second dose of vaccine was not given based on parental preference to not administer a second dose with 90 days of the COVID-19 diagnosis.

Review of all AEs occurring in subjects discontinued from the study for any reason did not reveal an imbalance suggesting discontinuations were attributable to AEs related to the vaccine product.

Pregnancies
No pregnancies were reported through the data cutoff.

4.3.6 Additional Follow-Up

The initial EUA amendment submission included data through the cutoff of May 8, 2021. On May 9, 2022, Moderna submitted additional data through the cutoff of January 31, 2022. This data included an updated analysis of vaccine efficacy including blinded data through May 31, 2021, and open-label data through January 31, 2022. The median duration of blinded follow-up was 136 days post Dose 2 for mRNA-1273 recipients and 78 days post Dose 2 for placebo recipients. For participants in the original mRNA-1273 group, the median total duration of follow-up including both blinded and open-label phases based on this updated data cutoff was 312 days post Dose 2. In this group, 2,376 participants (95.6%) were followed for at least 6 months since Dose 2.

Disposition
Following authorization of an alternative COVID-19 vaccine for this age group on May 10, 2021, the majority of the study participants requested to be unblinded. Of placebo recipients, 53.2% discontinued the blinded phase of the study to seek COVID-19 vaccine under EUA and 17.9% discontinued for “other” reasons, which also included receipt of another vaccine. In October 2021, the remaining placebo participants were given the option to crossover to receive mRNA-1273. As of the January 31, 2022, data cutoff, 7.3% of participants initially randomized to placebo had received at least one dose of mRNA-1273 in the open-label phase.

Efficacy
An updated analysis of vaccine efficacy during the blinded phase was conducted based on a data cutoff of May 31, 2021. Using the CDC definition, an additional 3 cases of COVID-19 (1 in the mRNA-1273 group, 2 in the placebo group) accumulated between the original data cutoff date and the new data cutoff date. The VE estimate was not substantially different between the two blinded data cutoff dates of May 8, 2021 (VE 93.3%), and May 31, 2021 (VE 89.9%), based on the CDC definition for COVID-19.

Table 20. Updated Analysis of Vaccine Efficacy During the Blinded Phase Through Data Cutoff of May 31, 2021, First Occurrence COVID-19 Starting 14 Days After Dose 2, Participants 12 Through 17 Years of Age, Per-Protocol Set for Efficacy

Endpoint	mRNA-1273 100 µg N=2142 Cases (%) Incidence Rate per 1,000 person-years (95% CI)[b]	Placebo N=1045 Cases (%) Incidence Rate per 1,000 person-years (95% CI)	Vaccine Efficacy (95% CI)[c]
P301 definition	0 (0) 0 (NE, 6.1)	6 (0.6) 21.6 (7.9, 46.9)	100% (61.2, NE)
CDC definition	2 (<0.1) 3.3 (0.4, 11.9)	9 (0.9) 32.4 (14.8, 61.6)	89.9% (51.0, 98.9)

Source: P203, Table 14.2.7.1.1.2 and Table 14.2.8.1.1.2.
NE=non-evaluable.
a Person-years is defined as the total years from randomization date to the date of event (CDC case definition of COVID-19, P301 case definition of COVID-19, 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 Vaccine efficacy, 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.

Safety

At the time of the initial data cutoff of May 8, 2021, 97% of study participants had been vaccinated and assessed for ARs within 7 days post vaccination and for unsolicited AEs within 28 days of vaccination. Since rates of these events were not expected to change with longer follow-up, review of the updated data (through January 31, 2022) focused on new AEs of clinical interest and SAEs accumulated since the original data cutoff.

Adverse events of clinical interest

At the time of the May 8, 2021, data cutoff, the only AESI as specified by the study protocol was MIS-C. Since then, the protocol has been revised to include collection of AESIs based on the list of potential COVID-19 or COVID-19 vaccine related AESIs developed by the Brighton Collaboration (Appendix A). AEs reported in study P203 were retrospectively reviewed to identify AESIs. Through the January 31, 2022, data cutoff, among mRNA-1273 recipients, a total of 16 AESIs were reported in 13 participants (0.5%). These AESIs are summarized below. By FDA assessment, in agreement with study investigator, all were considered not related to study vaccine, except the event of injection site hypersensitivity which is assessed as related.

- There were 7 events of anosmia and 4 events of ageusia reported by 8 participants (3 participants reported both events). These events occurred in the setting of COVID-19 for 7 of the 8 participants. In the 8th participant, anosmia was reported in the setting of a viral upper respiratory tract infection.
- There were 2 events reported as SAEs in the category of new onset or worsening of neurologic disease:
- A 14-year-old male with no relevant past medical history was diagnosed with idiopathic epilepsy after experiencing a generalized seizure 285 days after Dose 2 and had otherwise normal clinical evaluations after the event.
- A 12-year-old male with history of recent Chiari decompression surgery experienced aseptic meningitis with onset 301 days after Dose 2.
- There was one event of injection site hypersensitivity classified as an AESI in a 15-year-old female 11 days after Dose 1. The participant presented with erythema (measured 8 cm x 5 cm), warmth, and tenderness at the injection site. The event was

moderate in severity and resolved after 6 days. This event is considered related to study vaccine and is consistent with known safety profile of delayed injection site reaction, which occurs most commonly after Dose 1.

- There were 2 participants who reported events of appendicitis. Both were classified as SAEs and are summarized in the SAE sections of this review

Events identified under the Cardiomyopathy SMQ and other potential cardiac-related PTs, collected from the initial data cutoff of May 8, 2021, through the January 31, 2022, data cutoff are summarized below. There were no events of myocarditis or pericarditis reported among participants 12-17 years between the May 8, 2021, data cutoff and the January 31, 2022, data cutoff.

- In the original mRNA-1273 group, dyspnea was reported by 2 participants, and syncope was reported by 7 participants. All events occurred >28 days post Dose 2. One participant reported an event of bundle branch block 242 days after Dose 2, and one participant reported an event of supraventricular tachycardia 120 days after Dose 2. In FDA assessment of these cases, given the latency of onset after vaccination, none of these events were considered related to study vaccine.
- A 12-year-old male participant reported chest discomfort, not medically attended, 10 days following Dose 1 of open-label mRNA-1273. Concurrent symptoms included sneezing and coughing, which were infrequent, and had followed a rhinovirus diagnosis 23 days prior to the onset of chest discomfort symptoms. The investigator assessed this event as related to study vaccine and the participant did not receive Dose 2 of the vaccine. In FDA assessment of this case, although the event appears to have been benign and transient, lack of a cardiac evaluation precludes a definitive assessment of whether this event might represent vaccine-associated myocarditis.
- A 17-year-old male participant reported dyspnea and tachyarrhythmia 2 hours after receiving Dose 1 of open-label mRNA-1273 with subsequent normal physical exam and vital signs on evaluation, though ECG was not documented. These events were considered related to study vaccine by the investigator. The same participant reported a second event of dyspnea one day after receipt of Dose 2 of open-label mRNA-1273, however this event was not medically attended and was assessed as unrelated by the investigator. In FDA assessment, although the event appears to have been benign and transient, lack of a cardiac evaluation precludes a definitive assessment of whether this event might represent vaccine associated myocarditis.

In addition to the events noted above, there was one late-breaking event of chest pain reported after the January 31, 2022, data cutoff which was clinically concerning for vaccine-associated myocarditis:

This event occurred in a 14-year-old male participant with a history of gastroesophageal reflux disease who reported chest pain one day after receiving Dose 2 of crossover vaccination with mRNA-1273. The participant described “feeling like heart being squeezed or it was going to explode exacerbated by taking a deep breath.” The chest pain was accompanied by nausea, vomiting, and episodes of heart racing. The participant was seen in clinic by the investigator one day after symptom onset, where on exam, he was found to be afebrile, with heart rate of 89 beats per minute, blood pressure of 100/63 mmHg, and with no murmur on auscultation and no tactile chest wall tenderness. An ECG performed at the study clinic was interpreted by the investigator to show sinus tachycardia and ST segment elevation with right axis deviation. No further studies or laboratory testing were performed, and the participant was sent home with the recommendation for use of ibuprofen and rest. The study investigator suspected the event to be

mild myocarditis or costochondritis. At a follow-up phone call 6 days after onset of the event, the participant's mother reported the participant to be improving overall but still with chest pain with exertion and easily increased heart rate. At the follow-up phone call the next day, the chest pain was reported to be improved (but still 8.5 out of 10 on pain scale), and the participant was able to return to normal activities. At the Study Day 57 follow-up visit (28 days after onset of the event), the participant's parent reported that the symptoms had resolved completely by 8 days after onset of the event. The investigator reported this event as a non-serious AE of chest pain and related to study vaccine. FDA agrees with the investigator assessment that this event was likely related to study vaccine. The participant was seen by a pediatric cardiologist approximately 5 months after the event, with normal evaluation and normal ECG and echocardiogram. Clinical details regarding the event, including the initial abnormal ECG, was sent for evaluation by the Cardiac Event Adjudication Committee (CEAC) and was adjudicated as not meeting the CDC definition of confirmed or probable case of acute myocarditis, acute pericarditis, or myopericarditis.

Adverse events leading to discontinuation from study participation
One additional discontinuation from study participation was reported, in a 15-year-old male participant who experienced mild throat tightness one minute after Dose 1 of mRNA-1273, without other reported symptoms or abnormalities on physical exam. The AE resolved after 10 minutes and was considered related to study vaccine.

Serious adverse events
Between the May 8, 2021, data cutoff and the January 31, 2022, data cutoff, SAEs were reported by 15 mRNA-1273 recipients and one participant originally randomized to placebo and who crossed over to receive mRNA-1273 (placebo-mRNA-1273). These additional SAEs are summarized in the table below. None of the SAEs were assessed as related to the vaccine by the investigator or FDA.

The most frequently reported SAEs were from the system organ class (SOC) of psychiatric disorders in 8 participants who received mRNA-1273, of which 4 participants had psychiatric diagnoses prior to study enrollment; 3 participants had new diagnoses of mild or moderate depression reported after vaccination but prior to the onset of the SAE; and 1 participant had a new diagnosis of major depression that was considered a SAE. The predominance of SAEs related to psychiatric disorders are not unexpected given the known increased rates of depression and anxiety in the pediatric populations during the COVID-19 pandemic.[61] The lack of a placebo only group for the duration of the study conduct due to crossover mRNA-1273 vaccination precludes a complete assessment of mRNA-1273 with regard to vaccine emergent psychiatric disorders. However, the rates and clinical presentation of the reported SAEs in the available safety data do not suggest an underlying safety signal for psychiatric conditions in the evaluated adolescent 12-17 year population.

Table 21. SAEs Captured From Data Cutoff of May 8, 2021, Through Data Cutoff of January 31, 2022, Participants 12 Through 17 Years of Age, P203

Treatment Group	Age/ Sex	Preferred Term	Time to Onset after Most recent dose	Risk Factors/Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273	16F	Depression	46 days after Dose 2	History of depression, anxiety, post-traumatic stress disorder, substance use	Resolved with sequelae: ongoing depression	Not related	Not related
mRNA-1273	17F	Sunburn	67 days after Dose 2	Sunburn with 2nd and 3rd degree burns	Resolved	Not related	Not related
mRNA-1273	14M	Splenic injury; Femur fracture	68 days after Dose 2	All-terrain vehicle collision	Resolved	Not related	Not related
mRNA-1273	13M	Clavicle fracture; Concussion; Facial bone fracture	80 days after Dose 2	Skateboard accident	Resolved	Not related	Not related
mRNA-1273	16F	Suicidal ideation	83 days after Dose 2	History of anxiety, eating disorder, prior suicidal ideation	Resolved	Not related	Not related
mRNA-1273	12F	Suicide ideation	109 days after Dose 2	History of anxiety; reported significant domestic stressors around time of SAE	Resolved	Not related	Not related
mRNA-1273	16M	Appendicitis	182 days after Dose 2		Resolved	Not related	Not related
mRNA-1273	12M	Syringomyelia; Meningitis aseptic	214 days after Dose 2 308 days after Dose 2	History of Chiari I malformation; new symptomatic cervical cord syrinx requiring decompression surgery; developed aseptic meningitis, thought to be related to recent surgery	Resolved with sequelae: aseptic meningitis; Resolved	Not related Not related	Not related Not related
mRNA-1273	15F	Suicide attempt	220 days after Dose 2	AEs of depression (moderate) and anxiety (mild) 23 days after Dose 2 and was started on antidepressant medication. Reported worsening depression starting 202 days after Dose 2, prior to this SAE.	Resolved	Not related	Not related
mRNA-1273	16M	Major depression	225 days after Dose 2	New diagnosis	Resolved with	Not related	Not related

Treatment Group	Age/ Sex	Preferred Term	Time to Onset after Most recent dose	Risk Factors/Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
					sequelae: participant on medication and seeing a psychiatrist		
mRNA-1273	15F	Suicide attempt	235 days after Dose 2	AE of depression (moderate) 208 days after Dose 2 and was started on medication	Resolved	Not related	Not related
mRNA-1273	15F	Suicidal ideation	240 days after Dose 2	History of depression	Resolved	Not related	Not related
mRNA-1273	13F	Murine typhus	246 days after Dose 2		Resolved	Not related	Not related
mRNA-1273	14M	Seizure	285 days after Dose 2	New diagnosis of idiopathic epilepsy (generalized)	Resolved with sequelae: generalized epileptiform discharges on EEG	Not related	Not related
mRNA-1273	14F	Suicide attempt	311 days after Dose 2	AE of depression (mild) 183 days post Dose 2 and was started on medication	Resolved	Not related	Not related
Placebo-mRNA-1273	16M	Road traffic accident	68 days after OL Dose 2		Resolved	Not related	Not related

Source: FDA generated table based on case narratives, listings, and dataset submitted to EUA 27073 for P203
OL=open label

4.3.7 Summary for Participants 12 through 17 Years of Age

The comparison of immune response between adolescents in Study P203 and young adults in Study P301 provided the primary evidence to support effectiveness of the vaccine in individuals 12-17 years of age. The study met the pre-specified success criteria for the two co-primary endpoints of GMT ratio and difference in SRRs. The GMT ratio (adolescents to young adults) was 1.1 (95% CI 0.9, 1.2) which met the pre-specified success criterion of a LL of the 95% CI >0.67 and a point estimate of >0.8. The difference in SRRs (adolescents minus young adults) was 0.2% (95% CI -1.8, 2.4) which met the pre-specified success criterion of a LL of the 95% CI >-10% and a SRR difference point estimate of -5%. The immunogenicity data across demographic subgroups were generally consistent with those observed in the overall study population, though interpretability of vaccine effectiveness results in certain subgroups are limited by small subgroup sample sizes.

Descriptive analyses of VE in adolescents 12-17 years of age further supported and provided direct evidence of vaccine effectiveness. The observed VE against COVID-19 starting 14 days after Dose 2, based on the data cutoff of May 8, 2021, was 100% (95% CI 28.9, non-evaluable) when using the COVID-19 case definition used in Study P301, and 93.3% (95% CI 47.9, 99.9) when using the broader CDC case definition. The number of cases were too small to allow for meaningful assessment of vaccine efficacy in individual demographic subgroups. There were no reports of severe COVID-19 and no cases of COVID-19 in participants who were SARS-CoV-2 seropositive at baseline. An updated analysis of VE of the blinded phase based on the data cutoff of May 31, 2021, revealed similar results as those obtained from the May 8, 2021, data cutoff.

Local site reactions and systemic solicited events among adolescent vaccine recipients were frequent and were mostly mild to moderate in severity. The most common solicited adverse reactions after any dose were injection site pain (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%) and chills (49.1%); 13.8% and 16.7% of local and systemic solicited adverse reactions, respectively, were reported as Grade 3. In the adolescent population 99.2% of vaccine recipients reported at least one adverse reaction after any injection with 25.3% reporting a reaction that was Grade 3 or higher.

An imbalance was observed in the number of unsolicited AEs occurring within 28 days following vaccination between adolescent vaccine and placebo recipients that was mostly attributable to injection site reactions plausibly related to the study vaccine, which includes lymphadenopathy regional to the injection site. Analysis of the study data revealed a small imbalance (0.5% vs 0.2%, vaccine vs placebo) in cardiac events (SMQ *Cardiomyopathy)*, including syncope, dyspnea and palpitations. These events were all mild to moderate, and none were considered serious. Two adolescent mRNA-1273 recipients reported events clinically concerning for vaccine-associated myocarditis, though neither was assessed to be a probable or confirmed myocarditis case. Cases of myocarditis/pericarditis have also been reported following the authorization of mRNA-1273 in adults ≥18 years of age with routine pharmacovigilance/safety surveillance by the CDC and FDA, and among adolescents in countries where this vaccine has been authorized for use in this age group, as discussed in Section 2.3.2.

Other small numerical imbalances were detected for hypersensitivity-related events (1.9% vs 0.8%, vaccine vs placebo), which included injection site hypersensitivity, rash, dermatitis and urticaria, and dizziness (0.2% vs 0%). Based on the nature of the events and temporal relationship, these events are plausibly related to vaccination.

No deaths were reported in the adolescent population or in young adult vaccine recipients. SAEs were infrequent and occurred at the same rate among adolescent vaccine and placebo recipients (0.2%). Available evidence does not suggest a causal relationship between these SAEs and the vaccine.

Additional safety data from participants 12-17 years in Study P203, based on a data cutoff of January 31, 2022, corresponding to a median follow-up duration (including both blinded and open-label follow-up) of 312 days post Dose 2 in mRNA-1273 recipients, revealed no new safety concerns.

4.4 Study P204: Children 6 Months through 11 Years of Age

4.4.1 Study Design

Study P204 is an ongoing Phase 2/3 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months. The study consists of 3 parts: Part 1 is the open-label, dose-escalation, age de-escalation phase; Part 2 is the randomized, observer-blind, placebo-controlled expansion phase within each age group, and Part 3 will evaluate an open-label lower dose regimen in children 6 through 11 years old (including a pre-planned third dose). Enrollment for Part 3 is ongoing, and data from this Part of the study are not yet available, so this Part of the study will not be discussed in the context of this EUA amendment. Vaccine effectiveness is inferred from immunobridging based on a comparison of immunogenicity endpoints between children in each of the pediatric age cohorts and young adult (18 years - 25 years of age) participants in the Phase 3 study (Study P301).

Part 1 was an open-label dose-escalation and age de-escalation phase of the study that assessed 50 µg and 100 µg dose levels in the 6-11 years age cohort; 25 µg and 50 µg dose levels in the 2-5 years age cohort; and 25 µg dose level in the 6-23 months age cohort. Part 1 began with the oldest age group (6-11 years), with subsequent age de-escalation. Dose escalation and age de-escalation progressed only after confirming the safety of a dose level in each age group after each vaccination. Each age group advanced to Part 2 independently, and Part 2 did not begin until an interim analysis was performed for safety and immunogenicity in each age cohort at the selected dose level.

Part 2 was a randomized, placebo-controlled, observer-blind evaluation of the selected dose for each age cohort. Since the primary objectives of study P204 were to evaluate the safety (including reactogenicity) of the selected dose in each age cohort and to infer effectiveness based on immunobridging to young adults in study P301, the evaluations in this EUA review focus on Part 2 of the study. Participants were randomized 3:1 to receive either mRNA-1273 vaccine or placebo on Day 1 and Day 29. Immunobridging required demonstration of non-inferiority (in each pediatric age cohort compared to young adults) of immune response by both GMT/GMC and SRR as measured by neutralizing antibodies against SARS-CoV-2. Secondary objectives were to evaluate the incidence of COVID-19, SARS-CoV-2 infection regardless of symptoms, and asymptomatic SARS-CoV-2 infection

Evaluation of immunogenicity
The primary immunogenicity objectives were to infer effectiveness based on immunobridging to young adults enrolled in study P301. The immunogenicity endpoints for children 6 months through 11 years of age were as follows:

Coprimary endpoint 1: GMT/GMC: the ratio (children in the specified age group to young adults) of the GMT or GMC at Day 57 evaluated against a non-inferiority margin of 1.5 (LB of the 95% CI of the GMT/GMC ratio ≥0.67) AND a point estimate of GMT/GMC ≥0.8 (minimum threshold). The endpoint evaluated was GMT for the analysis in children 6-11 years of age and GMC in the analyses for children 6-23 months and 2-5 years of age, in accordance with the assay used for each of these age groups (see below).

Coprimary endpoint 2: SRR: the difference in the SRRs (children in the specified age group minus young adults) evaluated against a non-inferiority margin of 10% (LB of the 95% CI ≥−10%) AND a point estimate of difference in SRRs ≥−5% (minimum threshold). Seroresponse was defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ.

Assays used for evaluation of immunogenicity
In post-vaccination virology samples from participants 6-11 years (Part 1 and Part 2) and 6 months through 5 years (Part 1), immunogenicity of mRNA-1273 was assessed using the pseudotype virus neutralization assay validated at Duke University. The assay measures neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein. (D614G form of the USA-WA1/2020 Wuhan strain). Neutralization is measured as the serum dilution at which the RLU value is reduced by 50% (ID50) and 80% (ID80) relative to the mean RLU value in virus-control wells. The assay was validated using both convalescent serum samples and clinical samples from individuals who received the mRNA-1273 vaccine. The validation results met the pre-established acceptance criteria and support the suitability of the assay to accurately quantify neutralizing antibodies in human serum samples.

Post-vaccination serology samples from participants ages 6 months through 5 years (Study P204 Part 2) and from a comparator group of 18-25-year-olds were tested using the reporter virus microneutralization assay validated at (b) (4) after concordance was established between the Duke PsVNA assay and the (b) (4) reporter virus microneutralization assay. Similar to the assay developed at Duke University, this cell-based assay measures the ability of SARS CoV-2 neutralizing antibodies to inhibit the infection of 293T-ACE2 cells by SARS CoV-2 reporter virus particles (RVP). The serum antibody concentration per test sample is determined by interpolating the mean of the replicate foci forming unit values off the fitted reference standard curve. The reference standard was calibrated to the first WHO International Antibody Standard for SARS CoV-2 Lot 20/136. The interpolated antibody concentrations are then dilution corrected. The final concentration is the antibody concentration associated with the lowest dilution with an antibody concentration within the quantifiable range of the assay. The results are reported in final antibody GMC in AU/mL. The assay-validation study evaluated precision and ruggedness, relative accuracy, selectivity, dilutional linearity, LLOQ, upper limit of quantification, and specificity.

Evaluation of efficacy
In addition to the immunobridging analysis, children 6 months-11 years of age were followed for potential cases of COVID-19 for descriptive analyses of vaccine against laboratory-confirmed COVID-19. Vaccine efficacy to prevent asymptomatic SARS-CoV-2 infection and SARS-CoV-2 infection regardless of symptoms were also evaluated. COVID-19 case definitions for Study P204 may be found in Appendix B.

Evaluation of safety

The primary safety objective was to describe the safety and reactogenicity of up to three dose levels (25, 50, and 100 µg) of mRNA-1273 administered as two doses 28 days apart in three age cohorts. Participants' parents or legally authorized representatives recorded solicited local and systemic ARs, as well as antipyretic or analgesic medication use, in an e-diary through 7 days (day of injection and 6 subsequent days) after each dose. Unsolicited AEs were collected through 28 days after each dose, while MAAEs, SAEs, and AESIs, including MIS-C and myocarditis and/or pericarditis, were collected through the entire study period, up to 12 months after the 2nd dose. Any confirmed symptomatic SARS-CoV-2 infection in a participant was captured as a MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. This EUA amendment includes data from blinded follow-up through the data cutoff of November 10, 2021, for participants 6-11 years and February 21, 2022, for children 6 months through 5 years of age. Additional safety data was provided for participants 6-11 years of age, which includes unblinded follow-up through a data cutoff of February 21, 2022.

Safety calls scripts used at 7 days following each vaccination and every 4 weeks thereafter included language to specifically solicit for symptoms of myocarditis and pericarditis. If the caregiver reported any symptoms concerning for possible myocarditis or pericarditis in the participant, they were advised to seek medical evaluation and to report outcome back to the study site. An independent Cardiac Event Adjudication Committee (CEAC) consisting of pediatric and adult cardiologists was established to evaluate suspected cases of myocarditis, pericarditis, or myopericarditis based on the CDC working case definitions.

Table 22. Analysis Populations

Population	Description
Randomization Set	Part 2: All participants who were randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who received at least one dose of study vaccine. Participants were analyzed according to the treatment group for the treatment they received. Part 2: All randomly assigned participants who received at least one dose of study vaccine. Participants were analyzed according to the treatment group to which they were randomized.
Per Protocol (PP) Set for Efficacy	All participants in the FAS who met all the following criteria: • received planned doses of study vaccination per schedule • complied with the 2nd dose injection timing • had no major protocol deviations that impacted 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 The PP Set for Efficacy was used for all efficacy analyses in both parts unless otherwise specified. Participants were analyzed according to the treatment group for the treatment they received in Part 1 and to which they were randomized in Part 2.
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity sampling and testing who had a baseline SARS-CoV-2 status available and at least 1 post-injection antibody assessment for the analysis endpoint. This subset was used for sensitivity or supportive analyses. Participants were analyzed according to the treatment group to which they were randomized.

Population	Description
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS who met all the following criteria: • had baseline (Day 1) SARS-CoV-2 status available • had baseline and at least 1 post-injection Ab assessment for the analysis endpoint • received planned doses of study vaccination per schedule • complied with the immunogenicity window based on the second 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 • were 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 The PP Immunogenicity Subset was used for all analyses of immunogenicity unless otherwise specified. Participants were analyzed according to the treatment group for the treatment they received in Part 1 and to which they were randomized in Part 2.
Safety Set	All enrolled participants (in Part 1) and all randomly assigned participants (in Part 2) who received at least one dose of study vaccine. The Safety Set was used for all analyses of safety except for solicited ARs. Safety Sets were defined for each dose separately. Participants were included in the vaccination group for the treatment they received.
Solicited Safety Set	All participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set was used for the analyses of solicited ARs. Solicited Safety sets were defined for each dose separately. Participants were included in the vaccination group for the treatment they received.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of study vaccine (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline. Participants were analyzed according to the treatment group to which they were randomized.
mITT1 Set	All participants in the mITT Set excluding those who received the wrong treatment.

4.4.2 Participants 6 Years through 11 Years of Age

Participants 6-11 years of age began enrollment into Study P204 Part 1 on March 15, 2021, and Part 2 on August 9, 2021. The data cutoff of November 10, 2021, was triggered when all study participants reached Day 57 or study discontinuation, and also coincided with the time of the authorization of an alternative COVID-19 vaccine for this age group, thereby ending the blinded phase of the study.

4.4.2.1 Part 1: Dose-Finding and 50 µg Dose Selection

The open-label, dose-finding phase (Part 1) of P204 in participants 6-11 years included a total of 751 participants, of whom 380 received the 50-µg dose level and 371 received the 100-µg dose level of mRNA-1273. The first 75 participants to enroll received 50 µg of mRNA-1273, and safety data collected during 1-week post-Dose 1 were reviewed prior to enrollment for the 100-µg dose level.

A protocol-specified assessment of immunogenicity for dose selection was performed in Part 1 after the first 75 recipients of the 50-µg dose reached 28 days post Dose 2. Immunogenicity as measured by PsVNA ID50 in participants 6-11 years of age was compared to immunogenicity from a subset of participants 18-25 years of age from Study P301, for whom clinical efficacy has been demonstrated. Results of the analysis demonstrated a GMT ratio of 0.9 (95% CI 0.7, 1.2) and a difference in seroresponse of 1.0% (95% CI −4.4%, 3.0%). At the time of this scheduled assessment, immunogenicity results from the first 75 participants who received the 100-µg dose were not yet available.

Analyses of solicited adverse reactions after Dose 1 and Dose 2 of both dose levels informed dose selection for Part 2. Among participants 6-11 years of age, the rates of solicited ARs in the 50-µg group were comparable to those in young adults (Study P301), while the rates of solicited systemic ARs in the 100-µg group were higher than those in the 50-µg group. Notably, the rates of fever after any dose were 31.8% and 23.4% in the 100-µg group and the 50-µg group, respectively, while the rates of Grade 3 or higher fevers were 6.5% and 2.9% in the 100-µg group and the 50-µg group, respectively. Rates of solicited local ARs were similar between groups, but there was a higher rate of Grade 3 reactions reported in the 100-µg group than the 50-µg group.

Unsolicited AEs within 28 days in Part 1 were similar across both dose levels and were similar to those reported in Part 2; therefore, Part 1 unsolicited safety will not be discussed in detail. SAEs and AEs of clinical interest from Part 1 will be presented in the Part 2 safety section, as these analyses represent events that occurred during the entire study period. For Part 1 participants, the median duration of follow-up after Dose 2 through the data cutoff date of November 10, 2021, was 146 days and 141 days for the 50 µg and 100 µg groups, respectively.

Because immunogenicity results from the 50-µg dose group suggested that the pre-specified non-inferiority immunobridging criteria could be met in Part 2 with this dose level, and the safety profile was tolerable while also less reactogenic compared to the 100-µg dose, the 50-µg dose level was selected for evaluation in Part 2.

4.4.2.2 Part 2: Blinded, Placebo-Controlled Phase

Participant disposition and inclusion in analysis populations
Disposition tables for the double-blinded, placebo-controlled phase of the study (Part 2) are presented below in Table 23 (immunogenicity populations), Table 24 (efficacy populations) andTable 3 Table 25 (safety population).

For immunobridging, an immunogenicity subset of mRNA-1273 recipients was comprised of random sample of participants 6-11 years of age (n=364) from P204 Part 2 and young adult participants 18-25 years of age (n=340) from P301. No participants in the placebo group were included in the immunogenicity subset. The PP Immunogenicity Subset, used for the primary immunogenicity analyses, consisted of 320 participants 6-11 years of age and 295 young adult participants. As shown in Table 23 below, for the 6-11 years age cohort of mRNA-1273 recipients, the majority of exclusions from the PP Immunogenicity Subset were due to positive baseline SARS-CoV-2 status, which was observed more frequently than in the young adult cohort (10.4% compared to 3.5%). In the young adult age cohort, the majority of exclusions from the PP Immunogenicity Subset were due to participants not receiving Dose 2 per schedule.

Table 23. Disposition of Participants 6 Through 11 Years of Age, Study P204 Part 2, and 18 Through 25 Years of age, Study P301, Immunogenicity Populations

Disposition	6-11 Years P204 mRNA-1273 50 µg	18-25 Years P301 mRNA-1273 100 µg
Immunogenicity Subset[a]	N=364	N=340
PP Immunogenicity Subset[b]	N=320	N=295[d]
Excluded from PP Immunogenicity Subset[c], n (%)	44 (12.1)	45 (13.2)
Reason for exclusion, n (%)	--	--
Positive baseline SARS-CoV-2 status	38 (10.4)	12 (3.5)
Did not receive Dose 2 per schedule	0	21 (6.2)
Received Dose 2 out of window	1 (0.3)	2 (0.6)
Had no immunogenicity data at Day 57	4 (1.1)	9 (2.6)
Had other major protocol deviations	1 (0.3)	0
Participants with HIV infection	0	1 (0.3)

Source: P204 (6-11 years) Table 14.1.2.3.2
a. The Immunogenicity Subset consists of participants in the Full Analysis Set (FAS) who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
b. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.
c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.
d. Differs from number of participants in PP Immunogenicity Subset used for immunobridging analyses for P203 due to exclusion of participants who did not have D57 data available and exclusion of one participant with HIV on antiretrovirals

In the populations used to assess the efficacy endpoints, dispositions were overall similar between the mRNA-1273 and placebo groups. There was a higher percentage of participants in the placebo group who were excluded from the PP Set for Efficacy due to discontinuation of study treatment prior to Dose 2 and due to not receiving Dose 2 and passing the allowable vaccination window, likely as a result of eligibility to receive alternate COVID-19 vaccine under EUA.

Table 24. Disposition of Participants 6 Through 11 Years of Age, Study P204 Part 2, Efficacy Population

Disposition	mRNA-1273 50 µg	Placebo
Randomized	N=3012	N=1004
Full Analysis Set[a]	N=3005	N=997
mITT Set[b]	N=2701	N=882
mITT1 Set[c]	N=2687	N=880
PP Set for Efficacy[d]	N=2644	N=853
Excluded from PP Set for Efficacy, n (%)	368 (12.2)	151 (15.0)
Reason for exclusion, n (%)	--	--
Randomized but not dosed	7 (0.2)	7 (0.7)
Positive or missing baseline SARS-CoV-2 status	304 (10.1)	115 (11.5)
Discontinued study treatment or participation without receiving Dose 2	9 (0.3)	10 (1.0)
Did not receive Dose 2 and passed window of +14 days	7 (0.2)	12 (1.2)
Received incorrect vaccination[e]	14 (0.5)	2 (0.2)
Received Dose 2 out of window	24 (0.8)	5 (0.5)
Has other major protocol deviations	3 (<0.1)	0

Source: P204 (6-11 years) Table 14.1.2.1.2.1, Table 14.1.2.5
a. The FAS consists of all randomized participants who received at least one dose of IP. Numbers are based on planned treatment group.
b. The mITT Set consists of all participants in the FAS who had 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) before the first dose of IP, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.
c. The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (i.e., at least 1 dose received that is not as randomized or planned). Numbers are based on planned treatment group.
Percentages are based on the number of participants randomized.
d. The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a Negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group. Percentages are based on the number of participants randomized.
e. The 2 participants in the placebo group incorrectly received mRNA-1273. The 14 recipients in the mRNA-1273 group received mRNA-1273 but at an incorrect dose level.

The disposition of participants from the study who contributed to the assessment of safety are shown in Table 25. The vast majority of study participants from both the mRNA-1273 and the placebo groups completed both doses of study vaccine. The higher rates of study discontinuation in the placebo group (13.8%) compared to the mRNA-1273 group (1.3%) were largely due to participant withdrawal to receive an alternative COVID-19 vaccine under EUA. Discontinuations from study vaccination and from study participation due to AEs were uncommon (<0.1% in the mRNA-1273 group) and are discussed in under safety, below.

Table 25. Disposition of Randomized Participants 6 Through 11 Years of Age, Study P204 Part 2, Safety Population

Disposition	mRNA-1273 50 µg	Placebo
Randomized, n (%)	N=3012	N=1004
Completed one dose	3005 (99.8)	997 (99.3)
Completed two doses	2988 (99.2)	973 (96.9)
Discontinued from study vaccination[a]	13 (0.4)	14 (1.4)
Reason for discontinuation	--	--
Adverse event[b]	1 (<0.1)	2 (0.2)
Withdrawal of consent	6 (0.2)	4 (0.4)
Physician decision	2 (<0.1)	2 (0.2)
Subject entered open-label or crossover phase	3 (<0.1)	3 (0.3)
Subject receiving EUA vaccine outside of protocol	0	2 (0.2)
Other	1 (<0.1)	1 (<0.1)
Discontinued from study participation	39 (1.3)	139 (13.8)
Reason for discontinuation	--	--
Adverse event	1 (<0.1)	0
Withdrawal of consent	28 (0.9)	65 (6.5)
Lost to follow-up	4 (0.1)	1 (<0.1)
Protocol deviation	0	1 (<0.1)
Physician decision	3 (<0.1)	2 (0.2)
Subject receiving EUA vaccine outside of protocol	0	67 (6.7)
Other	1 (<0.1)	3 (0.3)
Missing	2 (<0.1)	0
Safety Set[c], n (%)	N=3007	N=995
Solicited Safety Set[d], n (%)	N=3006	N=994
First Injection Solicited Safety Set	3004 (>99.9)	993 (99.8)
Second Injection Solicited Safety Set	2988 (99.4)	969 (97.4)
Number of participants unblinded[e], n (%)	1071 (35.6)	662 (65.9)
Received first injection in open-label phase[e]	--	482 (48.0)

Source: P204 (6-11 years) Tables 14.1.1.1.2, 14.1.2.1.2.1
Note: Percentages based on participants randomized
a. Discontinuation from study vaccine is defined as a subject who received the first injection but didn't receive the second injection.
b. There were 3 total AEs leading to discontinuation from vaccine in the mRNA-1273 group. One case is listed under “physician decision.” For one other case, the CRF discontinuation page reported study vaccine discontinuation due to AE. However, action taken with study vaccine was recorded in the eCRF as dose not changed
c. Safety Set consists of all randomized participants who received any dose.
d. Solicited Safety Set consists of all participants who were randomized and received any dose and contributed any solicited AR data (i.e., had at least 1 postbaseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.
e. as of data cutoff date November 10, 2021

Following authorization of an alternative COVID-19 vaccine for this age range in October 2021, the protocol was revised to allow study participants the option for unblinding and for placebo recipients to crossover to receive the active vaccine. The open-label follow-up period for this age group began on November 1, 2021. As of the November 10, 2021, data cut, 1,071 mRNA-1273 participants (35.6%) and 662 placebo participants (65.9%) had been unblinded, and 482 participants initially randomized to placebo (48.0%) had received at least one dose of the crossover vaccine.

Durations of follow-up for Part 2 participants are displayed in Table 26. The median duration of blinded follow-up after Dose 2 for Part 2 participants was 51 days and comparable between the mRNA-1723 and placebo groups. A greater percentage of mRNA-1273 recipients compared to placebo recipients had at least 2 months of blinded follow-up post Dose 2 (35.5% compared to 21.9%, respectively). Including both the blinded and open-label phases of Part 2, the median duration of follow-up from Dose 2 for participants originally randomized to mRNA-1273 was 55 days. Duration of follow-up including the open-label phase for original placebo participants was not calculated as a large percentage of these participants had received crossover vaccination with mRNA-1273.

Table 26. Duration of Follow-Up After Dose 2 Through Data Cutoff of November 10, 2021, Participants 6 Through 11 Years of Age, Study P204 Part 2, Safety Set

Duration of Follow-Up	mRNA-1273 50 µg N=3007	Placebo N=995	Total N=4002
Blinded follow-up	--	--	--
≥28 days since Dose 2, n (%)	2981 (99.1)	966 (97.1)	3947 (98.6)
≥56 days since Dose 2, n (%)	1066 (35.5)	218 (21.9)	1284 (32.1)
Median follow-up from Dose 2, days (min, max)	52 (0, 65)	49 (0, 65)	51 (0, 65)
Including both blinded and open-label phases	--	--	--
≥56 days since Dose 2, n (%)	1498 (49.8)	--	--
Median follow-up from Dose 2, days (min, max)	55 (0, 65)	--	--

Source: P204 (6-11 years) Tables 14.1.5.2, 14.1.5.3

Demographic and baseline characteristics

The PP Immunogenicity Subset, which contributed to the co-primary endpoints for the study, consisted of 320 vaccinated participants 6-11 years of age from Study P204 Part 2 and 295 vaccinated young adult participants from Study P301 (Table 27). Baseline demographic characteristics were similar between the 6-11-year-old and young adult mRNA-1273 recipients, however a smaller proportion of pediatric participants self-identified as Hispanic (15.9%) compared to young adult participants (26.4%).

Table 27. Demographics and Other Baseline Characteristics, Participants 6 Through 11 Years of Age, Study P204, and Participants 18 Through 25 Years, Study P301, Per-Protocol Immunogenicity Subset

Characteristic	6-11 Years mRNA-1273 50 µg N=320	18-25 Years mRNA-1273 100 µg N=295
Sex, n (%)	--	--
Female	152 (47.5)	153 (51.9)
Male	168 (52.5)	142 (48.1)
Age	--	--
6-8 years, n (%)	156 (48.8)	--
9-11 years, n (%)	164 (51.3)	--
Mean (SD)	8.6 (1.74)	22.4 (2.19)
Median age, years	9	23
Race, n (%)	--	--
American Indian or Alaska Native	1 (0.3)	3 (1.0)
Asian	23 (7.2)	30 (10.2)
Black or African American	36 (11.3)	29 (9.8)
Native Hawaiian or other Pacific Islander	0	2 (0.7)
White	220 (68.8)	206 (69.8)
Other	6 (1.9)	8 (2.7)
Multiracial	29 (9.1)	14 (4.7)
Not reported	4 (1.3)	3 (1.0)
Missing	1 (0.3)	0
Ethnicity, n (%)	--	--
Hispanic or Latino	51 (15.9)	78 (26.4)
Not Hispanic or Latino	266 (83.1)	215 (72.9)
Not reported	3 (0.9)	0
Unknown	0	2 (0.7)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	178 (55.6)	145 (49.2)
Communities of Color	141 (44.1)	150 (50.8)
Missing	1 (0.3)	0
Country, n (%)	--	--
US	320 (100)	295 (100)
Canada	0	0
Obesity status[b], n (%)	--	--
Obese	62 (19.4)	68 (23.1)
Non-obese	258 (80.6)	226 (76.6)
Missing	0	1 (0.3)

Source: P204 (6-11 years) Table 14.1.3.3.2
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. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P204 and BMI ≥30 kg/m2 for P301

The demographics characteristics for participants 6-11 years included the safety population were similar between the mRNA-1273 and placebo groups (Table 28). Though not shown, the demographic characteristics for 6-11-year-old participants in the PP Set for Efficacy (N=2,644 vaccine group, N=853 placebo group) were similar to the baseline characteristics of safety population.

Table 28. Demographic and Baseline Characteristics, Participants 6 Through 11 Years of Age, P204 Part 2, Safety Set

Characteristic	mRNA-1273 50 µg N=3007	Placebo N=995
Sex, n (%)	--	--
Female	1453 (48.3)	514 (51.7)
Male	1554 (51.7)	481 (48.3)
Age	--	--
6-8 years, n (%)	1514 (50.3)	484 (48.6)
9-11 years, n (%)	1493 (49.7)	511 (51.4)
Mean (SD)	8.5 (1.65)	8.5 (1.64)
Median	8.0	9.0
Race, n (%)	--	--
White	1957 (65.1)	668 (67.1)
Black	309 (10.3)	93 (9.3)
Asian	298 (9.9)	100 (10.1)
American Indian or Alaska Native	14 (0.5)	3 (0.3)
Native Hawaiian or other Pacific Islander	4 (0.1)	0
Multiracial	327 (10.9)	97 (9.7)
Other	62 (2.1)	22 (2.2)
Not reported	23 (0.8)	10 (1.0)
Unknown	9 (0.3)	1 (0.1)
Missing	4 (0.1)	1 (0.1)
Ethnicity, n (%)	--	--
Hispanic or Latino	561 (18.7)	181 (18.2)
Not Hispanic or Latino	2417 (80.4)	805 (80.9)
Not reported	22 (0.7)	5 (0.5)
Unknown	7 (0.2)	4 (0.4)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	1542 (51.3)	536 (53.9)
Communities of color	1459 (48.5)	456 (45.8)
Missing	6 (0.2)	3 (0.3)
Country, n (%)	--	--
US	2977 (99.0)	985 (99.0)
Canada	30 (1.0)	10 (1.0)
Obesity status[b], n (%)	--	--
Obese	608 (20.2)	195 (19.6)
Non-obese	2399 (79.8)	800 (80.4)
Baseline SARS-CoV-2 status[c], n (%)	--	--
Positive	257 (8.5)	87 (8.7)
Negative	2703 (89.9)	880 (88.4)
Missing	47 (1.6)	28 (2.8)

Source: P204 (6-11 years) Table 14.1.3.2.
Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.
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. Obesity is defined as BMI >95th percentile of the WHO growth reference data for P204 and BMI >30 kg/m2 for P301
c. Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result on Day 1. Negative is defined as a negative RT-PCR test and negative Elecsys result on Day 1.

Demographic characteristics of Part 1 participants were similar to those of Part 2 participants.

Comorbidities at baseline

Participants with stable chronic medical conditions were eligible for enrollment, including those with comorbidities which may lead to increased risk of severe COVID-19 such as obesity, chronic lung disease (including asthma), clinically significant cardiac disorders, diabetes mellitus, and HIV infection. In Part 2, 27.9% of mRNA-1273 recipients and 26.1% of placebo recipients had at least one of these comorbidities. Obesity was the most common baseline comorbidity, reported by 20.2% of the mRNA-1273 recipients and by 19.6% of the placebo recipients. The rates of baseline comorbidities were similar between the Part 1 and Part 2 participants.

Table 29. Baseline Comorbidities, Participants 6 Through 11 Years of Age, Study P204 Part 2, Safety Set

Comorbidity	mRNA-1273 50 µg N=3007	Placebo N=995
Any of the following comorbidities, n (%)	840 (27.9)	260 (26.1)
Obesity[a]	608 (20.2)	195 (19.6)
Chronic lung disease (including asthma)[b]	279 (9.3)	90 (9.0)
Asthma[c]	250 (8.3)	83 (8.3)
Clinically significant cardiac disorders[d]	19 (0.6)	7 (0.7)
Diabetes mellitus	9 (0.3)	5 (0.5)
HIV	4 (0.1)	0

Source: P204 (6-11 years) Tables 14.1.3.2, 14.1.4.1.2.1.2, 14.1.4.1.2.2.2, 14.1.4.1.2.3.2, 14.1.4.1.2.4.2, 14.1.4.1.2.5.2; Sponsor response to IR dated April 15, 2022

a. BMI ≥ 95th percentile for age and gender (WHO definition)

b. Includes sleep apnea, wheezing, bronchospasm, bronchopulmonary dysplasia, pulmonary fibrosis, asthma, and cystic fibrosis

c. Includes bronchial hyperreactivity

d. Includes Aortic dilatation, Aortic dissection, Arterial switch operation, Atrioventricular block first degree, Bicuspid aortic valve, Cardiac ablation, Cardiac operation, Coarctation of the aorta, Double outlet right ventricle, Extrasystoles, Fallots tetralogy, Heart block congenital, Heart disease congenital, Hypertrophic cardiomyopathy, Hypoplastic left heart syndrome, Palpitations, Patent ductus arteriosus, Pulmonary valve disease, Pulmonary valve stenosis, Supraventricular tachycardia, Systemic-pulmonary artery shunt, Transposition of the great vessels, Ventricular extrasystoles, Ventricular septal defect, Ventricular septal defect repair, and Wolff-Parkinson-White syndrome

4.4.2.3 Vaccine Effectiveness

Primary immunogenicity endpoint

Vaccine effectiveness in 6-11 year old participants was inferred through immunobridging to data in young adult participants 18-25 years in Study P301 using the co-primary endpoints of GMT ratio and difference in SRRs at 28 days post-Dose 2.

Immunogenicity was assessed using a PsVNA assay (ID50). Results for the co-primary endpoint of GMT ratio (6-11 years age group to young adults) are displayed in Table 30 below. GMTs were measured at one month after Dose 2 (Day 57) in subjects in the PP Immunogenicity Subset. The GMT ratio was 1.2 (95% CI 1.1, 1.4) which met the pre-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >0.8.

Table 30. Geometric Mean SARS-CoV-2 Neutralizing Titers as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 6 Through 11 Years of Age, Study P204, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

6-11 Years 50 µg GMT (95% CI) [a] N1=319	18-25 Years 100 µg GMT (95% CI) [a] N1=295[c]	GMT Ratio[b] (6-11 Years/18-25 Years) (95% CI)	Met Success Criterion[b]
1610.2 (1456.6, 1780.0)	1299.9 (1171.2, 1442.7)	1.2 (1.1, 1.4)	Yes

Source: P204 (6-11 years), Table 14.2.1.1.3.1.2
LLOQ: 18.5, ULOQ: 45118
N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
GMT is estimated by geometric least square (LS) means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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. The noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is >0.67 based on the noninferiority margin of 1.5 and the GMR point estimate >0.8 (minimum threshold).
c. Differs from N1=296 used for the comparator group for study P203 as one participant was excluded from the P301 per-protocol immunogenicity subset due to differences in exclusion criteria as specified in the SAP for P203 and P204.

Results for the co-primary endpoint of difference in SRRs between participants 6-11 years of age and young adults are displayed in Table 31, below. The difference in SRRs was 0.1% (95% CI -1.9, 2.1) which met the pre-specified success criterion of a LL of the 95% CI greater than −10% and a point estimate >−5%. There were 3 participants 6-11 years in the PP Immunogenicity Subset who failed to meet the seroresponse definition. All 3 had baseline and post-vaccination ID50 titers below the lower limit of quantification (LLOQ).

Table 31. Seroresponse Rates as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 6 Through 11 Years of Age, Study P204, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

6-11 Years 50 µg Seroresponders[a] n (%) (95% CI)[b] N1=316	18-25 Years 100 µg Seroresponders[a] n (%) (95% CI)[b] N1=295[e]	Difference in Seroresponse Rate % (6-11 Years−18-25 Years) (95% CI)[c]	Met Success Criterion[d]
313 (99.1%) (97.3, 99.8)	292 (99.0%) (97.1, 99.8)	0.1% (-1.9, 2.1)	Yes

Source: Study P204 Table 14.2.1.2.3.1.2
N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint.
a. 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 N1.
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
d. The noninferiority of difference in seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is >-10% and the seroresponse difference point estimate is >-5%.
e. Differs from N1=296 used for the comparator group for study P203 as one participant was excluded from the P301 per-protocol immunogenicity subset due to differences in exclusion criteria as specified in the SAP for P203 and P204.

Subgroup analyses of primary immunogenicity endpoint

The GMT ratio and difference in SRRs across demographic subgroup were consistent with the results obtained based on the general study population, though some of these analyses were limited by small subgroup size. The majority of participants in both comparator groups included in the PP Immunogenicity Subset were SARS-CoV-2 negative at baseline, however subgroup analyses based on status at baseline demonstrated a numerically higher GMT (with non-overlapping CIs) at Day 57 in baseline positive participants compared to baseline negative participants.

Table 32. Subgroup Analyses of GMT Ratio and Difference in Seroresponse Rate as Measured by Pseudovirus nAb Assay (ID50) at Day 57, Participants 6 Through 11 Years of Age, Study P204, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

Characteristic	6-11 Years 50 µg N=320 GMT (95% CI)	18-25 Years 100 µg N=295 GMT (95% CI)	GMT Ratio[a] (95% CI)	6-11 Years 50 µg N=320 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years 100 µg N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponses, % (95% CI)[d]
Sex	--	--	--	--	--	--
Male	n=167 1665.1 (1441.9, 1922.9)	n=142 1349.5 (1154.5, 1577.5)	**1.2** **(1.0, 1.5)**	162/164 (98.8) (95.7, 99.9)	141/142 (99.3) (96.1, >99.9)	**-0.5** **(-3.7, 2.8)**
Female	n=152 1552.0 (1349.0, 1785.6)	n=153 1255.4 (1091.7, 1443.7)	**1.2** **(1.0, 1.5)**	151/152 (99.3) (96.4, >99.9)	151/153 (98.7) (95.4, 99.8)	**0.6** **(-2.4, 4.1)**
Race	--	--	--	--	--	--
Black or African American	n=36 1500.3 (1118.5, 2012.3)	n=29 1479.0 (1066.3, 2051.3)	**1.0** **(0.7, 1.6)**	35/35 (100) (90.0, 100)	29/29 (100) (88.1, 100)	**NE**
White	n=219 1690.4 (1496.7, 1909.1)	n=206 1312.6 (1157.8, 1488.1)	**1.3** **(1.1, 1.5)**	215/217 (99.1) (96.7, 99.9)	204/206 (99.0) (96.5, 99.9)	**<0.1** **(-2.4, 2.6)**
Other	n=64 1418.9 (1131.7, 1779.0)	n=60 1181.1 (935.1, 1491.9)	**1.2** **(0.9, 1.7)**	63/64 (98.4) (91.6, >99.9)	59/60 (98.3) (91.1, >99.9)	**0.1** **(-6.9, 7.5)**
Ethnicity	--	--	--	--	--	--
Hispanic or Latino	n=50 2214.4 (1800.7, 2723.1)	n=78 1502.3 (1273.1, 1772.9)	**1.5** **(1.1, 1.9)**	49/49 (100) (92.7, 100)	78/78 (100) (95.4, 100)	**NE**
Not Hispanic or Latino or Missing	n=269 1517.6 (1355.2, 1699.4)	n=217 1233.9 (1087.9, 1399.6)	**1.2** **(1.0, 1.5)**	264/267 (98.9) (96.8, 99.8)	214/217 (98.6) (96.0, 99.7)	**0.3** **(-2.1, 3.0)**
Race and ethnicity group	--	--	--	--	--	--
White non-Hispanic	n=178 1563.6 (1359.0, 1798.9)	n=145 1220.1 (1044.5, 1425.1)	**1.3** **(1.0, 1.6)**	175/177 (98.9) (96.0, 99.9)	143/145 (98.6) (95.1, 99.8)	**0.2** **(-2.8, 3.9)**
Communities of Color	n=140 1680.1 (1454.4, 1940.8)	n=150 1382.0 (1202.2, 1588.6)	**1.2** **(1.0, 1.5)**	137/138 (99.3) (96.0, >99.9)	149/150 (99.3) (96.3, >99.9)	**> -0.1** **(-3.4, 3.0)**

Characteristic	6-11 Years 50 µg N=320 GMT (95% CI)	18-25 Years 100 µg N=295 GMT (95% CI)	GMT Ratio[a] (95% CI)	6-11 Years 50 µg N=320 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years 100 µg N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponses, % (95% CI)[d]
Obesity Status	--	--	--	--	--	--
Obese[e]	n=62 1945.7 (1442.4, 2624.6)	n=68 1622.0 (1218.7, 2158.6)	**1.2** **(0.8, 1.8)**	60/61 (98.4) (91.2, >99.9)	68/68 (97.1) (89.8, 99.6)	**1.3** **(-6.1, 8.7)**
Non-obese	n=257 1538.3 (1392.0, 1700.0)	n=226 1219.7 (1096.4, 1356.9)	**1.3** **(1.1, 1.5)**	253/255 (99.2) (97.2, 99.9)	225/226 (99.6) (97.6, >99.9)	**-0.3** **(-2.4, 1.7)**
Baseline SARS-CoV-2 status	--	--	--	--	--	--
Negative[f,h]	n=321 1616.5 (1259.5, 1790.4)	n=300 1264.3 (1137.5, 1405.2)	**1.3** **(1.1, 1.5)**	n=318 315 (99.1) (97.3, 99.8)	n=300 294 (98.0) (95.7, 99.3)	**1.1** **(-1.0, 3.5)**
Positive[f,g]	n=38 4081.4 (2771.7, 6010.0)	n=15 1260.7 (676.4, 2349.9)	**3.2** **(1.5, 6.8)**	n=38 38 (100) (90.7, 100.0)	n=15 12 (80.0) (51.9, 95.7)	**20.0** **(7.0, 45.4)**

Source: Study P204 (6-11 years) Table 14.2.1.1.3.2.2, 14.2.1.1.3.3.2, 14.2.1.1.3.7.2, 14.2.1.1.3.8.2, 14.2.1.2.3.2.2, 14.2.1.2.3.3.2, 14.2.1.2.3.7.2, 14.2.1.2.3.8.2
LLOQ: 18.5, ULOQ: 45118
n = Number of subjects in subgroup with non-missing data at baseline and the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
GMT is estimated by geometric least square (LS) means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
e. Obesity is defined as BMI >= 95th percentile of the WHO growth reference data for P204 and BMI >=30 kg/m2 for P301.
f. Results by baseline SARS-CoV-2 status were based on the Immunogenicity Subset, which included for 6-11 years N= 364 and for 18-25 years N=340. Total Ns include participants for whom baseline SARS-CoV-2 status are missing. The Immunogenicity Subset consists of participants in the Full Analysis Set who have baseline (Day 1) SARS-CoV-2 status available and have baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
g. 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.
h. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Exploratory immunogenicity analyses against variants

Exploratory assessment of the immune response against the Delta variant was conducted in the Part 1 expansion PP immunogenicity set, which consisted of participants who received the 50-µg dose of mRNA-1273 in Part 1 of the study and who were previously not included in the Part 1 PP immunogenicity set used for dose selection for Part 2. Immunogenicity against Delta was measured by a qualified, non-validated PsVNA ID50 assay in which the Delta spike variant serves as the source of the spike protein (Duke University Medical Center). Comparison of the PsVNA levels against both the ancestral strain and the Delta variant are displayed in Table 33. In this group of participants 6-11 years of age, GMT observed at 4 weeks post Dose 2 against Delta was approximately 2.5-fold lower compared to those against the ancestral strain. This was consistent with the results observed in adults from Study P301.[62]

Table 33. Pseudovirus nAb Level Against the Ancestral Strain and Delta Strain, Participants 6 Through 11 Years of Age, Study P204 Part 1, Expansion Per-Protocol Immunogenicity Set

Measurement	Ancestral Strain mRNA-1273 50 µg N=134	Delta Strain (B.1.617.2) mRNA-1273 50 µg N=134
Baseline GMT	9.4	9.3
GMT observed at Day 57	1964.6	756.4
GMFR (95% CI)[a] at Day 57 from baseline	209.5 (182.9, 239.8)	81.8 (70.4, 95.0)
Seroresponse, n (%)[b] at Day 57 (95% CI)[c]	133 (99.3%) (95.9, 100.0)	133 (99.3%) (95.9, 100.0)

Source: P204 (6-11 years) Table 21 clincal-overview-peds-6-12-yrs.pdf, Tables 14.2.3.1.3.1, 14.2.1.1.3.4.1, 14.2.1.2.3.4.1
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.
a. 95% CI is calculated based on the t-distribution of the log-transformed values for GMFR, then 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.

Efficacy evaluation

Vaccine efficacy (VE) was descriptively analyzed as a secondary endpoint in the study, with the data cutoff date of November 10, 2021. As a result of the authorization of an alternative COVID-19 vaccine for this age group and subsequent unblinding and crossover, the median duration of blinded follow-up for efficacy was 51 days after Dose 2. The study evaluated the first occurrence of symptomatic COVID-19 among participants in the PP efficacy set without evidence of previous SARS-CoV-2 at baseline, using two different case definitions (defined in Appendix B). Using the CDC case definition, there were 3 cases among 2,644 mRNA-1273 recipients and 4 cases among 853 placebo recipients, for an estimated VE of 76.8% (95% CI −37.3, 96.6) (Table 34). Using the P301 definition, there were 3 cases in each group, for an estimated VE of 69.0% (95% CI −131.4, 95.8). Vaccine efficacy could not be reliably determined due to the small number of COVID-19 cases accrued during the study, resulting in wide 95% CIs that include zero.

Table 34. COVID-19 Incidence Starting 14 Days After Dose 2, Participants 6 Through 11 Years of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

COVID-19 Case Definition	mRNA-1273 50 µg N=2644 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=853 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
CDC definition[e]	3 (0.1%) 594.9 5.0 (1.0, 14.7)	4 (0.5%) 184.2 21.7 (5.9, 55.6)	76.8% (−37.3, 96.6)
P301 definition[d]	3 (0.1%) 595.2 5.0 (1.0, 14.7)	3 (0.4%) 184.5 16.3 (3.4, 47.5)	69.0% (−131.4, 95.8)

Sources: P204 (6-11 years) Table 14.2.7.1.1.2, 14.2.8.1.1.2
a. Person-years is defined as the total years from randomization date for Part 2 to the date of event (CDC case definition of COVID-19 or P301 case definition of COVID-19, depending on 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
d. COVID-19 (P301 primary definition) is at least 2 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF), 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; AND at least 1 positive RT-PCR test for SARS-CoV-2.
e. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.

For the discussion of clinical efficacy below, the broader CDC definition of COVID-19 will be used to maximize the number of cases and the precision of the estimate.

Subgroup analyses of vaccine efficacy
Vaccine efficacy by subgroup was not evaluated given the small number of cases in both treatment groups. Of the 7 COVID-19 cases per CDC case definition, the majority occurred in participants who identified as Hispanic or Latino and/or non-White (2 out of 3 cases in the mRNA-1273 group and 3 out of 4 cases in the placebo group). All the cases occurred in participants who were non-obese.

Vaccine efficacy: including participants with prior SARS-CoV-2 infection
Starting 14 days after Dose 2, among participants with evidence of prior SARS-CoV-2 infection at baseline, one placebo participant and no mRNA-1273 participants developed COVID-19 per the CDC definition. Thus, there were insufficient data to draw conclusions regarding vaccine efficacy among individuals with evidence of prior SARS-CoV-2 infection. Analysis of vaccine efficacy that includes a combined population of participants with and without evidence of prior SARS-CoV-2 infection are presented in Table 35 below. Vaccine efficacy in this combined population was similar to the VE for participants with negative SARS-CoV-2 status at baseline using the CDC definition. However, the VE for the combined population had greater precision around the point estimate (82.0% with 95% CI: 7.4, 97.2), compared those participants who were SARS-CoV-2 negative at baseline (76.8% with 95%: CI -37.3, 96.6).

Table 35. COVID-19 Incidence (CDC Case Definition) Starting 14 Days After Dose 2, Participants 6 Through 11 Years of Age Regardless of SARS-CoV-2 Status at Baseline, Study P204 Part 2, FAS

COVID-19 Case Definition	mRNA-1273 50 µg N=3005 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=997 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
CDC definition[d]	3/2980 (0.1) 312.9 9.6 (2.0, 28.0)	5/966 (0.5) 94.0 53.2 (17.3, 124.2)	82.0% (7.4, 97.2)

Source: P204 (6-11 years) Table 14.2.8.4.2.2
N1 is the number of participants at risk. Percentages are based on N1.
a. Person-years is defined as the total years from randomization date for Part 2 to the date of event (CDC case definition of COVID-19), 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
d. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.

COVID-19 cases in this study accrued during the time period when the Delta variant was the predominant circulating strain in the US. Of the 36 COVID-19 cases that occurred any time after Dose 1, sequencing data are available for 6 participants (1 mRNA-1273 and 5 placebo) at the time of this review. All 6 cases were sequenced to be from the Delta variant lineage.

Severe COVID-19 cases
There were no reports of severe COVID-19 cases in participants 6-11 years of age in this study as of the data cutoff date of November 10, 2021.

Additional efficacy analyses
Additional analyses of the efficacy endpoint were conducted to evaluate VE against COVID-19, based on the CDC case definition, by time period (Table 36). VE for the prevention of COVID-19 starting any time after Dose 1 was 80.5% (95% CI 59.6, 90.6). Although these data suggest some protection against COVID-19 following one dose, the follow-up time after one dose was limited as almost all study participants went on to receive a second dose. These data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Given the longer time period and broader population used for analyses of COVID-19 following Dose 1, a larger number of COVID-19 cases were accrued, resulting in tighter CIs around the VE point estimate, with LB of the 95% CIs well above 0.

Table 36. Incidence of COVID-19 (CDC Case Definition) by Time Period, Participants 6 Through 11 Years of Age, Study P204 Part 2, mITT1 Set

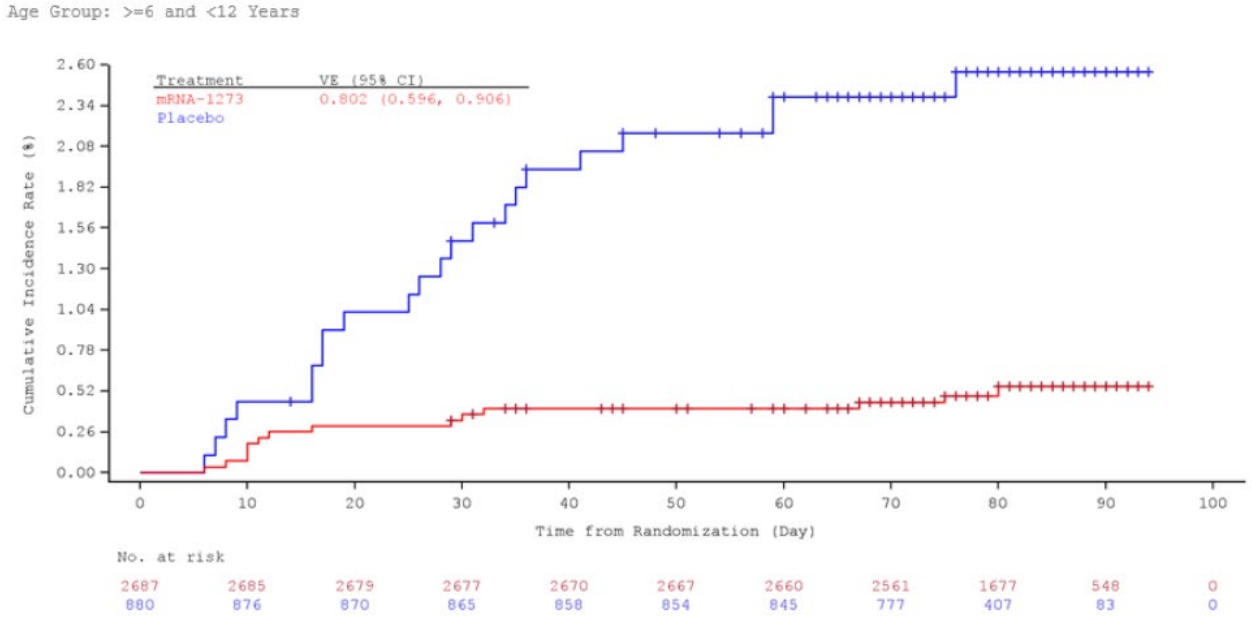
First COVID-19[d] Occurrence	mRNA-1273 50 µg N=2687 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=880 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
Any time after Dose 1	14/2687 (0.5) 602.7 23.2 (12.7, 39.0)	22/880 (2.5) 187.4 117.4 (73.6, 177.8)	80.2% (59.6, 90.6)
Any time after Dose 1 to before Dose 2	9/2687 (0.3) 220.2 40.9 (18.7, 77.6)	15/880 (1.7) 209.970 71.4 (117.5, 346.3)	80.5% (52.5, 92.5)
Any time after Dose 2	5/2668 (0.2) 381.8 13.1 (4.3, 30.6)	7/855 (0.8) 115.2 60.7 (24.4, 125.1)	78.4% (21.1, 94.6)

Source: P204 (6-11 years) Table 14.2.8.4.1.2.
N1 is the number of participants at risk. Percentages are based on N1.
a. Person-years for each time period is defined as the total years from the start of each time period to the date of CDC case definition of COVID-19, the end of each time period, last date of study participation, efficacy data cutoff date, whichever is earlier.
b. Incidence rate for each time period is defined as the number of participants with an event during the time period divided by the number of participants at risk at the beginning of each time period 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. Vaccine efficacy is 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 for the time period.
d. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.

Cumulative incidence curves

The cumulative incidence curve for COVID-19 in the mITT1 set is based on the CDC case definition and begins on the day of Dose 1 (Figure 2). Cases of COVID-19 remained similarly low in the mRNA-1273 and placebo groups until approximately 7 days after Dose 1, at which point the curves diverge, with more cases accumulating in the placebo group than in the mRNA-1273 group.

Figure 2. Cumulative Incidence Curve of COVID-19 (CDC Case Definition) Starting After Randomization, Participants 6 Through 11 Years of Age (P204 Part 2), mITT1 Set



Source: P204 (6-11 years) Figure 14.2.5.2.3.2

SARS-CoV-2 infection

Additional analyses evaluated VE against SARS-CoV-2 infection regardless of symptoms, which includes both COVID-19 cases as well as cases of asymptomatic infection. Asymptomatic SARS-CoV-2 infection is defined as absence of COVID-19 symptoms (i.e., not meeting the case definition for COVID-19 per CDC definition or P301 definition) and either of the following: (a) bAb levels against SARS-CoV-2 nucleocapsid (N) protein (as measured by *Roche Elecsys*) negative at Day 1 that becomes positive post-baseline or (b) positive RT-PCR test post-baseline. Per protocol, all participants are scheduled for collection of nasal swab samples for RT-PCR testing on Day 29 (pre-Dose 2), 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). Given the timing of the data cutoff, the Day 209 and Day 394 visits had not occurred for study participants and thus data are only available through the Day 57 visit. Additionally, N-serology testing was conducted at scheduled study visits based on the participant's assigned phlebotomy cohort, which included a blood collection on Day 57 for a small number of participants. Asymptomatic SARS-CoV-2 infections may also be identified at unscheduled study visits triggered by potential exposure to a close contact with SARS-CoV-2 infection. Given the limited number of RT-PCR and N-serology assessment time points, it is unlikely that all cases of asymptomatic SARS-CoV-2 infection which occurred during the study were captured.

Results for the analyses of vaccine efficacy against SARS-CoV-2 infection regardless of symptoms and against asymptomatic SARS-CoV-2 infection are shown in Table 37 below. The VE point estimates for these endpoints were generally similar to that observed for efficacy against symptomatic COVID-19. VE against SARS-CoV-2 infection regardless of symptoms was primarily driven by the larger number of asymptomatic cases compared to COVID-19 cases in the study. It is also important to note that these analyses include limited follow-up time during a period when Delta was the predominant SARS-CoV-2 strain.

Table 37. Incidence of SARS-CoV-2 Starting 14 Days After Dose 2, Participants 6 Through 11 Years of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Endpoint	mRNA-1273 50 µg N=2644 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=853 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
SARS-CoV-2 infection (regardless of symptoms)	12 (0.5) 591.2 20.3 (10.5, 35.5)	14 (1.6) 182.1 76.9 (42.0, 129.0)	73.6% (38.5, 88.8)
Asymptomatic SARS-CoV-2 infection	9 (0.3) 591.2 15.2 (7.0, 28.9)	10 (1.2) 182.1 54.9 (26.3, 101.0)	72.3% (24.1, 90.0)

Sources: P204 (6-11 years) Table 14.2.5.1.1.2, Table 14.2.6.1.1.2.1
a. Person-years is defined as the total years from 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 on 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

4.4.2.4 Safety

Overview of adverse events

Safety analyses are presented for data from participants 6-11 years of age in the blinded phase (Part 2) of Study P204 through the cutoff date of November 10, 2021, that includes a median duration of blinded follow-up of 51 days post-Dose 2. Additional safety analyses through the extended data cutoff of February 21, 2022, are presented in Section 4.4.2.5. From open-label phase (Part 1) of Study P204, only safety analyses of SAEs and other unsolicited AEs of clinical interest are presented.

Table 38 below summarizes AEs in the participants 6-11 years from Part 2. The proportions of MAAEs and SAEs were balanced between vaccine and placebo groups. SAEs were uncommon (0.2% for both groups), and no deaths were reported in either group. As compared to the placebo group, the vaccine group experienced higher rates of solicited local and systemic ARs, unsolicited AEs within 28 days after vaccination, and related unsolicited AEs.

Table 38. Participants 6 Through 11 Years of Age Reporting at Least One Safety Event, Study P204, Safety Set, Solicited Safety Set, Solicited Safety Set

Event Type	mRNA-1273 50 µg	Placebo
Solicited adverse reactions within 7 days	--	--
Solicited local adverse reaction (any dose), n/N (%)	2963/3006 (98.6)	649/994 (65.3)
Dose 1	2814/3004 (93.7)	480/993 (48.3)
Dose 2	2849/2988 (95.3)	490/969 (50.6)
Grade 3 or 4 solicited local adverse reaction (any dose)	167/3006 (5.6)	8/994 (0.8)

Event Type	mRNA-1273 50 µg	Placebo
Solicited systemic adverse reaction (any dose), n/N (%)	2603/3006 (86.6)	668/994 (67.2)
Dose 1	1740/3004 (57.9)	518/993 (52.2)
Dose 2	2335/2988 (78.1)	485/969 (50.1)
Grade 3 or 4 systemic adverse reaction (any dose)	406/3006 (13.5)	26/994 (2.6)
Immediate[a] unsolicited adverse events after vaccination, n/N (%)	--	--
After any dose	10/3007 (0.3)	6/995 (0.6)
Dose 1	3/3007 (<0.1)	3/995 (0.3)
Dose 2	7/2990 (0.2)	3/971 (0.3)
Unsolicited adverse events, n/N (%)	n/N (%)	n/N (%)
Unsolicited TEAE within 28 days after any injection	891/3007 (29.6)	250/995 (25.1)
Non-serious unsolicited TEAE	889/3007 (29.6)	249/995 (25.0)
Related non-serious unsolicited TEAE	319/3007 (10.6)	50/995 (5.0)
Severe non-serious unsolicited TEAE	11/3007 (0.4)	1/995 (0.1)
Related severe non-serious unsolicited TEAE	9/3007 (0.3)	1/995 (0.1)
Medically attended adverse event (MAAE)[b]	523/3007 (17.4)	180/995 (18.1)
Related MAAE[b]	36/3007 (1.2)	4/995 (0.4)
SAE[b]	6/3007 (0.2)	2/955 (0.2)
Related SAE[c]	0	0
AEs of special interest (AESI)[b]	4/3007 (0.1)	2/955 (0.2)
Deaths[b]	0	0
TEAE leading to discontinuation of study vaccine[b]	4/3007 (0.1)	2/995 (0.2)
TEAE leading to discontinuation from study participation[b]	1/3007 (<0.1)	0

Sources: P204 (6-11 years) Table 14.3.1.1.1.2.1, 14.3.1.1.2.2.1, 14.3.1.1.3.2.1, 14.3.1.7.1.2, 14.3.1.7.2.2, 14.3.1.7.1.7.1, 14.3.1.7.1.7.2, 14.3.1.7.1.7.3, 14.3.1.1.3.2.1

Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

a. Within 30 minutes after vaccination

b. Events during entire blinded study period

Table 39 summarizes safety events by baseline SARS-CoV-2 status in the mRNA-1273 group. In the Safety Set, approximately 8.5% of mRNA-1273 recipients had evidence of prior SARS-CoV-2 infection at baseline. Rates of AEs were similar between the two subgroups, with the exception of solicited systemic adverse reactions after Dose 1, which were more frequent among participants with positive than negative SARS-CoV-2 status at baseline.

Table 39. Safety Overview by Baseline SARS-CoV-2 Status, Participants 6 Through 11 Years of Age, P204 Part 2, Safety Set, Solicited Safety Set, Solicited Safety Set

Event Type	Baseline SARS-CoV-2 Negative n/N1 (%)	Baseline SARS-CoV-2 Positive n/N1 (%)
Solicited adverse reactions within 7 days	--	--
Solicited local adverse reaction (any dose)	2666/2702 (98.7)	251/257 (97.7)
Dose 1	2536/2700 (93.9)	236/257 (91.8)
Dose 2	2562/2686 (95.4)	242/255 (94.9)
Grade 3 local adverse reaction (any dose)	150/2702 (5.6)	14/257 (5.4)
Solicited systemic adverse reaction (any dose)	2340/2702 (86.6)	220/257 (85.6)
Dose 1	1531/2700 (56.7)	180/257 (70.0)
Dose 2	2112/2686 (78.6)	184/255 (72.2)
Grade 3 systemic adverse reaction (any dose)	357/2702 (13.2)	35/257 (13.6)

Event Type	Baseline SARS-CoV-2 Negative n/N1 (%)	Baseline SARS-CoV-2 Positive n/N1 (%)
Unsolicited adverse events	n/N (%)	n/N (%)
Unsolicited AE within 28 days after any injection	803/2703 (29.7)	73/257 (28.4)
Severe non-serious unsolicited AE	10/2703 (0.4)	1/257 (0.4)
MAAE within 28 days after any injection	360/2703 (13.3)	37/257 (14.4)

Sources: P204 (6-11 years) Tables 14.3.1.1.5.1, 14.3.1.1.5.2, 14.3.1.7.1.4.2.1; Response to Item #2 in IR dated May 11, 2022
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

Immediate adverse events

Immediate unsolicited AEs occurring within 30 minutes of vaccination were infrequent and occurred in 10 mRNA-1273 participants (0.3%) and 6 placebo participants (0.6%). Of these, 3 in the mRNA-1273 group (<0.1%) and 3 in the placebo group (0.3%) occurred after Dose 1, and 7 in the mRNA-1273 group (0.2%) and 3 in the placebo group (0.3%) occurred after Dose 2. The majority of events were related to vaccine administration or injection site reactions. None of the events were clinically concerning for anaphylaxis. One mRNA-1273 recipient reported flushing after vaccination, without any other symptoms or vital sign changes.

Solicited adverse reactions

Solicited local and systemic adverse reactions generally occurred more frequently and were more severe after Dose 2 than Dose 1. The rates of solicited adverse reactions after any dose of mRNA-1273 were as follows: pain at the injection site (98.4%), fatigue (73.1%), headache (62.1%), myalgia (35.3%), chills (34.6%), nausea/vomiting (29.3%), axillary swelling/tenderness (27.0%), fever (25.7%), erythema at the injection site (24.0%), swelling at the injection site (22.3%), and arthralgia (21.3%). Grade 3 local ARs were reported by 1.8% and 4.1% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. Grade 3 systemic ARs were reported by 1.8% and 12.2% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. The most commonly reported Grade 3 systemic ARs reported after Dose 2 were fatigue (6.4%) and headache (4.0%). Fever was reported by 3.3% and 23.9% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. Grade 3 fever (temperature 39-40°C) was reported by 0.6% and 3.8% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. The frequencies of local and systemic adverse reactions within 7 days after each vaccination in participants Part 2 study participants are summarized below in Table 40 and Table 41.

Table 40. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Participants 6 Through 11 Years of Age, Study P204 Part 2, Solicited Safety Set

Event	mRNA-1273 50 µg Dose 1 N=3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2988	Placebo Dose 2 N=969
Any local adverse reaction, n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	2814 (93.7)	480 (48.3)	2849 (95.3)	490 (50.6)
Grade 1	1929 (64.2)	448 (45.1)	1493 (50.0)	446 (46.0)
Grade 2	831 (27.7)	29 (2.9)	1234 (41.3)	39 (4.0)
Grade 3	54 (1.8)	3 (0.3)	122 (4.1)	5 (0.5)

Event	mRNA-1273 50 µg Dose 1 N=3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2988	Placebo Dose 2 N=969
Pain at injection site, n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	2796 (93.1)	465 (46.8)	2832 (94.8)	480 (49.5)
Grade 1	2019 (67.2)	440 (44.3)	1695 (56.7)	445 (45.9)
Grade 2	749 (24.9)	25 (2.5)	1056 (35.3)	33 (3.4)
Grade 3	28 (0.9)	0	81 (2.7)	2 (0.2)
Erythema (redness), n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	349 (11.6)	13 (1.3)	559 (18.7)	10 (1.0)
Grade 1	233 (7.8)	9 (0.9)	266 (8.9)	7 (0.7)
Grade 2	100 (3.3)	3 (0.3)	260 (8.7)	2 (0.2)
Grade 3	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Swelling (hardness), n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	354 (11.8)	12 (1.2)	507 (17.0)	12 (1.2)
Grade 1	255 (8.5)	9 (0.9)	315 (10.5)	12 (1.2)
Grade 2	80 (2.7)	2 (0.2)	172 (5.8)	0
Grade 3	19 (0.6)	1 (0.1)	20 (0.7)	0
Axillary swelling or tenderness, n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	465 (15.5)	84 (8.5)	537 (18.0)	65 (6.7)
Grade 1	400 (13.3)	81 (8.2)	412 (13.8)	55 (5.7)
Grade 2	62 (2.1)	2 (0.2)	122 (4.1)	8 (0.8)
Grade 3	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)

Source: P204 (6-11 years) Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1.
Note: Any=Grade 1 or higher. There were no Grade 4 solicited local ARs reported.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
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. 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.

Table 41. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 6 Through 11 Years of Age, Part 2, Solicited Safety Set

Event	mRNA-1273 50 µg Dose 1 N=3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2988	Placebo Dose 2 N=969
Any systemic adverse reaction, n (%)	N1=3004	N1=993	N1=2988	N1=969
Any	1740 (57.9)	518 (52.2)	2335 (78.1)	485 (50.1)
Grade 1	1101 (36.7)	347 (34.9)	828 (27.7)	322 (33.2)
Grade 2	586 (19.5)	158 (15.9)	1143 (38.3)	149 (15.4)
Grade 3	53 (1.8)	12 (1.2)	364 (12.2)	14 (1.4)
Fever, n (%)	N1=3003	N1=993	N1=2988	N1=969
≥38.0°C	99 (3.3)	15 (1.5)	714 (23.9)	19 (2.0)
38.0°C to 38.4°C	54 (1.8)	10 (1.0)	383 (12.8)	12 (1.2)
38.5°C to 38.9°C	28 (0.9)	2 (0.2)	216 (7.2)	5 (0.5)
39°C to 40.0°C	17 (0.6)	2 (0.2)	115 (3.8)	2 (0.2)
Headache, n (%)	N1=3002	N1=993	N1=2986	N1=969
Any	938 (31.2)	306 (30.8)	1622 (54.3)	275 (28.4)
Grade 1	672 (22.4)	228 (23.0)	760 (25.5)	187 (19.3)
Grade 2	248 (8.3)	74 (7.5)	743 (24.9)	80 (8.3)
Grade 3	18 (0.6)	4 (0.4)	119 (4.0)	8 (0.8)

Event	mRNA-1273 50 µg Dose 1 N=3004	Placebo Dose 1 N=993	mRNA-1273 50 µg Dose 2 N=2988	Placebo Dose 2 N=969
Fatigue, n (%)	N1=3002	N1=993	N1=2986	N1=969
Any	1298 (43.2)	334 (33.6)	1925 (64.5)	335 (34.6)
Grade 1	852 (28.4)	215 (21.7)	800 (26.8)	226 (23.3)
Grade 2	415 (13.8)	111 (11.2)	934 (31.3)	101 (10.4)
Grade 3	31 (1.0)	8 (0.8)	191 (6.4)	8 (0.8)
Myalgia, n (%)	N1=3002	N1=993	N1=2986	N1=969
Any	438 (14.6)	96 (9.7)	843 (28.2)	105 (10.8)
Grade 1	315 (10.5)	73 (7.4)	428 (14.3)	75 (7.7)
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)
Arthralgia, n (%)	N1=3002	N1=993	N1=2986	N1=969
Any	260 (8.7)	75 (7.6)	482 (16.1)	84 (8.7)
Grade 1	213 (7.1)	65 (6.5)	308 (10.3)	71 (7.3)
Grade 2	44 (1.5)	9 (0.9)	149 (5.0)	13 (1.3)
Grade 3	3 (<0.1)	1 (0.1)	25 (0.8)	0
Nausea/vomiting, n (%)	N1=3002	N1=993	N1=2986	N1=969
Any	325 (10.8)	107 (10.8)	716 (24.0)	97 (10.0)
Grade 1	273 (9.1)	93 (9.4)	531 (17.8)	78 (8.0)
Grade 2	47 (1.6)	14 (1.4)	166 (5.6)	19 (2.0)
Grade 3	5 (0.2)	0	19 (0.6)	0
Chills	N1=3002	N1=993	N1=2986	N1=969
Any	309 (10.3)	67 (6.7)	904 (30.3)	74 (7.6)
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)
Grade 3	3 (<0.1)	0	19 (0.6)	0
Use of antipyretic or pain medication, n (%)	N=3004	N=993	N=2988	N=969
Any	730 (24.3)	95 (9.6)	1423 (47.6)	93 (9.6)

Source: P204 (6-11 years) Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1, Table 14.1.8.1.2, Table 14.1.8.2.2, Table 14.3.1.1.2.2.1
a. This was later found to be a data entry error. Actual temperature 100.4° F.
Note: Any=Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). There were no grade 4 solicited systemic ARs reported.
Toxicity grade for headache, fatigue, myalgia, arthralgia is defined as Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity;. Toxicity grade for nausea/vomiting is defined as Grade 1=no interference with activity or 1-2 episodes/24 hours; Grade 2=some interference with activity or >2 episodes/24 hours; Grade 3=prevents daily activity;; Toxicity grade for chills is defined as Grade 1=no interference with activity; Grade 2=some interference with activity not requiring medical intervention; Grade 3=prevents daily activity and requires medical intervention;

Duration of Adverse Reactions

Most local and systemic reactions were mild to moderate in severity, with onset 1-2 days post-vaccination, and resolved within 1 to 3 days after onset. Delayed solicited injection site reactions, defined as beginning after 7 days post-vaccination, were reported by 2.7% of mRNA-1273 recipients and 0.2% of placebo recipients. The majority of these events occurred after Dose 1. None of these delayed local reactions were medically attended and none were considered severe. The most common delayed local reaction was erythema.

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the demographic subgroups, although some race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Solicited local and systemic reactions after vaccination among mRNA-1273 recipients by SARS-CoV-2 status at baseline are shown in Table 42. After Dose 1, the frequencies of solicited local ARs were similar between the two groups, except for axillary swelling or tenderness, which was higher among those with positive (24.5%) than with negative (14.6%) SARS-CoV2 status at baseline. In general, solicited systemic ARs after Dose 1 were more frequently reported among participants with positive than with negative SARS-CoV-2 status at baseline, most notably for the solicited ARs of fever (16.3% vs 2.0%), headache (49.4% vs 29.5%), myalgia (24.5% vs 13.6%), and chills (19.8% vs 9.3%). In general, the frequencies of solicited local and systemic adverse reactions after Dose 2 were similar between participants with baseline negative and baseline positive SARS-CoV-2 status.

Table 42. Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose by Baseline SARS-CoV-2 Status, Participants 6 Through 11 Years of Age, P204 Part 2, Solicited Safety Set

Event	Baseline SARS-CoV-2 Negative Dose 1 N=2703 n (%)	Baseline SARS-CoV-2 Positive Dose 1 N=257 n (%)	Baseline SARS-CoV-2 Negative Dose 2 N=2703 n (%)	Baseline SARS-CoV-2 Positive Dose 2 N=257 n (%)
Any local adverse reaction	N1=2700	N1=257	N1=2686	N1=255
Any	2536 (93.9)	236 (91.8)	2562 (95.4)	242 (94.9)
Grade 3	47 (1.7)	4 (1.6)	110 (4.1)	11 (4.3)
Pain at injection site	N1=2700	N1=257	N1=2686	N1=255
Any	2522 (93.4)	234 (91.1)	2547 (94.8)	240 (94.1)
Grade 3	23 (0.9)	3 (1.2)	72 (2.7)	8 (3.1)
Erythema (redness)	N1=2700	N1=257	N1=2686	N1=255
Any	317 (11.7)	26 (10.1)	518 (19.3)	34 (13.3)
Grade 3	15 (0.6)	0	32 (1.2)	1 (0.4)
Swelling (hardness)	N1=2700	N1=257	N1=2686	N1=255
Any	317 (11.7)	29 (11.3)	468 (17.4)	29 (11.4)
Grade 3	17 (0.6)	1 (0.4)	18 (0.7)	2 (0.8)
Axillary swelling or tenderness	N1=2700	N1=257	N1=2686	N1=255
Any	394 (14.6)	63 (24.5)	474 (17.6)	48 (18.8)
Grade 3	2 (<0.1)	1 (0.4)	3 (0.1)	0
Any systemic adverse reaction	N1=2700	N1=257	N1=2686	N1=255
Any	1531 (56.7)	180 (70.0)	2112 (78.6)	184 (72.2)
Grade 3	37 (1.4)	16 (6.2)	330 (12.3)	24 (9.4)
Fever	N1=2699	N1=257	N1=2686	N1=255
≥38.0°C	55 (2.0)	42 (16.3)	635 (23.6)	61 (23.9)
38.0°C to 38.4°C	33 (1.2)	20 (7.8)	340 (12.7)	34 (13.3)
38.5°C to 38.9°C	10 (0.4)	17 (6.6)	187 (7.0)	21 (8.2)
39°C to 40.0°C	12 (0.4)	5 (1.9)	108 (4.0)	6 (2.4)
Headache	N1=2698	N1=257	N1=2684	N1=255
Any	796 (29.5)	127 (49.4)	1468 (54.3)	134 (52.5)
Grade 3	10 (0.4)	8 (3.1)	103 (3.8)	11 (4.3)
Fatigue	N1=2698	N1=257	N1=2684	N1=255
Any	1145 (42.4)	129 (50.2)	1744 (65.0)	145 (56.9)
Grade 3	20 (0.7)	11 (4.3)	169 (6.3)	14 (5.5)

Event	Baseline SARS-CoV-2 Negative Dose 1 N=2703 n (%)	Baseline SARS-CoV-2 Positive Dose 1 N=257 n (%)	Baseline SARS-CoV-2 Negative Dose 2 N=2703 n (%)	Baseline SARS-CoV-2 Positive Dose 2 N=257 n (%)
Myalgia	N1=2698	N1=257	N1=2684	N1=255
Any	367 (13.6)	63 (24.5)	747 (27.8)	75 (29.4)
Grade 3	9 (0.3)	2 (0.8)	63 (2.3)	3 (1.2)
Arthralgia	N1=2698	N1=257	N1=2684	N1=255
Any	224 (8.3)	33 (12.8)	427 (15.9)	43 (16.9)
Grade 3	3 (0.1)	0	22 (0.8)	1 (0.4)
Nausea/vomiting	N1=2698	N1=257	N1=2684	N1=255
Any	281 (10.4)	36 (14.0)	646 (24.1)	54 (21.2)
Grade 3	4 (0.1)	1 (0.4)	18 (0.7)	0
Chills	N1=2698	N1=257	N1=2684	N1=255
Any	251 (9.3)	51 (19.8)	815 (30.4)	68 (26.7)
Grade 3	2 (<0.1)	1 (0.4)	17 (0.6)	1 (0.4)

Source: P204 (6-11 years) Table 14.3.1.1.5.1, 14.3.1.1.5.2, response to Item #2 in IR dated May 11, 2022
Note: Any=Grade 1 or higher. There were no Grade 4 solicited ARs reported among mRNA-1273 participants.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 3=>100 mm. 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 3=prevents daily activity. Toxicity grade for headache, fatigue, myalgia, arthralgia is defined as Grade 1=no interference with activity, Grade 3=prevents daily activity; Toxicity grade for nausea/vomiting is defined as Grade 1=no interference with activity or 1-2 episodes/24 hours; Grade 3=prevents daily activity; Toxicity grade for chills is defined as Grade 1=no interference with activity; Grade 3=prevents daily activity and requires medical intervention

Unsolicited adverse events

The table below shows rates of unsolicited AEs in Part 2 that occurred within 28 days of vaccination and at rates of ≥1% in any group. The proportions of participants with any unsolicited AE were 29.6% and 25.1% in the vaccine and placebo groups, respectively. This observed difference was driven primarily by events in the System Organ Class (SOC) *General disorders and administration site conditions* that were mostly injection site adverse reactions, consistent with local reactogenicity reported by participants in the e-Diary. The most commonly reported unsolicited AEs among mRNA-1273 participants were upper respiratory tract infection (3.9%), injection site erythema (3.1%), and headache (2.6%).

Table 43. Unsolicited Adverse Events Occurring in ≥1% of Any Treatment Group Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Participants 6 Through 11 Years of Age, Study P204 Part 2, Safety Set

Unsolicited AE	mRNA-1273 50 µg N=3007 Any	Placebo N=995 Any	mRNA-1273 50 µg N=3007 Severe	Placebo N=995 Severe
Number of participants reporting unsolicited adverse events, n (%)	891 (29.6)	250 (25.1)	12 (0.4)	2 (0.2)
Number of unsolicited adverse events	1499	430	12	6
Infections and infestations, n (%)	302 (10.0)	106 (10.7)	1 (<0.1)	1 (0.1)
Upper respiratory tract infection	116 (3.9)	25 (2.5)	0	0
COVID-19	11 (0.4)	22 (2.2)	0	1 (0.1)*
Asymptomatic COVID-19	19 (0.6)	11 (1.1)	0	0
Psychiatric disorders, n (%)	9 (0.3)	11 (1.1)	0	1 (0.1)
Nervous system disorders, n (%)	84 (2.8)	33 (3.3)	1 (<0.1)	1 (0.1)
Headache	77 (2.6)	29 (2.9)	1 (<0.1)	1 (0.1)

Unsolicited AE	mRNA-1273 50 µg N=3007 Any	Placebo N=995 Any	mRNA-1273 50 µg N=3007 Severe	Placebo N=995 Severe
Respiratory, thoracic and mediastinal disorders, n (%)	184 (6.1)	70 (7.0)	0	0
Oropharyngeal pain	68 (2.3)	30 (3.0)	0	0
Nasal congestion	65 (2.2)	26 (2.6)	0	0
Cough	64 (2.1)	22 (2.2)	0	0
Rhinorrhoea	62 (2.1)	23 (2.3)	0	0
Gastrointestinal disorders, n (%)	81 (2.7)	29 (2.9)	0	0
Vomiting	24 (0.8)	11 (1.1)	0	0
Skin and subcutaneous tissue disorders, n (%)	71 (2.4)	10 (1.0)	2 (<0.1)	0
Musculoskeletal and connective tissue disorders, n (%)	48 (1.6)	18 (1.8)	0	1 (0.1)
General disorders and administration site conditions, n (%)	296 (9.8)	41 (4.1)	7 (0.2)	1 (0.1)
Injection site erythema	94 (3.1)	1 (0.1)	0	0
Fatigue	45 (1.5)	16 (1.6)	3 (<0.1)	1 (0.1)
Injection site lymphadenopathy	51 (1.7)	4 (0.4)	0	0
Injection site pain	28 (0.9)	11 (1.1)	2 (<0.1)	0
Injury, poisoning and procedural complications, n (%)	55 (1.8)	17 (1.7)	1 (<0.1)	0

Source: P204 (6-11 years) Table 14.3.1.8.1.2, Table 14.3.1.17.2.1.
Note: Percentages are based on the number of safety participants (N).
* Long COVID, further discussed in section on SAEs

Within 28 days after vaccination, lymphadenopathy-related events were reported by 1.9% of mRNA-1273 recipients and 0.6% of placebo recipients. These events included lymphadenopathy, lymph node pain, injection-site lymphadenopathy, and vaccination-site lymphadenopathy are plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected arm.

Within 28 days of vaccination, there was a numerical imbalance in abdominal pain (including events under the PTs of abdominal pain, abdominal pain upper, and abdominal pain lower) between the mRNA-1273 group and the placebo group. Abdominal pain was reported by 1.1% of participants in the mRNA-1273 group compared to 0.6% of participants in the placebo group. All events were mild to moderate in severity. The events assessed as related (n=6 in the mRNA-1273 group and none in the placebo group) all occurred within 7 days after vaccination and may represent post-vaccination reactogenicity that is clinically related to solicited adverse reactions of nausea/vomiting reported by 29.3% of mRNA-1273 recipients in the 7-day reporting period after any dose.

Within 28 days after vaccination, some respiratory tract infection-related PTs were reported more frequently in the vaccine group compared to the placebo group, such as Respiratory syncytial virus infection (0.3% vs 0%) and Upper respiratory tract infection (3.9% vs 2.5%). An analysis including all respiratory-tract infection related PTs, except COVID-19, showed a small imbalance of 5.9% in the vaccine group compared to 4.4% in the placebo group. Most events were mild in severity and no events were assessed as severe or serious. There was no imbalance noted between the two groups when assessing the rates of individual upper respiratory tract infection symptoms (e.g., nasal congestion, cough, rhinorrhea). FDA agrees with the investigator assessments that there is unlikely to be a causal association between the occurrence of these events and the study vaccine. Overall, the frequency and clinical course for

these events do not appear unusual for this pediatric study population during the late summer to fall season.

Adverse events of clinical interest
Participants are monitored in the study for AESIs based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (Appendix A).

Double Blind Phase (Part 2)
In Part 2 of the study, through the data cutoff of November 10, 2021, there were 5 AESIs among 4 participants in the mRNA-1273 group (0.1%) and 3 AESIs among 2 participants in the placebo group (0.2%). None of these events were assessed as related to the study vaccine. AESIs reported in the mRNA-1273 group included:

- Two events of appendicitis (further discussed in the SAE section)
- Events of ageusia and anosmia in a participant with onset 25 days after Dose 2 who had concurrent symptoms of nasal congestion, rhinorrhea, and oropharyngeal pain and one event of ageusia in a participant with onset 7 days after Dose 2 who had concurrent symptoms of myalgia, diarrhea, and injection site pain. No COVID-19 diagnosis was documented around the time of these events.

AESIs reported in the placebo group included ageusia (n=2) and anosmia (n=1). All occurred in the setting of COVID-19.

Search of the safety database by PTs revealed 3 additional events in 2 mRNA-1273 recipients which met the criteria for AESI. One participant reported anosmia and ageusia 9 days after Dose 1, with concurrent symptoms of cough, rhinorrhea, and oropharyngeal pain. One participant reported anosmia 20 days after Dose 1, with concurrent symptoms of oropharyngeal pain and cough.

Open-label Phase (Part 1)
In Part 1 of the study, 4 participants reported 4 AESIs in the 50-µg group (1.1%) and 3 participants reported 3 AESIs in the 100-µg group (0.8%). All events were considered unrelated to study vaccine per FDA assessment.

Events in the 50-µg group included:

- Two events of appendicitis (further discussed in the SAE section)
- One event of palpitations and one event of non-cardiac chest pain (both events further discussed under the section on SMQ *Cardiomyopathy*, below)

Events in the 100-µg group included:

- One event of ageusia with onset 29 days after Dose 1 in a participant with concurrent symptoms of pyrexia, cough, nasal congestion, and oropharyngeal pain. No COVID-19 diagnosis was documented around the time of the event.
- One event of bullous impetigo with onset 48 days after Dose 2
- One event of pancreatitis acute (further discussed in the SAE section)

FDA Standard MedDRA Queries (Double Blind Part 2 and Open Label Part 1)
FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following Dose 1 through the data cutoff date or unblinding (whichever was earlier). The median duration of blinded follow-up for safety in Part 2 was 51 days after Dose 2. For Part 1 participants, the median duration of follow-up after Dose 2 through the data cutoff date of November 10, 2021, was 146 days and 141 days for the 50 µg

and 100 µg groups, respectively. SMQs were conducted on AE PTs that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in imbalance between the two treatment groups, and which captured events considered clinically relevant by the FDA, will be discussed.

For the SMQ *Hypersensitivity*, in Part 2, 155 events were reported in 140 mRNA-1273 recipients (4.7%) compared to 27 events in 25 placebo recipients (2.5%). The most frequently reported events in mRNA-1273 recipients were classified under PTs of injection site rash, seasonal allergy, and urticaria. Within the first 28 days after vaccination, hypersensitivity events were reported by 4.3% of mRNA-1273 participants and 2.1% of placebo participants. The higher frequencies of events in the mRNA-1273 group compared to the placebo group were driven largely by injection site reactions. Within the first 48 hours after any dose, hypersensitivity events were reported by 0.5% of mRNA-1273 recipients and 0.4% of placebo recipients. None of the events yielded by the SMQ *Hypersensitivity* were clinically consistent with anaphylaxis. In Part 1, 27 events were reported in 25 participants (6.6%) in the 50-µg group and 43 events were reported in 36 participants (9.7%) in the 100-µg group. Events were similar in nature to those reported by Part 2 participants and similar between the two dose levels.

In Part 2, for the SMQ *Autoimmune disorders*, 4 events were reported by 3 mRNA-1273 recipients (<0.1), and no events were reported in placebo recipients. The events in the vaccine group were type 1 diabetes mellitus (discussed in the SAE section), 2 events of inflammatory bowel disease reported by the same participant (one report for work-up and one report for diagnosis (discussed in the section on AEs leading to study discontinuation), and an event of alopecia areata with onset 27 days post-Dose 1. In FDA's assessment, a causal relationship between the vaccine and these events is unlikely. No events in this SMQ were identified in Part 1 of the study.

In Study P204, scripted safety calls were included in the study design to solicit for symptoms of myocarditis and pericarditis. This resulted in enhanced reporting frequency of associated symptoms in Study P204 compared to those reported (unsolicited) in adults in Study P301 and adolescents in study P203. In Part 2 of P204, 11 participants (0.4%) in the mRNA-1273 group and 2 participants (0.2%) in the placebo group reported PTs included in the SMQ *Cardiomyopathy*. The median time to onset was 14 days (range 0-85 days). In Part 1, two participants (0.5%) in the 50-µg group and five participants (1.3%) in the 100-µg group reported PTs included in the SMQ *Cardiomyopathy*. All cardiac associated symptoms reported in Blinded Phase (BP) Part 2 and Open Label (OL) Part 1 included in this SMQ are described briefly in the table below and include investigator and FDA reviewer assessments of relatedness to study vaccine.

Table 44. Adverse Events Through Data Cutoff of November 10, 2021, Participants 6 Through 11 Years of Age, Standard MedDRA Query *Cardiomyopathy*, Study P204 Blinded Phase Part 2 and Open Label Part 1, Safety Set

Treatment Arm	Age Sex	Preferred Term	Time to Onset After Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
Part 2 Blinded	--	--	--	--		--	--
mRNA-1273 50 µg	8y/F	Chest pain	8 days after Dose 1	History of asthma; investigator assessed symptoms to be related to GI/reflux etiology	Resolved	Not related	Not related
Placebo	8y/M	Chest pain	85 days after Dose 1	Chest pain with exertion; had symptomatic COVID-19 68 days prior to onset	Not resolved	Not related	Not related
mRNA-1273 50 µg	11y/M	Chest pain	1 day after Dose 2	History of asthma; participant reported symptoms to be similar in nature to his previous asthma exacerbations	Resolved	Related	Possibly related
mRNA-1273 50 µg	7y/M	Chest pain; Dyspnea	3 days after Dose 2	Intermittent chest pain; evaluated in ER where ECG and echocardiogram were performed and identified no abnormalities	Resolved	Related	Possibly related
mRNA-1273 50 µg	11y/M	Chest pain	13 days after Dose 2	History of anxiety and allergic rhinitis; reported concurrent symptoms of cough, fever, and rhinorrhea	Resolved	Not related	Not related
mRNA-1273 50 µg	9y/M	Dyspnea	Day of vaccination of Dose 1	History of anxiety; in setting of worsening anxiety after vaccination, ECG normal	Resolved	Not related	Not related
mRNA-1273 50 µg	6y/F	Dyspnea	7 days after Dose 1	In setting of seasonal allergies; concomitant medications included albuterol and loratadine	Resolved	Not related	Not related

Treatment Arm	Age Sex	Preferred Term	Time to Onset After Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 50 µg	11y/F	Dyspnea	22 days after Dose 1	History of asthma; concurrent symptoms of rhinorrhea and cough	Resolved	Not related	Not related
mRNA-1273 50 µg	9y/F	Dyspnea	1 days after Dose 2	Concurrent diagnosis of urinary tract infection	Resolved	Not related	Not related
mRNA-1273 50 µg	10y/M	Dyspnea; Non-cardiac chest pain	9 days after Dose 2	History of ADHD on methylphenidate; reported symptoms to be intermittent and brief (lasting seconds); symptoms did not interfere with playing sports	Resolved	Related	Possibly related
mRNA-1273 50 µg	8y/F	Dyspnea; Chest discomfort	15 days after Dose 2	Symptoms improved with albuterol	Resolved	Not related	Not related
mRNA-1273 50 µg	10y/F	Syncope	1 days after Dose 1	History of asthma; lasting one minute, no other reported symptoms	Resolved	Not related	Not related
Placebo	9y/F	Dyspnea	22 days after Dose 1	Concurrent symptoms of rhinorrhea and cough	Resolved	Not related	Not related
OL Part 1	--	--	--	--		--	--
mRNA-1273 100 µg	9y/M	Chest pain	18 days after Dose 2	History of ADHD on methylphenidate; symptoms occurred while training for boxing; evaluation included ECG and chest x-ray which were both normal; resolved same day	Resolved	Related	Not related; more likely to be attributed to upper body exertion
mRNA-1273 100 µg	9y/M	Dyspnea, Non-cardiac chest pain	3 days after Dose 2	History of asthma; concurrent symptom of musculoskeletal discomfort (back pain); all symptoms resolved within 3 hours after onset	Resolved	Not related	Not related

Treatment Arm	Age Sex	Preferred Term	Time to Onset After Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 50 µg	11y/F	Dyspnea	24 days after Dose 2	History of asthma; concurrent symptoms of cough, nasal congestion, oropharyngeal pain, and wheezing	Resolved	Not related	Not related
mRNA-1273 100 µg	8y/M	Dyspnea	92 days after Dose 2	Concurrent symptoms of headache, cough, nasal congestion, oropharyngeal pain, and rhinorrhea	Resolved	Not related	Not related
mRNA-1273 100 µg	11y/F	Palpitations	Day of vaccination after Dose 2	"felt her heart skipped a few beats for a brief time"; parents reported oxygen saturation and pulse measured at home were normal; symptoms all resolved on the same day	Resolved	Related	Not related given onset hours after vaccination and rapid resolution
mRNA-1273 100 µg	10y/F	Palpitations	7 days after Dose 2	Upon exertion; no other associated symptoms; event resolved on same day	Resolved	Related	Not related given onset with exertion and rapid resolution
mRNA-1273 50 µg	7y/F	Palpitations [a]	31 days after Dose 2	History of palpitations; reported multiple episodes of worsening palpitations; Evaluated by cardiologist with normal physical exam and ECG. Placed on cardiac telemetry for 30-day event monitoring which did not reveal any significant arrhythmia.	Resolved	Not related	Not related

Source: FDA generated table based on listings, narratives, and dataset submitted to EUA 27073, P204 (6-11 years)
a. Event initially assessed as SAE. Later downgraded to non-serious after data cutoff.

Additional clinical AEs that were cardiac related were queried by preferred terms (PTs) in the P204 safety database that were suggestive of myocarditis/pericarditis or associated symptoms/clinical signs that were not included in the SMQ *Cardiomyopathy.* These events *a*re summarized in the table below and include investigator and FDA reviewer assessments of relatedness to study vaccine.

Table 45. Additional Cardiac-Related Preferred Terms Through Data Cutoff of November 10, 2021, Study P204 Blinded Phase Part 2 and Open Label Part 1, Safety Set

Treatment Arm	Age/ Sex	Preferred Term	Time to Onset After Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
Part 2 Blinded	--	--	--	--		--	--
mRNA-1273 50 µg	10y/M	Angina pectoris	Day of vaccination after Dose 1	Reported "squeezing around the heart that lasted a few seconds"; ECG, troponin, echocardiogram all within normal limits	Resolved	Not related	Not related
mRNA-1273 50 µg	10y/M	Cardiac flutter	7 days after Dose 1	Reported feeling his heart racing that lasted less than 20 seconds; no workup or treatment reported	Resolved	Not related	Not related
mRNA-1273 50 µg	9y/M	Chest discomfort	Day of vaccination after Dose 1	History of autism and ADHD; event lasted 25 minutes; normal vitals; resolved with reassurance	Resolved	Related	Not related given rapid resolution with reassurance
mRNA-1273 50 µg	10y/F	Chest discomfort	5 days after Dose 2	Chest tightness without other associated symptoms. Resolved within 24 hours.	Resolved	Not related	Possibly related
Placebo	9y/F	Chest discomfort	23 days after Dose 1	Concurrent symptoms of nausea and fatigue	Resolved	Not related	Not related
mRNA-1273 50 µg	11y/M	Musculoskeletal chest pain	3 days after Dose 2	History of asthma; event reported to be brief (seconds); physical exam and ECG reported to be normal	Resolved	Not related	Not related
mRNA-1273 50 µg	8y/M	Musculoskeletal chest pain	14 days after Dose 2	Normal ECG	Resolved	Not related	Not related

Treatment Arm	Age/ Sex	Preferred Term	Time to Onset After Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 50 µg	7y/M	Musculoskeletal chest pain	23 days after Dose 2	History of chronic lung disease, asthma, autism. No workup or treatment reported.	Resolved	Not related	Not related
Placebo	7y/F	Musculoskeletal chest pain	23 days after Dose 2	No workup or treatment reported	Resolved	Not related	Not related
Part 1 (Open Label)	--	--	--	--		--	--
mRNA-1273 50 µg	10y/M	Musculoskeletal chest pain	61 days after Dose 2	No abnormalities found on evaluation by primary care physician	Resolved	Not related	Not related
mRNA-1273 50 µg	11y/M	Non-cardiac chest pain	72 days after Dose 2	Evaluated in clinic with normal exam and vital signs, resolved within few hours	Resolved	Related	Not related given latency of onset

Source: FDA generated table based on listings, narratives, and dataset submitted to EUA 27073, P204 (6-11 years)

None of the events captured by the SMQ *Cardiomyopathy* or in the additional analyses (Table 44 and Table 45) met CDC criteria for probable or confirmed myocarditis or pericarditis.[63] Few participants underwent workup for their symptoms; among the small number of participants who had cardiac evaluation of their symptoms, all were reported to be normal. A majority of the events reported in the study were non-specific in nature, and many were associated with concurrent upper respiratory tract infection symptoms.

Serious adverse events

In blinded Phase Part 2, from Dose 1 through the data cutoff, SAEs were reported in 6 mRNA-1273 recipients (0.2%) and 2 placebo recipients (0.2%). None were considered related to study vaccination by the study investigator or by the FDA reviewer. No additional SAEs were reported during the open-label crossover phase of Part 2. In Part 1, SAEs were reported by 7 participants: 5 in the 50-µg group and 2 in the 100-µg group. None were assessed as related to study vaccination by the investigator or by the FDA reviewer. There was one event of palpitations in a Part 1 mRNA-1273 50 µg recipient, described previously in the AEs of Clinical Interest section above, that was downgraded to non-serious after the data. A summary of reported SAEs during Part 2 and Part 1 are shown in the table below and include principal investigator (PI) and FDA reviewer assessments of relatedness to study vaccine.

Table 46. Serious Adverse Events Through Data Cutoff of November 10, 2021, Study P204 Part 1 Open-Label and Part 2 Blinded, Safety Set

Treatment Group	Age/ Sex	SAE Preferred Term	Time to Onset After Most Recent Dose	Risk Factors/ Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
Part 2 Blinded	--	--	--	--		--	--
mRNA-1273 50 µg	7y/F	Appendicitis	26 days after Dose 1		Resolved	Not related	Not related
mRNA-1273 50 µg	10y/M	Appendicitis	49 days after Dose 2		Resolved	Not related	Not related
mRNA-1273 50 µg	9y/M	Cellulitis orbital	2 days after Dose 2		Resolved	Not related	Not related
mRNA-1273 50 µg	9y/M	Cellulitis	16 days after Dose 2	Cellulitis on elbow in area of mosquito bite, requiring IV antibiotic treatment	Resolved	Not related	Not related
mRNA-1273 50 µg	9y/F	Type I diabetes mellitus	35 days after Dose 2	Parent indicated after diagnosis that participant had been having symptoms prior to study entry	Resolved with sequelae: Type I diabetes	Not related	Not related
mRNA-1273 50 µg	11y/M	Urosepsis; pyelonephritis	31 days after Dose 2	History of tethered spinal cord	Resolved	Not related	Not related
Placebo	7y/M	Affective disorder	4 days after Dose 2	History of depression and mood disorder	Resolved with sequelae: on medication	Not related	Not related
Placebo	10y/M	COVID-19	25 days after Dose 2	COVID-19 diagnosis between Dose 1 and Dose 2; presented with “long COVID” symptoms post Dose 2 (tingling/numbness/weakness)	Resolved	Not related	Not related
Part 1 Open-label	--	--	--	--		--	--
mRNA-1273 50 µg	10y/M	Foreign body ingestion	20 days after Dose 1		Resolved	Not related	Not related
mRNA-1273 50 µg	7y/F	Palpitations*	31 days after Dose 2	History of palpitations	Resolved	Not related	Not related
mRNA-1273 50 µg	10y/M	Appendicitis	72 days after Dose 2		Resolved	Not related	Not related
mRNA-1273 50 µg	7y/M	Appendicitis	97 days after Dose 2		Resolved	Not related	Not related

Treatment Group	Age/ Sex	SAE Preferred Term	Time to Onset After Most Recent Dose	Risk Factors/ Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 50 µg	9y/F	Optic disc drusen	151 days after Dose 2		Resolved with sequelae: optic nerve drusen	Not related	Not related
mRNA-1273 100 µg	9y/M	Constipation	1 days after Dose 2	Hospitalized for workup for mesenteric adenitis versus early appendicitis	Resolved	Not related	Not related
mRNA-1273 100 µg	11y/M	Pancreatitis acute	3 days after Dose 2	History of chronic kidney disease, pancreatic insufficiency, pancreatic pseudocyst	Resolved with sequelae: pancreatic insufficiency	Not related	Not related

FDA generated table based on case narratives, listings, and dataset submitted to EUA 27073, P204 (6-11 years)
*Event was downgraded to non-serious after data cutoff

AEs leading to discontinuation from study vaccination or study participation
AEs leading to discontinuation from study vaccination after Dose 1 and before Dose 2 were reported by 3 mRNA-1273 recipients and 2 placebo recipients in Part 2. One additional participant from Part 1 discontinued from study vaccination after Dose 1 of 50 µg of mRNA-1273. All discontinuations in the mRNA-1273 group were related to AE of rash (PTs: rash pruritic, rash, urticaria, urticaria papular). These events all occurred >7 days post-vaccination, were not localized to the injection site, and were unlikely to be related to vaccination. The two discontinuations in the placebo group were both associated with COVID-19 diagnoses.

There was a single discontinuation from study participation due to an AE. This was an 8-year-old male who was initially diagnosed with Inflammatory Bowel Disease (IBD) 21 days after Dose 2 of mRNA-1273 in Part 2. The participant had been having intermittent abdominal pain for many years but had not undergone clinical evaluation for his symptoms until this time. Endoscopy obtained approximately one month after the report of the AE was positive for granulomas but failed to demonstrate IBD, and additional immunologic and genetic testing were being conducted to evaluate for other medical conditions. The parent of this participant chose to withdraw him from the study due to associated multiple medical appointments. FDA agrees with assessment by the investigator that this event was unrelated to vaccine. After the data cutoff and following the availability of new clinical information, the AE term for this participant's AE was revised by the investigator from Inflammatory Bowel Disease to Familial Mediterranean Fever.

4.4.2.5 Additional Safety Follow-Up

The initial EUA amendment submission was based on a data cutoff of November 10, 2021, and the safety and effectiveness results from this data cutoff are discussed in the sections above. On May 4, 2022, Moderna submitted updated longer term follow-up data from participants 6-11 years from this study. The updated data includes safety data from the data cutoff date through February 21, 2022, for study participants in Part 2 and Part 1. For mRNA-1273 recipients in Part 2, the median total duration of follow-up including both the blinded and open-label crossover phases was 158 days post Dose 2 and 98.7% had at least 2 months of follow-up post Dose 2. For participants in Part 1 of the study, the median follow-up duration was 245 days post Dose 2.

After authorization of another COVID-19 vaccine (October 29, 2021) for children 5 years and older, participants in Part 2 of Study P204 were offered to be unblinded to their treatment group, and placebo recipients were given the option to crossover to receive mRNA-1273 and to continue to be followed for the open-label phase of the study. As of the February 21, 2022, data cutoff, 68.3% of participants initially randomized to placebo had received at least one dose of mRNA-1273 in the open-label phase. The median duration of follow-up for participant who have received two doses of crossover vaccine was 77 days after Dose 2.

As the rates of solicited ARs and unsolicited AEs within 28 days are not expected to differ substantially from the November 10, 2021, data cutoff, review of the updated longer-term safety data will be focused on new AEs of Clinical Interest and SAEs accumulated since the original data cutoff.

<u>Adverse events of clinical interest</u>
New AESIs reported since the initial November 10, 2021, data cutoff are summarized below. All were considered unrelated to study vaccine.

- An 8-year-old female mRNA-1273 recipient was diagnosed with epilepsy 83 days after Dose 2. Diagnosis was made by her primary care physician at an annual check-up and later confirmed with electroencephalogram.

- An 11-year-old female placebo-mRNA-1273 recipient with family history of seizures reported an event of generalized seizure 9 days after crossover Dose 1. The participant did not report fever or other symptoms around the time of the event. Per the study investigator, the participant later reported having experienced a similar event approximately 7 months prior. A second event of seizure was reported 42 days after cross-over Dose 1. After evaluation by a neurologist and review of EEG, the participant was diagnosed with epilepsy syndrome.
- 5 events of ageusia and 4 events of anosmia were reported by 5 mRNA-1273 recipients and 1 placebo-mRNA-1273 recipient. Three of the mRNA-1273 recipients and the single placebo-mRNA-1273 recipient had COVID-19 diagnosed around the same time period. The remaining 2 mRNA-1273 recipients with ageusia and anosmia had concurrent upper respiratory tract infection symptoms but did not have a positive COVID-19 test.
- An 8-year-old male participant in the 50-µg group (Part 1) reported a seizure in the setting of human metapneumovirus infection with onset 146 days after Dose 2.
- A 9-year-old female participant in the 100-µg group (Part 1) reported new diagnosis of Tourette's Syndrome 146 days after Dose 2.

No events of myocarditis or pericarditis were reported among participants 6-11 years as of the February 21, 2022, data cutoff. Events identified under the *Cardiomyopathy* SMQ and other potential cardiac-related PTs, collected from the initial data cutoff of November 10, 2021, through the February 21, 2022, data cutoff, are summarized below. Event were assessed as unrelated to study vaccine, unless otherwise noted.

- A 7-year-old male mRNA-1273 recipient reported two events of chest pain and dyspnea, with onset 3 days post Dose 2. He was evaluated in the Emergency Department with normal physical examination, echocardiogram, and electrocardiogram. The events of chest pain and dyspnea were assessed as related to vaccine. In FDA assessment, relationship to vaccine cannot be excluded due to lack of alternative etiology. However, normal cardiac evaluation is reassuring against vaccine-associated cardiomyopathy.
- A 10-year-old female placebo-mRNA-1273 recipient reported dyspnea 32 days after crossover Dose 2. She reported concurrent symptoms of fever, cough, rhinorrhea, oropharyngeal pain, and rash.
- A 7-year-old female mRNA-1273 recipient reported dyspnea 145 days after Dose 2, with concurrent symptoms of fever, cough, wheezing, and oropharyngeal pain.
- A 10-year-old male mRNA-1273 recipient reported palpitations 32 days after Dose 2. The event resolved on the same day without treatment and without further evaluation. This event was considered related by the investigator. In FDA's assessment, given timing of onset outside of the usual interval for vaccine-associated myocarditis and rapid resolution, event was unlikely to be related to vaccine. The same participant reported an event of dyspnea 84 days after Dose 2, which was assessed as unrelated to vaccine.
- A 10-year-old male mRNA-1273 recipient reported musculoskeletal chest pain 70 days after Dose 2.
- An 11-year-old female mRNA-1273 recipient reported palpitations and musculoskeletal chest pain 92 days after Dose 2, associated with cough and RSV infection.
- A 10-year-old male mRNA-1273 recipient reported vasovagal syncope 3 days after Dose 2.

- Among participants in Part 1, in the 50-µg group, one participant reported dyspnea with onset 210 days post Dose 2 and another participant reported chest pain with onset 234 days after Dose 2.

AEs leading to discontinuation from study participation

One additional participant discontinued from study participation due to an AE since the initial data cutoff. This occurred in an 11-year-old female participant in the 50-µg mRNA-1273 group in Part 1 who reported urticarial and papular rash on the arm, elbows, hands, and feet 9 days after Dose 1. The event was graded moderate in intensity and resolved after 6 days.

Serious adverse events

New SAEs captured from data cutoff through February 21, 2022, are summarized in the table below for participants in Part 2 and Part 1. All events were assessed as unrelated to study vaccine, except for the SAE of ileus that occurred 1 day after crossover Dose 2 of mRNA-1273 in a participant who crossed over from placebo to mRNA-1273 and was assessed as related by the investigator. In FDA's review of this SAE, causality cannot be established with mRNA-1273 vaccination because of the participant's complex medical history; however, the possibility that mRNA-1273 vaccination contributed cannot be excluded due to its close temporal relationship with ileus onset.

Table 47. Serious Adverse Events During Additional Follow-Up From Data Cutoff of November 10, 2021, Through Data Cutoff of February 21, 2022, Participants 6 Through 11 Years of Age, Study P204

Treatment Group	Age/ Sex	Preferred Term	Time to Onset/ Most Recent Dose	Risk Factors/Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
Part 2	--	--	--	--		--	--
mRNA-1273 50 µg	8y/M	Abdominal pain upper; Cholecystitis	21 days/ Dose 1 65 days/ Dose 2	Gallbladder polyps found on HIDA scan	Resolved	Not related Not related	Not related Not related
mRNA-1273 50 µg	8y/F	Epiphyseal fracture	45 days/ Dose 2	Distal fracture in the growth plate of the left big toe; occurred while in dance class	Resolved	Not related	Not related
mRNA-1273 50 µg	6y/M	Suicidal ideation; Disruptive mood dysregulation disorder; Oppositional defiant disorder	68 days/ Dose 2 70 days/ Dose 2 72 days/ Dose 2	AEs of ADHD and anxiety around the time of event onset	Resolved	Not related Not related Not related	Not related Not related Not related
mRNA-1273 50 µg	6y/F	Febrile neutropenia; Post-procedural complication	83 days/ Dose 2 130 days/ Dose 2	After chemotherapy for ependymoma Afebrile neutropenia and anemia after chemotherapy	Resolved Resolved	Not related Not related	Not related Not related
mRNA-1273 50 µg	7y/M	Gastrointestinal disorder	89 days/ Dose 2	Vomiting and abdominal pain requiring hospitalization	Resolved	Not related	Not related
mRNA-1273 50 µg	10y/F	Asthma	89 days/ Dose 2	History of asthma; hospitalized for asthma exacerbation	Resolved	Not related	Not related
mRNA-1273 50 µg	9y/M	Synovitis	127 days/ Dose 2	Transient synovitis of bilateral hips	Resolved	Not related	Not related
mRNA-1273 50 µg	6y/F	Neck pain	128 days/ Dose 2	Diagnosed with pinched nerve of neck after falling during skiing	Resolved	Not related	Not related

Treatment Group	Age/ Sex	Preferred Term	Time to Onset/ Most Recent Dose	Risk Factors/Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 50 µg	11y/M	Suicidal ideation*	164 days/ Dose 2	Participant's guardian reported that participant may have depression/suicidal ideation and participant was referred to psychiatrist after evaluation by primary care physician; started on antidepressant	Resolved	Not related	Not related
mRNA-1273 50 µg	7y/M	Kawasaki's disease	190 days/ Dose 2	Diagnosis of streptococcal pharyngitis 2 days prior to event; met Kawasaki criteria and treated with IVIG, echocardiogram normal	Resolved	Not related	Not related
Placebo-mRNA-1273 50 µg	6y/F	Ileus	1 day/ OL Dose 2	Complex medical history including imperforate anus status post repair and cecostomy, atrial septal defect, gross motor delay, anxiety; hospitalized for abdominal pain after routine enema, abdominal x-ray suggestive of diffuse ileus, passed oral challenge	Resolved	Related	Possibly related or contributed to onset
Part 1	--	--	--	--		--	--
mRNA-1273 100 µg	11y/M	Abdominal pain; Bradycardia	140 days/ Dose 2	History of chronic kidney disease and pancreatic insufficiency, prior SAE of acute pancreatitis; cardiac evaluation showed normal cardiac function and normal troponin; no clear etiology found for symptoms, resolved after 5 days	Resolved	Not related	Not related

Source: FDA generated table based on case narratives, listings, and dataset submitted to EUA 27073, P204 (6-11 years)
OL=open label
*Event downgraded to non-serious after data cutoff

4.4.2.6 Summary for Participants 6 Through 11 Years of Age

A comparison of immune responses between children 6-11 years who received two doses of 50 µg of mRNA-1273 in Study P204 and young adults 18-25 years who received two doses of 100 µg of mRNA-1273 in Study P301 provided the primary evidence to support effectiveness of the vaccine in the age group of individuals 6-11 years. The study met the pre-specified success criteria for the two co-primary endpoints of GMT ratio and difference in SRRs. The GMT ratio (children 6-11 years to young adults) was 1.2 (95% CI 1.1, 1.4) which met the pre-specified success criterion of a LL of the 95% CI >0.67 and a point estimate of >0.8. The difference in SRRs (children 6-11 years minus young adults) was 0.1% (95% CI −1.9, 2.1) which met the pre-specified success criterion of a LL of the 95% CI >-10% and an SRR difference point estimate of -5%. The immunogenicity data across demographic subgroups were generally consistent with those observed in the overall study population, though interpretability of subgroup-specific effectiveness results is limited by the small number of participants in certain subgroups. The small number of participants with evidence of prior SARS-CoV-2 infection had higher immune responses at 1-month post-Dose 2 compared to participants with no evidence of prior SARS-CoV-2 infection.

In descriptive analyses of vaccine efficacy in children 6-11 years, the observed VE against COVID-19 starting 14 days after Dose 2 was 69.0% (95% CI −131.4, 95.8) when using the COVID-19 case definition used in Study P301, and 76.8% (95% CI −37.3, 96.6) when using the broader CDC case definition. Vaccine efficacy could not be reliably determined due to the small number of COVID-19 cases accrued as a result study group unblinding and crossover vaccination after authorization of an alternate COVID-19 vaccine for this age group. When VE was assessed using a more inclusive study population (e.g., including participants with evidence of prior SARS-CoV-2 at baseline) or over a longer time period (e.g., starting 14 days after Dose 1 or any time after Dose 2), there was a greater number of COVID-19 cases accrued, resulting in tightening of the CI with the LB above 0. No cases of severe COVID-19 were reported among study participants 6-11 years of age.

Solicited local and systemic adverse reactions were mostly mild to moderate in severity, generally of short duration, and occurred more frequently and were more severe after Dose 2 than Dose 1. The most frequently reports solicited adverse reactions after any dose were injection site pain (98.4%), fatigue (73.1%), and headache (62.1%). Fever was reported by 3.3% and 23.9% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. Grade 3 fever (temperature 39-40^{o}C) was reported by 0.6% and 3.8% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. In participants with evidence of prior SARS-CoV-2 infection at baseline, higher frequencies of solicited systemic ARs after Dose 1 were observed compared to participants without evidence of prior SARS-CoV-2 infection.

Unsolicited AEs reported within 28 days after vaccination were reported by a slightly higher percentage of mRNA-1273 recipients (29.6%) than placebo recipients (25.1%). This difference was driven largely by injection site reactions and vaccine reactogenicity, including lymphadenopathy-related events reported by 1.8% of mRNA-1273 recipients and 0.6% of placebo recipients and hypersensitivity-related events reported by 4.3% and 2.1% of mRNA-1273 and placebo recipients, respectively. None of the hypersensitivity-related events were clinically concerning for anaphylaxis. Within 28 days following any vaccination, an imbalance was observed in events of abdominal pain, which was reported by 1.1% of mRNA-1273 recipients and 0.6% of placebo recipients. The majority of these events were mild to moderate and were not medically attended. Currently available information is insufficient to determine a causal relationship with the vaccine.

Participants were actively solicited for symptoms suggestive of myocarditis or pericarditis through scripted safety calls as part of the study design for P204. In the blinded phase of the study, there was a small imbalance observed (0.4% vs 0.2%, vaccine vs placebo) in AEs identified using the SMQ *Cardiomyopathy*, including chest pain, dyspnea, and syncope. Of all potential cardiac-related events identified during the study, only one event of palpitations was initially assessed as serious (later downgraded to non-serious after the data cutoff). Most events were non-specific in nature and resolved rapidly without workup or intervention. Of the small number of cases evaluated by ECG, troponin, or echocardiogram, none showed abnormalities. No events of probable or confirmed myocarditis or pericarditis based on CDC criteria were reported in the study through the time of data cutoff. However, cases of myocarditis/pericarditis have been reported following the authorization of mRNA-1273 in adults ≥18 years of age with routine pharmacovigilance/safety surveillance by the CDC and FDA, as discussed in Section 2.3.2.

No deaths were reported in participants 6-11 years in the study. SAEs were infrequent and occurred at the same rate among mRNA-1273 and placebo recipients (0.2%).

Longer-term safety data based on a data-cutoff of February 21, 2022, corresponding to a median follow-up duration (including both blinded and open-label follow-up) of 158 days post Dose 2 in mRNA-1273 recipients, revealed no new safety concerns.

4.4.3 Participants 2 through 5 Years of Age

Participants 2 through 5 years of age began enrollment into Study P204 Part 1 on April 21, 2021, and Part 2 on October 18, 2021. As of the February 21, 2022, data cutoff for this EUA amendment, safety data were available from a total of 4,262 children 2 through 5 years of age (3,255 in the mRNA-1273 groups and 1,007 in the placebo group) enrolled in Part 1 and Part 2 who received at least one dose. The data cutoff was triggered when a minimum of 1000 mRNA-1273 recipients had received two doses (25 µg each, 28 days apart) and had ≥2 months of follow-up after Dose 2 in Part 2.

4.4.3.1 Part 1: Dose-Finding and 25 µg Dose Selection

The open-label, dose-finding phase (Part 1) of P204 in participants 2-5 years of age included a total of 224 participants, of whom 75 participants received the 25-µg dose level and 149 participants received 50 µg dose level of mRNA-1273. In the 2-5 years age group, enrollment into Part 1 began with the 50-µg dose group. Based on the observed rate of solicited adverse reactions, especially for rates of fevers after vaccination, the study then proceeded to enroll the remaining Part 1 participants into a lower dose level (25 µg).

A protocol-specified assessment of immunogenicity for dose selection was performed in Part 1. Immunogenicity results as measured by PsVNA ID50 in participants 2-5 years and 6-23 months of age were compared to those from a subset of participants 18-25 years from Study P301, for whom clinical efficacy had been demonstrated. At the time of dose selection, immunogenicity results were only available in 69 participants 2-5 years of age who received the 50-µg dose and not yet available for the participants who received the 25-µg dose. Results of the analysis in the 50-µg group (n=69) demonstrated a GMT ratio of 1.4 (95% CI 1.1, 1.8) and a difference in seroresponse of 1.0% (95% CI-4.3%, 3.0%). Based on these results and the immunogenicity results of the 25-µg dose level in participants 6-23 months, along with the more tolerable safety profile of the 25-µg dose (see below), the DSMB recommended the selection of the 25-µg dose level for both the 2-5 years and 6-23 months age cohorts.

Analyses of solicited adverse reactions after Dose 1 and Dose 2 of both dose levels were reviewed to guide dose selection for Part 2. In general, participants in the 50-µg group experienced higher rates of solicited systemic ARs compared to participants in the 25-µg group. The following ARs occurred at higher rates in the 50-µg group than the 25-µg group: fever after any dose (28.6% vs 11.6%); Grade 3 or higher fever (7.1% vs 1.4%); erythema after any injection (23.4% vs 13.0%); and axillary (or groin) swelling or tenderness (14.3% vs 2.9%). Irritability/crying, however, was reported at a higher rate in the 25-µg group (88.9%) compared to the 50-µg group (69.2%). Overall, there was a higher percentage of Grade 3 or above reactions reported in the 50-µg group (11.7%) compared to the 25-µg group (1.4%). The more tolerable reactogenicity profile of the 25-µg dose level supported the selection of this dose level for advancement into Part 2.

In Part 1, rates of unsolicited AEs within 28 days were reported at higher rates in the 50-µg group (36.1%) compared to the 25-µg group (23.2%). In the mRNA group, the rates of unsolicited AEs in Part 1 were similar to those in Part 2 (29.6%) and will not be discussed in detail. SAEs and AEs of clinical interest from Part 1 are presented in the Part 2 safety section, below. Median duration of follow-up after Dose 2 for Part 1 participants through the data cutoff date of February 21, 2022, was 207 days and 237 days for the 25 µg and 50 µg groups, respectively.

4.4.3.2 Part 2: Blinded, Placebo-Controlled Phase

Participant disposition and inclusion in analysis populations
Disposition of participants in the blinded phase of the study (Part 2) is summarized below in Table 48 (immunogenicity populations), Table 49 (efficacy populations) andTable 3 Table 50 (safety populations).

For immunobridging, a random sample of 302 mRNA-1273 recipients 2-5 years of age from P204 Part 2 and 340 mRNA-1273 recipients 18-25 years (young adults) from P301 were selected for inclusion in the Immunogenicity Subset, which did not include placebo recipients. The primary analyses of immunogenicity were based on the PP Immunogenicity Subset consisting of 264 participants 2-5 years of age and 295 young adults. Among 2-5 year-olds, the majority of exclusions from the PP Immunogenicity Subset were for positive baseline SARS-CoV-2 status (7.0%), followed by lack of immunogenicity data at Day 57 (4.3%). Among young adults, the most common reasons for exclusion from the PP Immunogenicity Subset were positive baseline SARS-CoV-2 status (5.0%) and not receiving Dose 2 per schedule (4.7%).

Table 48. Disposition of Participants 2 Through 5 Years of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Immunogenicity Populations

Disposition	2-5 Years mRNA-1273 25 µg	18-25 Years mRNA-1273 100 µg
Immunogenicity Subset[a], n (%)	N=302	N=340
PP Immunogenicity Subset[b], n (%)	N=264 (87.4)	N=295 (86.8)
Excluded from PP Immunogenicity Subset[c]	38 (12.6)	45 (13.2)
Reason for exclusion	--	--
Positive baseline SARS-CoV-2 status[d]	21 (7.0)	17 (5.0)
Did not receive Dose 2 per schedule	1 (0.3)	16 (4.7)
Received Dose 2 out of window	2 (0.7)	2 (0.6)
No immunogenicity data at Day 57	13 (4.3)	9 (2.6)

Disposition	2-5 Years mRNA-1273 25 µg	18-25 Years mRNA-1273 100 µg
Other major protocol deviations	0	0
HIV infection	0	1 (0.3)
Age outside randomized age group	1 (0.3)	0

Source: Study P204 (2-5years) Table 14.1.2.3.2
a. The Immunogenicity Subset consists of participants in the Full Analysis Set (FAS) who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
b. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; had no HIV infection; had age within the randomized age group; and had no major protocol deviations that impact key or critical data.
c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.
d. Adapted from EUA 27073. Am 399, dated 4May2022; response to information request: Five participants 18 to 25 years of age in P301 who had positive baseline SARS-CoV-2 Status and did not receive Dose 2 were counted in the category of positive baseline SARS-CoV-2 status.

In the populations used to assess the efficacy endpoints, dispositions were overall similar between the mRNA-1273 and placebo groups. A higher percentage of participants in the placebo group than the mRNA-1273 group were excluded from the PP Set for Efficacy due to discontinuation of study treatment or participation prior to Dose 2, possibly related to eligibility to receive alternate COVID-19 vaccine under EUA in children 5 years of age and older.

Table 49. Disposition of Participants 2 Through 5 Years of Age, Study P204 Part 2, Efficacy Population

Disposition	mRNA-1273 25 µg	Placebo
Randomized, n (%)	N=3040	N=1008
Full Analysis Set[a], n (%)	N=3031 (99.7)	N=1007 (99.9)
mITT Set[b], n (%)	N=2695 (88.7)	N=898 (89.1)
mITT1 Set[c], n (%)	N=2693 (88.6)	N=898 (89.1)
PP Set for Efficacy[d], n (%)	N=2594 (85.3)	N=858 (85.1)
Excluded from PP Set for Efficacy	446 (14.7)	150 (14.9)
Reason for exclusion	--	--
Randomized but not dosed	9 (0.3)	1 (<0.1)
Positive or missing baseline SARS-CoV-2 status	336 (11.1)	109 (10.8)
Discontinued study treatment or participation without receiving Dose 2	16 (0.5)	17 (1.7)
Did not receive Dose 2 and passed window of +14 days	37 (1.2)	10 (1.0)
Received incorrect vaccination	1 (<0.1)	0
Received Dose 2 out of window	47 (1.5)	13 (1.3)
Had other major protocol deviations	0	0

Source: Study P204 (2-5 years) Tables 14.1.2.1.2.1, 14.1.2.5
a. The FAS consists of all randomized participants who received at least one dose of IP. Numbers are based on planned treatment group.
b. The mITT Set consists of all participants in the FAS who had 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) before the first dose of IP, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.
c. The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (i.e., at least 1 dose received that is not as randomized or planned). Numbers are based on planned treatment group.
Percentages are based on the number of participants randomized.
d. The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of second dose of injection; had a negative
RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group. Percentages are based on the number of participants randomized.

Table 50 presents the disposition of participants whose data contributed to the assessment of safety. Most study participants from both the mRNA-1273 group (97.4%) and the placebo group (96.2%) completed both doses of study vaccine. There was a higher rate of discontinuation from study vaccination in the placebo group (2.1%) as compared to the mRNA-1273 group (0.7%), likely due to the crossover of placebo recipients to receive another COVID-19 vaccine under EUA. Similarly, placebo recipients discontinued from study participation at higher rates (3.1%) compared to mRNA-1273 recipients (1.9%), with the most common reason due to discontinue withdrawal of consent. One participant (<0.1%) in the mRNA-1273 group discontinued from study vaccination and participation due to an AE (discussed in Section 4.4.3.4).

Table 50. Disposition of Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Population

Disposition	mRNA-1273 25 µg	Placebo
Randomized, n (%)	N=3040	N=1008
Completed one dose	3031 (99.7)	1007 (99.9)
Completed two doses	2960 (97.4)	970 (96.2)
Discontinued from study vaccination[a]	20 (0.7)	21 (2.1)
Reason for discontinuation	--	--
Adverse event	1 (<0.1)	0
Withdrawal of consent	11 (0.4)	1 (<0.1)
Participant entered open-label or crossover phase	5 (0.2)	15 (1.5)
Participant receiving EUA vaccine outside of protocol	0	5 (0.5)
Lost to follow-up	1 (<0.1)	0
Other	1 (<0.1)	0
Missing	1 (<0.1)	0
Discontinued from study participation	57 (1.9)	31 (3.1)
Reason for discontinuation	--	--
Adverse event	1 (<0.1)	0
Withdrawal of consent	40 (1.3)	17 (1.7)
Lost to follow-up	7 (0.2)	0
Protocol deviation	0	2 (0.2)
Physician decision	2 (<0.1)	0
Participant receiving EUA vaccine outside of protocol	0	8 (0.8)
Other	4 (0.1)	3 (0.3)
Missing	3 (<0.1)	1 (<0.1)
Safety Set[b], n (%)	N=3031	N=1007
Solicited Safety Set[c], n (%)	N=3016 (99.5)	N=997 (99.0)
First Injection Solicited Safety Set	2957 (97.6)	970 (96.3)
Second Injection Solicited Safety Set	2938 (96.9)	959 (95.2)
Number of participants unblinded, n (%)	89 (2.9)	51 (5.1)
Received first injection in open-label phase	5 (0.2)	39 (3.9)

Source: Study P204 (2-5 years) Tables 14.1.1.1.2, 14.1.2.1.2.1
Abbreviations: n=number of participants with indicated comorbidity; N=number of participants in cohort; SD=standard deviation
Percentages based on participants randomized
a. Study Vaccine Discontinuation is defined as a subject who received the first injection but didn't receive the second injection.
b. The Safety Set consists of all randomized participants who received at least one dose.
c. The Solicited Safety Set consists of all participants who were randomized and received at least one dose and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.

Given the emergency use authorization of an another COVID-19 vaccine for individuals 5-11 years of age on October 29, 2021, the protocol was revised to allow study participants (5-11 years of age) the option to unblind and crossover to receive the active vaccine (for original placebo recipients). The open-label/cross-over phase of Part 2 began on November 1, 2021. As

of the February 21, 2022, data cutoff, a total of 51 participants (5.1%) initially randomized to placebo were unblinded, and 39 (3.9%) received at least one dose of the crossover vaccination.

Table 51. Duration of Follow-Up After Dose 2 Through Data Cutoff of February 21, 2022, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set

Duration of Follow-Up	mRNA-1273 25 µg N=3031	Placebo N=1007	Total N=4038
Blinded follow-up	--	--	--
≥28 days since Dose 2, n (%)	2713 (89.5)	892 (88.6)	3605 (89.3)
≥56 days since Dose 2, n (%)	2180 (71.9)	710 (70.5)	2890 (71.6)
Median follow-up from Dose 2, days (min, max)	71 (0, 99)	70 (0, 99)	71 (0, 99)
Including both blinded and open-label phases	--	--	--
≥56 days since Dose 2, n (%)	2248 (74.2)	733 (72.8)	2981 (73.8)
Median follow-up from Dose 2, days (min, max)	74 (0, 99)	71 (0, 99)	74 (0, 99)

Source: P204 (2-5 years) Tables 14.1.5.2, 14.1.5.3

Demographic and baseline characteristics

The PP Immunogenicity Subsets, which contributed to the co-primary endpoints for the study, consisted of 264 vaccinated participants 2-5 years of age from Study P204 Part 2 and 295 vaccinated young adult participants 18-25 years of age from Study P301 (Table 52). Compared to the young adult population, the 2-5 year-old age group included a lower proportion of Asian participants (6.1% 2-5-year-olds vs 10.2% young adults); a slightly lower proportion of Black participants (7.6% vs 9.8%); and higher proportion of multiracial participants (12.9% vs 4.7%). A lower proportion of 2-5-year-olds self-identified as Hispanic (17.8%) compared to young adults (26.4%), and a lower proportion were considered obese (8.7%) at baseline compared to young adults (23.1%).

Table 52. Demographics and Other Baseline Characteristics, Participants 2 Through 5 Years of Age, Study P204 Part 2, Participants 18 Through 25 Years, Study P301, Per-Protocol Immunogenicity Subset

Characteristic	2-5 Years mRNA-1273 25 µg N=264	18-25 Years mRNA-1273 100 µg N=295
Sex, n (%)	--	--
Female	123 (46.6)	153 (51.9)
Male	141 (53.4)	142 (48.1)
Age	--	--
<2 years, n (%)	0	--
≥2 years and ≤36 months, n (%)	69 (26.1)	--
>36months and <6 years, n (%)	195 (73.9)	--
Mean (SD)	3.3 (0.95)	22.4 (2.19)
Median age (years)	3.0	23.0
Race, n (%)	--	--
American Indian or Alaska Native	1 (0.4)	3 (1.0)
Asian	16 (6.1)	30 (10.2)
Black	20 (7.6)	29 (9.8)
Native Hawaiian or other Pacific Islander	0	2 (0.7)
White	188 (71.2)	206 (69.8)
Other	2 (0.8)	8 (2.7)
Multiracial	34 (12.9)	14 (4.7)
Not reported	2 (0.8)	3 (1.0)
Unknown	1 (0.4)	0

Characteristic	2-5 Years mRNA-1273 25 µg N=264	18-25 Years mRNA-1273 100 µg N=295
Ethnicity, n (%)	--	--
Hispanic or Latino	47 (17.8)	78 (26.4)
Not Hispanic or Latino	217 (82.2)	215 (72.9)
Not reported	0	0
Unknown	0	2 (0.7)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	152 (57.6)	145 (49.2)
Communities of Color	112 (42.4)	150 (50.8)
Country, n (%)	--	--
US	264 (100)	295 (100)
Canada	0	0
Obesity Status[b], n (%)	--	--
Obese	23 (8.7)	68 (23.1)
Non-obese	241 (91.3)	226 (76.6)
Missing	0	1 (0.3)

Source: Study P204 (2-5 years) Table 14.1.3.3.2
Abbreviations: n=number of participants with indicated comorbidity; N=number of participants in cohort; SD=standard deviation
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. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P204 and BMI ≥30 kg/m2 for P301

In the Safety Set, the demographic characteristics were similar between the mRNA-1273 and placebo groups (Table 53). The demographic characteristics for the PP Set for Efficacy in participants 2-5 years of age (data not shown) that included 2,594 mRNA-1273 recipients and 858 placebo recipients were similar to the baseline characteristics of Safety Set.

Table 53. Demographic and Baseline Characteristics, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set

Characteristic	mRNA-1273 25 µg N=3031	Placebo N=1007
Sex, n (%)	--	--
Female	1488 (49.1)	497 (49.4)
Male	1543 (50.9)	510 (50.6)
Age	--	--
<2 years[a], n (%)	24 (0.8)	12 (1.2)
≥2 years and ≤36 months, n (%)	999 (33.0)	345 (34.3)
>36months and <6 years, n (%)	2032 (67.0)	662 (65.7)
Mean (SD)	3.0 (0.88)	3.0 (0.89)
Median	3.0	3.0
Race, n (%)	--	--
White	2297 (75.8)	792 (78.6)
Black	142 (4.7)	38 (3.8)
Asian	191 (6.3)	51 (5.1)
American Indian or Alaska Native	12 (0.4)	3 (0.3)
Native Hawaiian or other Pacific Islander	7 (0.2)	4 (0.4)
Multiracial	322 (10.6)	99 (9.8)
Other	43 (1.4)	16 (1.6)
Not reported	13 (0.4)	4 (0.4)
Unknown	4 (0.1)	0

Characteristic	mRNA-1273 25 µg N=3031	Placebo N=1007
Ethnicity, n (%)	--	--
Hispanic or Latino	433 (14.3)	142 (14.1)
Not Hispanic or Latino	2579 (85.1)	856 (85.0)
Not reported	14 (0.5)	8 (0.8)
Unknown	5 (0.2)	1 (<0.1)
Race and ethnicity group[b], n (%)	--	--
White non-Hispanic	1975 (65.2)	678 (67.3)
Communities of color	1054 (34.8)	327 (32.5)
Missing	2 (<0.1)	2 (0.2)
Country	--	--
US	2866 (94.6)	952 (94.5)
Canada	165 (5.4)	55 (5.5)
Obesity status[c]	--	--
Obese	326 (10.8)	106 (10.5)
Non-obese	2703 (89.2)	899 (89.3)
Missing	2 (<0.1)	2 (0.2)
Baseline SARS-CoV-2 status[d], n (%)	--	--
Positive	266 (8.8)	82 (8.1)
Negative	2695 (88.9)	898 (89.2)
Missing	70 (2.3)	27 (2.7)

Source: Study P204 (2-5 years) Table 14.1.3.2.
Abbreviations: n=number of participants with indicated comorbidity; N=number of participants in cohort; SD=standard deviation
Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.
a. Some participants <2 years were included in the ≥ 2 to 6 year subgroup, likely because of coincident enrollment of both age groups, entry errors at the time of randomization, and other limitations of the IRT system.
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. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.
d. Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result on Day 1. Negative is defined as a negative RT-PCR test and negative Elecsys result on Day 1.

Comorbidities at baseline

Participants with stable chronic medical conditions were included in the study. Comorbidities which may lead to increased risk of severe COVID-19 include obesity, chronic lung disease (including asthma), clinically significant cardiac disorders, diabetes mellitus, and HIV infection. In Part 2, 13.9% of mRNA-1273 recipients and 15.5% of placebo recipients in the 2-5 years age cohort had at least one of these comorbidities. Obesity was the most common baseline comorbidity, reported by 10.8% of the mRNA-1273 recipients and by 10.5% of the placebo recipients. The rates of baseline comorbidities were similar between the Part 1 and Part 2 participants.

Table 54. Baseline Comorbidities, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set

Comorbidity	mRNA-1273 25 µg N=3031	Placebo N=1007
Any of the following comorbidities, n (%)	421 (13.9)	156 (15.5)
Obesity[a], n (%)	326 (10.8)	106 (10.5)
Chronic lung disease (including asthma)[b], n (%)	103 (3.4)	46 (4.6)
Asthma[c]	92 (3.0)	42 (4.2)

Comorbidity	mRNA-1273 25 µg N=3031	Placebo N=1007
Clinically significant cardiac disorders[d], n (%)	16 (0.5)	7 (0.7)
Diabetes mellitus, n (%)	1 (<0.1)	1 (<0.1)
HIV, n (%)	0	0

Source: P204 (2-5 years) Tables 14.1.3.2, 14.1.4.1.2.1.2, 14.1.4.1.2.2.2, 14.1.4.1.2.3.2, 14.1.4.1.2.4.2, 14.1.4.1.2.5.2
Abbreviations: BMI=body mass index; HIV=human immunodeficiency virus; n=number of participants with indicated comorbidity; N=number of participants in cohort; WHO=World Health Organization
a. BMI ≥ 95th percentile for age and gender (WHO definition)
b. Includes sleep apnea, wheezing, bronchospasm, bronchopulmonary dysplasia, pulmonary fibrosis, asthma, and cystic fibrosis
c. Includes bronchial hyperreactivity
d. Includes Aortic dilatation, Aortic dissection, Arterial switch operation, Atrioventricular block first degree, Bicuspid aortic valve, Cardiac ablation, Cardiac operation, Coarctation of the aorta, Double outlet right ventricle, Extrasystoles, Fallots tetralogy, Heart block congenital, Heart disease congenital, Hypertrophic cardiomyopathy, Hypoplastic left heart syndrome, Palpitations, Patent ductus arteriosus, Pulmonary valve disease, Pulmonary valve stenosis, Supraventricular tachycardia, Systemic-pulmonary artery shunt, Transposition of the great vessels, Ventricular extrasystoles, Ventricular septal defect, Ventricular septal defect repair, and Wolff-Parkinson-White syndrome

4.4.3.3 Vaccine Effectiveness

Primary immunogenicity endpoint

Vaccine effectiveness in participants 2-5 years of age was inferred through immunobridging to participants 18-25 years of age in Study P301 using the co-primary endpoints of GMC ratio and difference in SRRs at 28 days post-Dose 2 (Day 57). Results for the co-primary endpoint of GMC ratio (2-5 years to 18-25 years) are displayed below in Table 55. GMCs were based on neutralizing antibody concentrations measured by (b) (4) PsVNA assay 1 month after Dose 2 (Day 57) in participants in both groups (2-5 years and 18-25 years) in the PP Immunogenicity Subset. The GMC ratio was 1.0 (95% CI 0.9, 1.2), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI ≥0.67 and a point estimate of GMC ratio ≥0.8.

Table 55. Geometric Mean SARS-CoV-2 Neutralizing Antibody Concentration as Measured by Pseudovirus nAb Assay at Day 57, Participants 2 Through 5 Years of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

2-5 Years mRNA-1273 25 µg GMC (95% CI) N1=264	18-25 Years mRNA-1273 100 µg GMC (95% CI) N1=291	GMC Ratio[a,b] (2-5 Years/18-25 Years) (95% CI)	Met Success Criterion[b]
1410.0 (1273.8, 1560.8)	1390.8 (1262.5, 1532.1)	1.0 (0.9, 1.2)	Yes

Source: Study P204 (2-5 years) Tables 14.2.1.1.3.1.3
Abbreviations: CI=confiedence interval; GMC=geometric mean concentration; LS=least squares; N1=number of participants with non-missing data at baseline and the corresponding timepoint.
Lower limit of quantification: 10
Based on pseudovirus nAb assay by (b) (4). Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
GMC is estimated by geometric LS means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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. The noninferiority of geometric mean value will be considered demonstrated if the lower bound of the 95% CI of the GMR is ≥0.67 based on the noninferiority margin of 1.5 and the GMC ratio point estimate ≥0.8 (minimum threshold).

Results for the co-primary endpoint of difference in SRRs between participants 2-5 years of age and participants 18-25 years of age are displayed in Table 56, below. The difference in SRRs was −0.4% (95% CI −2.7, 1.5) which met the pre-specified success criterion of a LL of the 95% CI greater than −10%. Of the participants in the PP Immunogenicity Subset who had non-missing data at baseline and at Day 57, there were 3 participants who failed to meet the seroresponse definition. All 3 had baseline antibody concentrations below the LLOQ (10). At Day 57, 1 participant had antibody concentrations below the LLOQ (10) and 2 had antibody

concentrations above the LLOQ but below the seroresponse-defined fold rise of at least 4 x LLOQ (1.2-fold rise and 2.3-fold rise).

Table 56. Seroresponse Rates as Measured by Pseudovirus nAb Assay at Day 57, Participants 2 Through 5 Years of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

2-5 Years mRNA-1273 25 µg Seroresponse[a] n (%) (95% CI)[b] N1=264	18-25 Years mRNA-1273 100 µg Seroresponse[a] n (%) (95% CI)[b] N1=291	Difference in Seroresponse Rate % (2-5 Years−18-25 Years) (95% CI)[c]	Met Success Criterion[d]
261 (98.9) (96.7, 99.8)	289 (99.3) (97.5, 99.9)	-0.4 (-2.7, 1.5)	Yes

Source: Study P204 (2-5 years) Table 14.2.1.2.3.1.3, 14.2.3.1.1.3
Abbreviations: CI=confiedence interval; n=number of participants with seroresponse; N1=number of participants with non-missing data at baseline and the corresponding timepoint.
Lower limit of quantification: 10
Based on pseudovirus nAb by (b) (4).
a. 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 N1.
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
d. The noninferiority of difference in seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is >-10% and the point estimate of seroresponse rate difference >-5% (minimum threshold).

Subgroup analyses of primary immunogenicity endpoint

The GMC ratio and difference in SRRs across demographic subgroups were generally consistent with the results of the primary immunogenicity analyses, though some of these analyses were limited by small subgroup size. The majority of 2-5 years and 18-25 years participants included in the PP Immunogenicity Subset were SARS-CoV-2 negative at baseline; however, subgroup analyses based on status at baseline demonstrated numerically higher GMCs (with non-overlapping CIs) at Day 57 in baseline positive participants compared to baseline negative participants.

Table 57. Subgroup Analyses of GMC Ratio and Difference in Seroresponse Rate as Measured by Pseudovirus nAb Assay at Day 57, Participants 2 Through 5 Years of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

Characteristic	2-5 Years mRNA-1273 25µg N=264 GMC (95% CI)	18-25 Years mRNA-1273 100µg N=295 GMC (95% CI)	GMC Ratio[a] (95% CI)	2-5 Years mRNA-1273 25µg N=264 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years mRNA-1273 100µg N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponse Rate, % (95% CI)[d]
Sex	--	--	--	--	--	--
Male	n=141 1403.1 (1202.7, 1637.0)	n=141 1407.3 (1206.3, 1641.9)	1.0 (0.8, 1.2)	n=141 138 (97.9) (93.9, 99.6)	n=141 140 (99.3) (96.1, >99.9)	-1.4 (-5.5, 2.0)
Female	n=123 1417.9 (1243.3, 1617.1)	n=150 1375.4 (1221.1, 1549.2)	1.0 (0.9, 1.2)	n=123 123 (100) (97.0, 100.0)	n=150 149 (99.3) (96.3, >99.9)	0.7 (-2.4, 3.7)
Race	--	--	--	--	--	--
Black or African American	n=20 1643.7 (1201.6, 2248.6)	n=29 1706.7 (1315.7, 2213.8)	1.0 (0.6, 1.4)	n=20 20 (100) (83.2, 100.0)	n=29 29 (100) (88.1, 100.0)	NE (NE, NE)
White	n=188 1379.1 (1224.2, 1553.7)	n=203 1378.0 (1228.7, 1545.5)	1.0 (0.8, 1.2)	n=188 186 (98.9) (96.2, 99.9)	n=203 202 (99.5) (97.3, >99.9)	-0.6 (-3.4, 1.8)
Others	n=56 1437.8 (1125.2, 1837.4)	n=59 1298.2 (1022.3, 1648.5)	1.1 (0.8, 1.6)	n=56 55 (98.2) (90.4, >99.9)	n=59 58 (98.3) (90.9, >99.9)	-0.1 (-8.0, 7.5)
Ethnicity	--	--	--	--	--	--
Hispanic or Latino	n=47 1503.2 (1208.1, 1870.4)	n=75 1586.2 (1334.2, 1885.8)	0.9 (0.7, 1.3)	n=47 47 (100) (92.5, 100.0)	n=75 75 (100) (95.2, 100.0)	NE (NE, NE)
Not Hispanic or Latino or missing	n=217 1390.6 (1239.6, 1560.0)	n=216 1328.7 (1184.1, 1491.0)	1.0 (0.9, 1.2)	n=217 214 (98.6) (96.0, 99.7)	n=216 214 (99.1) (96.7, 99.9)	-0.5 (-3.2, 2.1)
Race and ethnicity	--	--	--	--	--	--
White non-Hispanic	n=152 1382.1 (1205.8, 1584.1)	n=144 1292.4 (1123.4, 1486.9)	1.1 (0.9, 1.3)	n=152 150 (98.7) (95.3, 99.8)	n=144 143 (99.3) (96.2, >99.9)	-0.6 (-4.1, 2.6)
Communities of Color	n=112 1448.8 (1243.0, 1688.7)	n=147 1494.4 (1307.3, 1708.2)	1.0 (0.8, 1.2)	n=112 111 (99.1) (95.1, >99.9)	n=147 146 (99.3) (96.3, >99.9)	-0.2 (-4.3, 3.0)

Characteristic	2-5 Years mRNA-1273 25µg N=264 GMC (95% CI)	18-25 Years mRNA-1273 100µg N=295 GMC (95% CI)	GMC Ratio[a] (95% CI)	2-5 Years mRNA-1273 25µg N=264 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years mRNA-1273 100µg N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponse Rate, % (95% CI)[d]
Obesity Status	--	--	--	--	--	--
Obese	n=23 1986.6 (1181.2, 3341.4)	n=65 1655.4 (1215.0, 2255.4)	1.2 (0.7, 2.2)	n=23 23 (100) (85.2, 100.0)	n=65 63 (96.9) (89.3, 99.6)	3.1 (-11.5, 10.6)
Non-obese	n=241 1364.6 (1243.7, 1497.4)	n=225 1326.3 (1204.9, 1460.1)	1.0 (0.9, 1.2)	N=241 238 (98.8) (96.4, 99.7)	n=225 225 (100) (98.4, 100.0)	-1.2 (-3.6, 0.4)
Baseline SARS-CoV-2 status	--	--	--	--	--	--
Negative[f,h]	n=268 1425.2 (1285.0, 1580.7)	n=296 1358.7 (1231.2, 1499.4)	1.0 (0.9, 1.2)	n=268 265 (98.9) (96.8, 99.8)	n=296 293 (99.0) (97.1, 99.8)	-0.1 (-2.3, 2.0)
Positive[f,g]	n=20 4791.3 (2649.2, 8665.2)	n=15 3930.0 (1942.7, 7949.9)	1.2 (0.4, 3.3)	n=20 20 (100) (83.2, 100.0)	n=15 14 (93.3) (68.1, 99.8)	6.7 (-10.5, 30.3)

Source: Study P204 (2-5 years) Table 14.2.1.1.3.2.3, Table 14.2.1.1.3.3.3, Table 14.2.1.1.3.8.3, Table 14.2.1.2.3.2.3, Table 14.2.1.2.3.3.3, and Table 14.2.1.2.3.8.3.
Lower limit of quantification (LLOQ): 10
Abbreviations: n=Number of subjects in subgroup with non-missing data at baseline and the corresponding timepoint; N=number of participants in cohort; NE=not estimable
Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
GMC is estimated by geometric least square (LS) means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
e. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P204 and BMI ≥30 kg/m2 for P301
f. Results by baseline SARS-CoV-2 status were based on the Immunogenicity Subset, which included for 2-5 years N= 302 and for 18-25 years N=340. Total Ns include participants for whom data are missing.
The Immunogenicity Subset consists of participants in the Full Analysis Set who have baseline (Day 1) SARS-CoV-2 status available and have baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
g. 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.
h. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Exploratory immunogenicity analyses against SARS-CoV-2 variants
Immunogenicity against variants of concern based on neutralizing antibodies have not been assessed for this age cohort.

Efficacy evaluation
Vaccine efficacy (VE) was descriptively analyzed as a secondary endpoint in the study, with the data cutoff date of February 21, 2022. The median duration of blinded follow-up for efficacy was 71 days after Dose 2. The study evaluated the first occurrence of symptomatic COVID-19, in participants without evidence of previous SARS-CoV-2 at baseline, using two different COVID-19 case definitions (CDC case definition and P301 COVID-19 definition). Using the CDC case definition, there were 119 cases among the 2,594 mRNA-1273 recipients and 61 cases among the 858 placebo recipients, for an estimated VE of 36.8% (95% CI 12.5, 54.0). Using the P301 definition, there were 71 cases in the mRNA-1273 group and 43 cases in the placebo group, for an estimated VE of 46.4% (95% CI 19.8, 63.8).

Table 58. COVID-19 Incidence Starting 14 Days After Dose 2, Participants 2 Through 5 Years of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Disease/Infection	mRNA-1273 25 µg N=2594 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=858 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
COVID-19 based on CDC definition[d]	119 (4.6) 679.9 175.0 (145.0, 209.4)	61 (7.1) 220.2 277.0 (211.9, 355.8)	36.8% (12.5, 54.0)
COVID-19 based on P301 definition[e]	71 (2.7) 684.3 103.8 (81.0, 130.9)	43 (5.0) 222.2 193.5 (140.1, 260.7)	46.4% (19.8, 63.8)

Sources: P204 (2-5 years) Table 14.2.7.1.1.2.1, 14.2.8.1.1.2.1
Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID-19=coronavirus disease-2019; N=included 25 individuals younger than 2 years of age randomized in the 2 through 5 years of age group stratum (18 in the Moderna COVID-19 Vaccine group and 7 in the placebo group), and one in each treatment group had a COVID-19 case starting 14 days after Dose 2; RT-PCR=reverse transcriptase polymerase chain reaction
a. Person-years is defined as the total years from randomization date to the first date of COVID-19 (P301 primary definition or CDC definition, as applicable), 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
d. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.
e. COVID-19 (P301 primary definition) is at least 2 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF), 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; AND at least 1 positive RT-PCR test for SARS-CoV-2.

The date of first enrollment of the blinded phase of the study was October 18, 2021, and the date of the data cutoff was February 21, 2022, and so, the time period in which the efficacy endpoint (starting 14 days after Dose 2) was evaluated coincided with the emergence and rapid surge of the Omicron variant in the US. Among the 180 CDC-defined cases of COVID-19 in the PP Set for Efficacy, there were 79 participants (51 in the mRNA-1273 group and 28 in the placebo group) with SARS-CoV-2 sequencing data available. Of those 79 cases, 78 were sequenced to be Omicron variant, predominantly BA.1 and BA.1.1 lineages (cases occurring

December 2021 through February 2022), and one was sequenced to be Delta variant (a case in the placebo group which occurred in November 2021). Vaccine efficacy against symptomatic COVID-19 observed in this study appears consistent with the vaccine efficacy observed among adults during the Omicron surge, based on observational studies in the US.

For additional discussion of clinical efficacy below, the broader CDC definition of COVID-19 will be used to maximize the number of cases and the precision of the estimate.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of vaccine efficacy against COVID-19, per the CDC case definition, starting 14 days after Dose 2 are displayed below in Table 59. In general, vaccine efficacy across demographic subgroups were consistent with the VE efficacy results from the secondary analyses. Notable exceptions are the lower VE estimates for males (26.8%) compared to females (45.9%) and the lower VE estimates for obese participants (-15.4%) compared to non-obese participants (40.4%), although the CIs for both VE estimates are wide and overlap with those for females and non-obese participants, respectively, thus limiting the interpretation of these results. In addition, the number of participants included in some subgroups were small, resulting in VE estimates with wide or non-estimable 95% CIs (including a case split of 7 cases in the mRNA-1273 group and 0 cases in the placebo group for Black or African American participants).

Table 59. Subgroup Analysis, Participants 2 Through 5 Years of Age With COVID-19 (CDC Case Definition) Starting 14 Days After Dose 2, P204 Part 2, Per-Protocol Set for Efficacy

Characteristic	mRNA-1273 25 µg Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Placebo Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Vaccine Efficacy[c] (95% CI)
Sex	--	--	--
Male	66/1316 (5.0) 190.2 (147.1, 241.9)	29/434 (6.7) 259.9 (174.1, 373.3)	26.8% (-17.5, 53.4)
Female	53/1278 (4.1) 159.2 (119.3, 208.3)	32/424 (7.5) 294.5 (201.4, 415.7)	45.9% (13.3, 65.8)
Race	--	--	--
Black or African American	7/110 (6.4) 234.3 (94.2, 482.8)	0/33 0 (NE, 391.7)	NE (NE, NE)
White	95/1972 (4.8) 185.0 (149.7, 226.2)	51/678 (7.5) 297.5 (221.5, 391.2)	37.8 (10.8, 56.2)
Other	17/512 (3.3) 124.4 (72.5, 199.2)	10/147 (6.8) 253.7 (121.7, 466.6)	51.0% (-19.9, 78.8)
Ethnicity	--	--	--
Hispanic or Latino	18/364 (4.9) 181.1 (107.4, 286.3)	10/118 (8.5) 319.1 (153.0, 586.7)	43.2% (-37.7, 75.2)
Not Hispanic or Latino	101/2230 (4.5) 174.0 (141.7, 211.4)	51/740 (6.9) 270.0 (201.0, 355.0)	35.6% (7.9, 54.4)
Race and ethnicity group	--	--	--
White non-Hispanic	82/1701 (4.8) 186.4 (148.3, 231.4)	45/585 (7.7) 305.8 (223.0, 409.2)	39.0% (10.2, 58.1)
Communities of Color	36/891 (4.0) 150.3 (105.3, 208.1)	16/272 (5.9) 219.9 (125.7, 357.1)	31.7% (-31.9, 63.0)

Characteristic	mRNA-1273 25 µg Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Placebo Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Vaccine Efficacy[c] (95% CI)
Obesity status	--	--	--
Obese	14/263 (5.3) 205.6 (112.4, 344.9)	4/87 (4.6) 178.2 (48.6, 456.2)	-15.4% (-381.4, 63.8)
Non-obese	105/2329 (4.5) 171.8 (140.5, 208.0)	57/770 (7.4) 288.5 (218.5, 373.7)	40.4% (16.3, 57.3)

Source: P204 (2-5 years) 14.2.8.1.1.3.1
Abbreviations: CI=confidence interval; n=number of participants with indicated characteristic; N=number of participants in chort; NE=not evaluable
Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.
a. Person-years is defined as the total years from randomization date to the first date of COVID-19 per CDC definition, 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 Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

The number of COVID-19 cases among SARS-CoV-2 baseline positive participants was too small to reliably estimate VE in this subgroup. Starting 14 days after Dose 2, among the 190 participants in the Full Analysis Set who developed COVID-19 per CDC definition, only 7 cases were in participants who had evidence of prior SARS-CoV-2 infection at baseline (6 in the mRNA-1273 group compared to 1 in the placebo group). Among these 7 participants, the majority were White and non-Hispanic or Latino, and none reported baseline comorbidities for risk of more severe COVID-19 (i.e., obesity, chronic lung disease including asthma, clinically significant cardiac disorders, diabetes mellitus, or HIV). The onset of COVID-19 cases in these participants ranged from 29 to 58 days following the administration of the second dose.

Vaccine efficacy: including participants with prior SARS-CoV-2 infection
The VE estimate using the CDC case definition of COVID-19 was similar to the protocol-specified efficacy analysis when assessed in a population of participants both with and without evidence of prior SARS-CoV-2 infection (or unknown) at baseline (FAS), with a VE estimate of 34.5% (95% CI 9.8, 52.0) starting 14 days after Dose 2.

SARS-CoV-2 infection
Efficacy was also evaluated against SARS-CoV-2 infection, regardless of symptoms, which includes both COVID-19 cases as well as cases of asymptomatic infection. Asymptomatic SARS-CoV-2 infection is defined as absence of COVID-19 symptoms (i.e., not meeting the case definition for COVID-19 per CDC definition or P301 definition) and either of the following: (a) bAb levels against SARS-CoV-2 nucleocapsid (N) protein (as measured by *Roche Elecsys*) negative at Day 1 that becomes positive post-baseline or (b) positive RT-PCR test post-baseline. Per protocol, all participants were scheduled for collection of nasal swab samples for RT-PCR testing on Day 1, Day 29 (pre-Dose 2), 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). Given the timing of the data cutoff, Day 209 and Day 394 had not yet occurred and thus data are only available through the Day 57 visit. Additionally, N-serology testing was conducted at pre-specified scheduled study visits at Day 1, Day 57, and depending on the participant's assigned phlebotomy cohort, either Day 29, Day 209, or Day 394. Asymptomatic SARS-CoV-2 infections were also identified at unscheduled study visits triggered by potential exposure with no subsequent development of clinical symptoms. Given the limited number of RT-PCR and N-serology assessment time points, it is unlikely that all cases of asymptomatic SARS-CoV-2 infection which occurred during the study were captured.

As shown in Table 60 below, VE against SARS-CoV-2 infections regardless of symptoms included more COVID-19 symptomatic cases than asymptomatic cases in both groups, with a similar proportion of symptomatic cases in the vaccine group (60.1%) compared to the placebo group (64.5%).

Vaccine efficacy against asymptomatic infection starting at least 14 days after Dose 2 was 22.9% (95% CI −19.5, 49.3). As noted, the 95% CI includes zero, making it difficult to draw conclusions regarding efficacy against asymptomatic infection.

Table 60. Incidence of SARS-CoV-2 Infection Starting 14 Days After Dose 2, Participants 2 Through 5 Years of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Disease/Infection	mRNA-1273 25 µg N=2594 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=858 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
SARS-CoV-2 Infection[d] (regardless of symptoms)	198 (7.6) 666.8 296.9 (257.0, 341.3)	93 (10.8) 214.6 433.4 (349.8, 530.9)	31.5% (11.4, 46.7)
Asymptomatic SARS-CoV-2 infection[e]	79 (3.0) 666.9 118.5 (93.8, 147.6)	33 (3.8) 214.7 153.7 (105.8, 215.9)	22.9% (-19.5, 49.3)

Sources: P204 (2-5 years) Table 14.2.5.1.1.2.1, Table 14.2.6.1.1.2.1.1

a. Person-years is defined as the total years from randomization date to the first date of SARS-CoV-2 infection, or asymptomatic SARS-CoV-2 infection, as applicable, to the last date of study participation, 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

d. SARS-CoV-2 infection (regardless of symptoms) is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline. Participants have 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) or positive RT-PCR post-baseline

e. Asymptomatic infection is identified by the absence of symptoms and the presence of infection as detected by RT-PCR or serology tests for participants with negative SARS-CoV-2 status at baseline. Specifically, the absence of COVID-19 symptoms and at least one of the following: 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.

Severe COVID-19 cases

There were no reports of severe COVID-19 cases in participants 2-5 years of age in this study as of the data cutoff.

Additional efficacy analyses

COVID-19 cases by time period

Additional analyses of the efficacy endpoint were conducted to evaluate VE against COVID-19, based on the CDC case definition, by time period (Table 61). VE for the prevention of COVID-19 starting any time after Dose 1 was 38.7% (95% CI 18.5%, 53.6%). Although these data suggest some protection against COVID-19 following one dose, the follow-up time after one dose was limited, as almost all study participants went on to receive a second dose. In addition, the small number of COVID-19 cases and the wide 95% CI for the time period after Dose 1 to before Dose 2 make it difficult to accurately draw conclusions on vaccine efficacy during this time.

These data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

VE estimates from analyses any time after Dose 1 and any time after Dose 2 were overall similar to the primary efficacy analysis against COVID-19 starting 14 days after Dose 2 (36.8% [12.5%, 54.0%]).

Table 61. Incidence of COVID-19 (CDC Case Definition) by Time Period, Participants 2 Through 5 Years of Age, Study P204 Part 2, mITT1 Set

First COVID-19[d] Occurrence	mRNA-1273 25 µg N=2693 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=898 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
Any time after Dose 1	150/2693 (5.6) 697.8 215.0 (181.9, 252.2)	79/898 (8.8) 225.3 350.7 (277.7, 437.1)	38.7% (18.5%, 53.6%)
Any time after Dose 1 to before Dose 2	22/2693 (0.8) 224.4 98.0 (61.4, 148.4)	9/898 (1.0) 74.6 120.7 (55.179, 229.1)	18.8% (−100.4%, 64.0%)
Any time after Dose 2	128/2601 (4.9) 470.8 271.9 (226.8, 323.2)	70/866 (8.1) 150.4 465.5 (362.9, 588.1)	41.6% (20.7%, 56.7%)

Source:Study P204 (2-5 years) Table 14.2.8.4.1.2.1
N1 is the number of participants at risk. Percentages are based on N1.
a. Person-years for each time period is defined as the total years from the start of each time period to the date of CDC case definition of COVID-19, the end of each time period, last date of study participation, efficacy data cutoff date, whichever is earliest.
b. Incidence rate for each time period is defined as the number of participants with an event during the time period divided by the number of participants at risk at the beginning of each time period 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. Vaccine efficacy is 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 for the time period.
d. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.

Sensitivity analysis accounting for different COVID-19 testing methods during the Omicron surge

During the Omicron surge, in-person illness visits were not always possible due to COVID-19 restrictions. Results of home testing were recorded, and participants were encouraged to obtain a confirmatory RT-PCR test following a positive home test; therefore, cases identified from a positive home test without a confirmatory RT-PCT test were not included in the protocol-specified efficacy analyses. Given that the number of potential cases based on home testing increased during this time period due to greater availability of home tests and the reluctance of many families to bring their children to the study site during the peak of the Omicron surge, a sensitivity analysis of VE was performed to include all reported cases of COVID-19 irrespective of test performed and location of testing, which could include RT-PCR performed at a CLIA-certified central laboratory, RT-PCR performed at a local laboratory, home testing, and unknown testing modality. Results are shown in Table 62 below. As expected with a broader allowance for test results, the number of COVID-19 cases and SARS-CoV-2 infections was higher than in the protocol-specified vaccine efficacy analysis. As shown in Table 62, VE estimates in this sensitivity analysis were lower than in the protocol-specified VE analyses. However, the CIs for the sensitivity analyses overlap with those for the protocol-specified analyses, and it is possible

that the sensitivity test could be subject to unknown biases influencing the observed differences in VE estimates.

Table 62. Sensitivity Analysis of All Reported Cases Irrespective of Testing Method and Location* Starting 14 Days After Dose 2, Participants 2 Through 5 Years of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

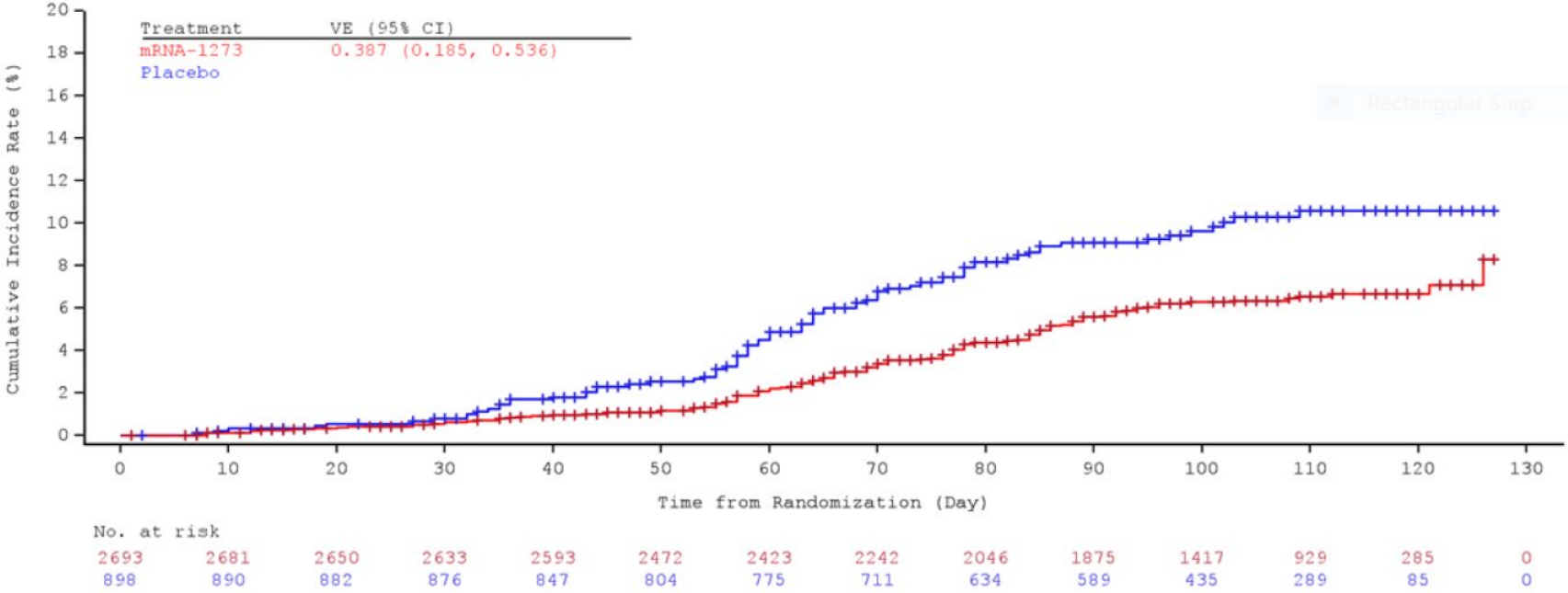
Disease/Infection	mRNA-1273 25 µg N=2594 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=858 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
CDC case definition of COVID-19	179 (6.9) 674.2 265.5 (228.0, 307.4)	81 (9.4) 218.1 371.4 (295.0, 461.6)	28.5% (5.9%, 45.3%)
P301 case definition of COVID-19	106 (4.1) 681.2 155.6 (127.4, 188.2)	55 (6.4) 221.0 248.9 (187.5, 324.0)	37.5% (11.8%, 55.3%)

Source: Study P204 (2-5 years) Table 14.2.7.1.1.2, Table 14.2.8.1.1.2
*Testing Method and Location could include RT-PCR performed at a CLIA-certified central laboratory, RT-PCR performed at a local laboratory, home testing, and unknown testing modality
a. Person-years is defined as the total years from the randomization date to the date of event (CDC case definition of COVID-19, P301 case definition of COVID-19, 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 is 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.

Cumulative incidence curves

The cumulative incidence curve for COVID-19 based on the CDC case definition starting after randomization (same day as Dose 1), in the mITT1 Set (Figure 3, below), shows that cases of COVID-19 remained similarly low in both the mRNA-1273 and placebo groups until approximately 1 week after Dose 2, at which time point the curves diverge, with more cases accumulating in the placebo group than in the mRNA-1273 group.

Figure 3. Cumulative Incidence Curve of CDC Case Definition of COVID-19 Starting After Randomization, Participants 2 Through 5 Years of Age, Study P204 Part 2, mITT1 Set



Source: P204 (2-5 years) Figure 14.2.5.2.3.2.1
Vaccine efficacy (VE) based on number of participants at risk at 14 days after first injection in mITT1 set, 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.

4.4.3.4 Safety

Overview of adverse events

Safety analyses presented in this section of the review focus on data from the blinded phase of the study (Part 2) through the cutoff date of February 21, 2022, with a median duration of blinded follow-up of 71 days post Dose 2. From the open-label portion of the study (Part 1), only the analyses of SAEs and unsolicited AEs of clinical interest are presented.

Table 63 below summarizes AEs in participants 2-5 years of age from Part 2 of Study P204. Overall, the proportion of MAAEs was balanced between vaccine and placebo groups. SAEs were uncommon (0.3% for the mRNA-1273 group and 0.2% for the placebo group), and no deaths were reported in either group. The rate of unsolicited AEs within 28 days after vaccination, including related unsolicited AEs, was similar across groups. As compared to the placebo group, a greater percentage of participants in the vaccine group experienced local and systemic solicited ARs. Overall, the percentage of mRNA-1273 recipients who experienced local and systemic solicited ARs was higher following Dose 2 than following Dose 1.

Table 63. Safety Overview, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set, Solicited Safety Set, Solicited Safety Set

Adverse Event	mRNA-1273 25µg	Placebo
Solicited adverse reactions within 7 days, n/N1 (%)	--	--
Solicited local adverse reaction (any dose), n/N1 (%)	2518/3015 (83.5)	576/997 (57.8)
Dose 1	1874/2956 (63.4)	407/970 (42.0)
Dose 2	2157/2938 (73.4)	404/959 (42.1)
Grade 3 or 4 solicited local adverse reaction (any dose), n/N1 (%)	54/3015 (1.8)	4/997 (0.4)
Solicited systemic adverse reaction (any dose), n/N1 (%)	2300/3015 (76.3)	642/997 (64.4)
Dose 1	1595/2955 (54.0)	488/970 (50.3)
Dose 2	1814/2938 (61.7)	428/959 (44.6)
Grade 3 or 4 systemic adverse reaction (any dose)	199/3015 (6.6)	37/997 (3.7)
Immediate[a] unsolicited adverse events after vaccination, n/N1 (%)	--	--
After any dose	8/3031 (0.3)	3/1007 (0.3)
Dose 1	4/3031 (0.1)	3/1007 (0.3)
Dose 2	4/2960 (0.1)	0/970 (0.0)
Unsolicited adverse events, n/N1 (%)	--	--
Unsolicited TEAE within 28 days after any injection	1212/3031 (40.0)	378/1007 (37.5)
Non-serious unsolicited TEAE	1211/3031 (40.0)	378/1007 (37.5)
Related non-serious unsolicited TEAE	286/3031 (9.4)	80/1007 (7.9)
Severe non-serious unsolicited TEAE	21/3031 (0.7)	9/1007 (0.9)
Related severe non-serious unsolicited TEAE	18/3031 (0.6)	8/1007 (0.8)
Medically attended adverse event (MAAE)[b], n/N1 (%)	1002/3031 (33.1)	344/1007 (34.2)
Related MAAE[b]	31/3031 (1.0)	3/1007 (0.3)
SAE [b], n/N1 (%)	9/3031 (0.3)	2/1007 (0.2)
Related SAE[b]	0	0

Adverse Event	mRNA-1273 25µg	Placebo
AEs of special interest (AESI) [b], n/N1 (%)	5/3031 (0.2)	1/1007 (<0.1)
Deaths[b], n/N1 (%)	0	0
TEAE leading to discontinuation of study vaccine[b,c], n/N1 (%)	1	0
TEAE leading to discontinuation from study[c] participation[b], n/N1 (%)	1	0

Sources: EUA 27073 P204 (2-5 years) Am 395 Table 14.3.1.1.1.2.1, 14.3.1.1.2.2.1, 14.3.1.1.3.2.1, 14.3.1.7.1.2, 14.3.1.7.2.2 and Am 413

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; n=number of participants with indicated AE; N=number of participants in cohort; N1=number of participants who submitted data; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

a. Within 30 minutes after vaccination

b. Events during entire blinded study period

In the Safety Set, approximately 8.8% of mRNA-1273 recipients and 8.1% of placebo recipients had evidence of prior SARS-CoV-2 infection at baseline. Table 64 summarizes safety by baseline SARS-CoV-2 status in the mRNA-1273 group. Overall, rates of solicited local adverse reactions were similar between participants with negative SARS-CoV-2 status at baseline (84.1%) and those with positive SARS-CoV-2 status at baseline (78.5%). Rates of solicited systemic adverse reactions were also similar across groups (76.2% in baseline negative participants; 78.9% in baseline positive participants).

Table 64. Safety Overview by Baseline SARS-CoV-2 Status, mRNA-1273 Recipients 2 Through 5 Years of Age, Study P204 Part 2, Safety Set, Solicited Safety Set, Solicited Safety Set

Adverse Event	Baseline SARS-CoV-2 Negative	Baseline SARS-CoV-2 Positive
Solicited adverse reactions within 7 days, n/N1 (%)	--	--
Solicited local adverse reaction (any dose), n/N1 (%)	2256/2682 (84.1)	208/265 (78.5)
Dose 1	1678/2632 (63.8)	154/258 (59.7)
Dose 2	1932/2617 (73.8)	177/256 (69.1)
Grade 3 or 4 local AR (any dose), n/N1 (%)	50/2682 (1.9)	2/265 (0.8)
Solicited systemic AR (any dose), n/N1 (%)	2043/2682 (76.2)	209/265 (78.9)
Dose 1	1405/2631 (53.4)	156/258 (60.5)
Dose 2	1618/2617 (61.8)	156/256 (60.9)
Grade 3 or 4 systemic AR (any dose), n/N1 (%)	170/2682 (6.3)	21/209 (7.9)
Unsolicited adverse events within 28 days, n/N1 (%)	--	--
Unsolicited AE (any dose), n/N1 (%)	1091/2695 (40.5)	99/266 (37.2)
Non-serious unsolicited AE (any dose), n/N1 (%)	1090/2695 (40.4)	99/266 (37.2)
Severe non-serious unsolicited AE (any dose), n/N1 (%)	18/2695 (0.7)	2/266 (0.8)
MAAE within 28 days after any dose, n/N1 (%)	594/2695 (22.0)	55/266 (20.7)
SAE within 28 days after any injection (any dose), n/N1 (%)	2/2695 (<0.1)	1/266 (0.4)

Sources: P204 (2-5 years) Table 14.3.1.1.5.1, 14.3.1.1.5.2, 14.3.1.1.5.3, 14.3.1.7.1.4.2.1
Abbreviations: AE=adverse event; AR=adverse reaction; MAAE=medically attended adverse event; n=number of participants with indicated AE; N=number of participants in cohort; N1=number of participants who submitted data; SAE=serious adverse event; TEAE=treatment-emergent adverse event
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.Immediate adverse events

Immediate unsolicited AEs occurring within 30 minutes of vaccination were infrequent and were reported by 8 mRNA-1273 recipients (0.3%) and 3 placebo recipients (0.3%). Of these, 4 in the mRNA-1273 group (0.1%) and 3 in the placebo group (0.3%) occurred after Dose 1 and 4 in the mRNA-1273 group (0.1%) and 0 in the placebo group (0.3%) occurred after Dose 2. The majority of events were related to vaccine administration or injection site reactions. A 3-year-old male participant in the mRNA-1273 group reported a mild (Grade 1) swelling and redness of the bottom lip after Dose 2; however, he was also reported to have eaten a red popsicle. The participant was given antihistamine medication and the event resolved after 1 hour. The PI considered the event related to vaccination; however, in FDA's review of this event, there was another possible etiology.

Solicited adverse reactions
Solicited local and systemic adverse reactions in the 2-5 years age group generally occurred more frequently and were more severe after Dose 2 compared to Dose 1.

The most common solicited local AR was injection site pain, which was reported by 61.4% of mRNA-1273 recipients after Dose 1 and 71.4% of mRNA-1273 recipients after Dose 2. In mRNA-1273 recipients, injection site erythema, injection site swelling, and axillary (or groin) swelling/tenderness were reported by 4.5%-6.9% of participants after Dose 1 and 8.2%-9.1% of participants after Dose 2. Grade 3 (severe) solicited local ARs were reported by 0.8% of mRNA-1273 recipients after Dose 1 and by 1.2% of mRNA-1273 recipients after Dose 2. The frequencies of local adverse reactions within 7 days after each dose in Part 2 study participants 2-5 years of age are summarized in
Table 65.

Table 65. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Participants 2 Through 5 Years of Age, Study P204 Part 2, Solicited Safety Set

Event	mRNA-1273 25µg Dose 1 N=2957	Placebo Dose 1 N=970	mRNA-1273 25µg Dose 2 N=2938	Placebo Dose 2 N=959
Any local adverse reaction, n (%)	N1=2956	N1=970	N1=2938	N1=959
Any	1874 (63.4)	407 (42.0)	2157 (73.4)	404 (42.1)
Grade 1	1642 (55.5)	388 (40.0)	1691 (57.6)	390 (40.7)
Grade 2	209 (7.1)	15 (1.5)	432 (14.7)	14 (1.5)
Grade 3	23 (0.8)	4 (0.4)	34 (1.2)	0
Pain at injection site, n (%)	N1=2954	N1=970	N1=2938	N1=959
Any	1813 (61.4)	382 (39.4)	2099 (71.4)	395 (41.2)
Grade 1	1663 (56.3)	370 (38.1)	1734 (59.0)	386 (40.3)
Grade 2	146 (4.9)	12 (1.2)	354 (12.0)	9 (0.9)
Grade 3	4 (0.1)	0	11 (0.4)	0

Event	mRNA-1273 25µg Dose 1 N=2957	Placebo Dose 1 N=970	mRNA-1273 25µg Dose 2 N=2938	Placebo Dose 2 N=959
Erythema (redness), n (%)	N1=2955	N1=970	N1=2938	N1=959
Any	164 (5.5)	14 (1.4)	259 (8.8)	15 (1.6)
Grade 1	110 (3.7)	9 (0.9)	176 (6.0)	13 (1.4)
Grade 2	42 (1.4)	2 (0.2)	71 (2.4)	2 (0.2)
Grade 3	12 (0.4)	3 (0.3)	12 (0.4)	0
Swelling (hardness), n (%)	N1=2955	N1=970	N1=2938	N1=959
Any	134 (4.5)	17 (1.8)	240 (8.2)	11 (1.1)
Grade 1	84 (2.8)	15 (1.5)	167 (5.7)	11 (1.1)
Grade 2	40 (1.4)	0	60 (2.0)	0
Grade 3	10 (0.3)	2 (0.2)	13 (0.4)	0
Axillary (or groin) swelling or tenderness, n (%)	N1=2954	N1=970	N1=2938	N1=959
Any	205 (6.9)	56 (5.8)	267 (9.1)	31 (3.2)
Grade 1	194 (6.6)	55 (5.7)	247 (8.4)	28 (2.9)
Grade 2	11 (0.4)	1 (0.1)	19 (0.6)	3 (0.3)
Grade 3	0	0	1 (<0.1)	0

Source: P204 (2-5 years), Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1.
Abbreviations: AR=adverse reaction; G=grade; n=number of participants with indicated AE; N=number of participants in cohort; N = Included 36 individuals younger than 2 years of age randomized in the 2 through 5 years of age group stratum (24 in the mRNA-1273 group and 12 in the placebo group). All of these 36 individuals had eDiary for 6 months to ≤36 months age group.
N1=number of participants who submitted data
Note: Any=Grade 1 or higher. There were no Grade 4 solicited local ARs reported.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants age 24-36 months is defined as: G1 = 5-20 mm; G2 = >20-50 mm; G3 = >50 mm
Toxicity grade for injection stie erythema (redness) or swelling (hardness) for participants 37 months-5 years is defined as: G1 = 25 — 50 mm; G2 = 51-100 mm; G3 = >100 mm
Toxicity grade for Groin or underarm swelling or tenderness for subject age 6 to ≤36 months, or for Axillary swelling or tenderness for subject age 37 months to <12 years is defined as: G1 = Some swelling or tenderness but no interference with normal daily activities/No interference with activity; G2 = Swelling or tenderness that interferes with normal daily activities/Some interference with activity; G3 = Swelling or tenderness that prevents normal daily activities/Prevents daily activity.

For solicited systemic reactions, different adverse reactions were assessed in participants 37 months through 5 years of age and in participants 24 through 36 months of age. For participants 37 months through 5 years of age, assessments included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and use of antipyretic/pain medications; and for participants 24 through 36 months of age, assessments included fever, irritability, crying, sleepiness, loss of appetite, and use of antipyretic/pain medications.

In participants ages 37 months through 5 years of age, the most common solicited systemic AR reported by mRNA-1273 recipients was fatigue, reported by 40.1% of participants after Dose 1 and by 48.4% of participants after Dose 2. Fever was reported by 7.7% of mRNA-1273 recipients after Dose 1 and 16.0% of mRNA-1273 recipients after Dose 2.

Grade 3 and Grade 4 solicited systemic ARs in mRNA-1273 recipients were reported by 2.3% and <0.1% (n=1) of participants after Dose 1 and by 5.1% & 0.2% (n=4) of participants after Dose 2, respectively. The most common Grade 3 event in mRNA-1273 recipients was fever (39.0C-40.0C), reported in 1.1% of participants after Dose 1 and 2.9% of participants after Dose 2; followed by fatigue, reported in 1.0% of participants after Dose 1 and 2.3% of participants after Dose 2. Grade 4 events were reported only for fever (>40.0C) and included no events after mRNA-1273 Dose 1, 2 events after mRNA-1273 Dose 2, and one event after placebo Dose 1. The frequencies of systemic adverse reactions within 7 days after each dose in Part 2 study for participants 37 months through 5 years are provided in Table 66.

In the participants 24 through 36 months of age, the most common solicited systemic AR reported by mRNA-1273 recipients was irritability/crying (~54% after either Dose), followed by sleepiness (30.3% after Dose 1 and 36.0% after Dose 2), and loss of appetite (23.9% after Dose 1 and 30.5% after Dose 2). Fever was reported by 11.3% of mRNA-1273 recipients after Dose 1 and 18.9% of mRNA-1273 recipients after Dose 2.

Grade 3 systemic ARs in mRNA-1273 recipients were reported by 1.9% of participants after Dose 1 and 2.9% of participants after Dose 2, the most common of which were Grade 3 fever (0.3% after Dose 1 and 1.2% after Dose 2) and irritability/crying (1.3% after Dose 1 and 1.0% after Dose 2). Grade 3 fever (temperature 39.6-40°C) was reported by 0.3% and 1.2% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. Grade 4 events were reported only for fever (>40.0C) and included 3 events after mRNA-1273 Dose 1, 3 events after mRNA-1273 Dose 2, and one event after placebo Dose 1. The frequencies of systemic adverse reactions within 7 days after each dose in Part 2 study participants 24-36 months are provided Table 67.

Table 66. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 37 Months Through 5 Years of Age, Study P204 Part 2, Solicited Safety Set

Adverse Reaction	37m-5y mRNA-1273 25 µg Dose 1 N=2013	37m-5y Placebo Dose 1 N=650	37m-5y mRNA-1273 25 µg Dose 2 N=1975	37m-5y Placebo Dose 2 N=629
Any systemic adverse reaction, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	983 (48.8)	290 (44.6)	1163 (58.9)	234 (37.2)
Grade 1	613 (30.5)	176 (27.1)	559 (28.3)	149 (23.7)
Grade 2	322 (16.0)	99 (15.2)	500 (25.3)	74 (11.8)
Grade 3	47 (2.3)	14 (2.2)	100 (5.1)	11 (1.7)
Grade 4	1 (<0.1)	1 (0.2)	4 (0.2)	0
Fever, n (%)	1=2013	N1=650	N1=1974	N1=627
Any: ≥38.0°C	155 (7.7)	33 (5.1)	316 (16.0)	28 (4.5)
Grade 1: 38.0°C to 38.4°C	93 (4.6)	20 (3.1)	159 (8.1)	19 (3.0)
Grade 2: 38.5°C to 38.9°C	38 (1.9)	8 (1.2)	95 (4.8)	7 (1.1)
Grade 3: 39.0°C to 40.0°C	23 (1.1)	4 (0.6)	58 (2.9)	2 (0.3)
Grade 4: >40.0°C	0	1 (0.2)	2 (0.1)	0
Headache, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	232 (11.5)	78 (12.0)	310 (15.7)	51 (8.1)
Grade 1	181 (9.0)	66 (10.2)	193 (9.8)	43 (6.8)
Grade 2	46 (2.3)	10 (1.5)	109 (5.5)	7 (1.1)
Grade 3	5 (0.2)	2 (0.3)	8 (0.4)	1 (0.2)
Grade 4	0	0	0	0
Fatigue, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	807 (40.1)	236 (36.3)	956 (48.4)	185 (29.4)
Grade 1	503 (25.0)	138 (21.2)	476 (24.1)	113 (18.0)
Grade 2	283 (14.1)	87 (13.4)	435 (22.0)	64 (10.2)
Grade 3	21 (1.0)	11 (1.7)	45 (2.3)	8 (1.3)
Grade 4	0	0	0	0
Myalgia, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	200 (9.9)	60 (9.2)	310 (15.7)	47 (7.5)
Grade 1	138 (6.9)	46 (7.1)	191 (9.7)	30 (4.8)
Grade 2	57 (2.8)	12 (1.8)	110 (5.6)	14 (2.2)
Grade 3	5 (0.2)	2 (0.3)	9 (0.5)	3 (0.5)
Grade 4	0	0	0	0

Adverse Reaction	37m-5y mRNA-1273 25 µg Dose 1 N=2013	37m-5y Placebo Dose 1 N=650	37m-5y mRNA-1273 25 µg Dose 2 N=1975	37m-5y Placebo Dose 2 N=629
Arthralgia, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	124 (6.2)	32 (4.9)	168 (8.5)	28 (4.5)
Grade 1	101 (5.0)	28 (4.3)	118 (6.0)	18 (2.9)
Grade 2	21 (1.0)	3 (0.5)	47 (2.4)	10 (1.6)
Grade 3	2 (<0.1)	1 (0.2)	3 (0.2)	0
Grade 4	0	0	0	0
Nausea/vomiting, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	137 (6.8)	50 (7.7)	194 (9.8)	30 (4.8)
Grade 1	113 (5.6)	38 (5.8)	152 (7.7)	25 (4.0)
Grade 2	17 (0.8)	10 (1.5)	36 (1.8)	5 (0.8)
Grade 3	7 (0.3)	2 (0.3)	6 (0.3)	0
Grade 4	0	0	0	0
Chills, n (%)	N1=2013	N1=650	N1=1975	N1=629
Any	129 (6.4)	40 (6.2)	245 (12.4)	31 (4.9)
Grade 1	99 (4.9)	29 (4.5)	164 (8.3)	21 (3.3)
Grade 2	29 (1.4)	11 (1.7)	77 (3.9)	8 (1.3)
Grade 3	1 (<0.1)	0	4 (0.2)	2 (0.3)
Grade 4	0	0	0	0
Use of antipyretic or pain medication, n (%)	N=2013	N=650	N=1975	N=629
Any	305 (15.2)	62 (9.5)	508 (25.7)	43 (6.8)

Source: EUA 27073 Study P204 (2-5 years) Am 395 Table 14.3.1.1.4.19, Table 14.3.1.1.4.20, Table 14.1.8.1.2.1, Table 14.1.8.2.2.1 and Am 417 Table 1

Abbreviations: AR=adverse reaction; n=number of participants with indicated AE; N=number of participants in cohort; N1=number of participants who submitted data

Note: Any=Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1).

Toxicity grade for headache, fatigue, myalgia, arthralgia, and chills 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. Toxicity grade for nausea/vomiting is defined as Grade 1=1-2 episodes/ 24 hours; Grade 2=>2 episodes/24 hours; Grade 3=prevents daily activity; Grade 4=requires emergency room visit or hospitalization. Medications were collected on an eDiary.

Table 67. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 24 Months Through 36 Months of Age, Study P204 Part 2, Solicited Safety Set

Adverse Reaction	24-36m mRNA-1273 25 µg Dose 1 N=944	24-36m Placebo Dose 1 N=320	24-36m mRNA-1273 25 µg Dose 2 N=963	24-36m Placebo Dose 2 N=330
Any systemic adverse reaction, n (%)	N1=942	N1=320	N1=963	N1=330
Any	612 (65.0)	198 (61.9)	651 (67.6)	194 (58.8)
Grade 1	423 (44.9)	142 (44.4)	401 (41.6)	133 (40.3)
Grade 2	168 (17.8)	46 (14.4)	219 (22.7)	59 (17.9)
Grade 3	18 (1.9)	9 (2.8)	28 (2.9)	2 (0.6)
Grade 4	3 (0.3)	1 (0.3)	3 (0.3)	0
Fever, n (%)	N1=942	N1=320	N1=962	N1=330
Any: ≥38.0°C	106 (11.3)	25 (7.8)	182 (18.9)	35 (10.6)
Grade 1: 38.0°C to 38.5°C	64 (6.8)	9 (2.8)	89 (9.3)	15 (4.5)
Grade 2: 38.6°C to 39.5°C	36 (3.8)	12 (3.8)	78 (8.1)	20 (6.1)
Grade 3: 39.6°C to 40.0°C	3 (0.3)	3 (0.9)	12 (1.2)	0
Grade 4: >40.0°C	3 (0.3)	1 (0.3)	3 (0.3)	0

Adverse Reaction	24-36m mRNA-1273 25 µg Dose 1 N=944	24-36m Placebo Dose 1 N=320	24-36m mRNA-1273 25 µg Dose 2 N=963	24-36m Placebo Dose 2 N=330
Irritability/crying, n (%)	N1=941	N1=319	N1=963	N1=330
Any	513 (54.5)	163 (51.1)	523 (54.3)	148 (44.8)
Grade 1	366 (38.9)	122 (38.2)	347 (36.0)	108 (32.7)
Grade 2	135 (14.3)	35 (11.0)	166 (17.2)	38 (11.5)
Grade 3	12 (1.3)	6 (1.9)	10 (1.0)	2 (0.6)
Grade 4	0	0	0	0
Sleepiness, n (%)	N1=941	N1=319	N1=963	N1=330
Any	285 (30.3)	92 (28.8)	347 (36.0)	89 (27.0)
Grade 1	275 (29.2)	88 (27.6)	334 (34.7)	89 (27.0)
Grade 2	8 (0.9)	4 (1.3)	12 (1.2)	0
Grade 3	2 (0.2)	0	1 (0.1)	0
Grade 4	0	0	0	0
Loss of appetite, n (%)	N1=941	N1=319	N1=963	N1=330
Any	225 (23.9)	71 (22.3)	294 (30.5)	69 (20.9)
Grade 1	190 (20.2)	61 (19.1)	243 (25.2)	61 (18.5)
Grade 2	28 (3.0)	9 (2.8)	43 (4.5)	8 (2.4)
Grade 3	7 (0.7)	1 (0.3)	8 (0.8)	0
Grade 4	0	0	0	0
Use of antipyretic or pain medication, n (%)	N=944	N=320	N=963	N=330
Any	193 (20.4)	59 (18.4)	292 (30.3)	62 (18.8)

Source: P204 (2-5 years) Table 14.3.1.1.4.19, Table 14.3.1.1.4.20, Table 14.1.8.1.2.1, Table 14.1.8.2.2.1
Abbreviations: n=number of participants with indicated AE; N=number of participants in cohort; N1=number of participants who submitted data
Note: Any=Grade 1 or higher.
N = Included 36 individuals younger than 2 years of age randomized in the 2 through 5 years of age group stratum (24 in the mRNA-1273 group and 12 in the placebo group). All of these 36 individuals had eDiary for 6 months to ≤36 months age group.
Percentages are based on the number of exposed participants who submitted any data for the event (N1). The incorrect diary (i.e., older age group diary) was used for some participants following Dose 1. The entries from the incorrect diaries were inactivated, and the correct diary was assigned for Dose 2, leading to N1 being greater following Dose 2.
Toxicity grade for irritability/crying, sleepiness, and loss of appetite 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. Medications were collected on an eDiary.

The adverse reactions in participants 37 months through 5 years of age after any dose were pain at the injection site (83.8%), fatigue (61.9%), headache (22.9%), myalgia (22.1%), fever (20.9%), chills (16.8%), nausea/vomiting (15.2%), axillary swelling/tenderness (14.3%), arthralgia (12.8%), erythema at the injection site (9.5%), and swelling at the injection site (8.2%).

The adverse reactions in participants 24 through 36 months of age after any dose were pain at the injection site (76.8%), irritability/crying (71.0%), sleepiness (49.7%), loss of appetite (42.4%), fever (26.1%), erythema at the injection site (17.9%), swelling at the injection site (15.7%), and axillary swelling/tenderness (11.5%).

Duration of Adverse Reactions

Most local and systemic reactions were mild to moderate in severity and resolved within 2 days. In the mRNA-1273 group, time to onset of most solicited local reactions was within 1 day after any dose, and time to onset of most solicited systemic reactions was within 2 days after any dose.

Solicited local ARs persisting beyond 7 days after any dose were reported more frequently in the mRNA-1273 group (1.4%) than in the placebo group (0.4%). The majority of events were mild (Grade 1). Among mRNA-1273 recipients, axillary (or groin) swelling/tenderness was the local AR most frequently reported as persisting (0.3% and 0.5% after Dose 1 and Dose 2, respectively). Solicited systemic ARs persisting beyond 7 days after any dose were reported in similar proportions in both groups (4.7% mRNA-1273 vs 5.8% placebo). The majority of events were mild (Grade 1) or moderate (Grade 2). Overall, 2.9% and 2.3% of mRNA-1273 recipients reported solicited systemic ARs that persisted beyond the 7-day reporting period following Dose 1 and Dose 2, respectively. Among children 37 months through 5 years of age, fatigue was the most frequently reported persisting systemic AR (1.7% post-Dose 1 and 1.1% post-Dose 2). Among children 24-36 months of age, irritability/crying was the most frequently reported systemic AR that persisted (3.0% post-Dose 1 and 2.6% post-Dose 2).

Delayed solicited injection site reactions, defined as beginning after 7 days post-vaccination, were reported by 1.3% of mRNA-1273 recipients after Dose 1 and <0.1% after Dose 2. Less than 0.1% of these delayed local reactions were medically attended, and none were considered severe. The most common delayed local reaction was erythema. Delayed solicited systemic reactions were reported in 0.4% of participants in both the mRNA-1273 and placebo groups.

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing mRNA-1273 and placebo groups by sex, race, ethnicity, and SARS-CoV-2 status at baseline. No notable differences were observed among the demographic subgroups. Solicited local and systemic reactions after vaccination among mRNA-1273 recipients by baseline SARS-CoV-2 status are shown in Table 68. Overall, the frequencies of solicited local and systemic ARs were similar between the two groups, except for fever which was reported more frequently after each dose among participants with positive SARS-CoV-2 at baseline (13.2% Dose 1; 20.7% Dose 2) than participants with negative SARS-CoV-2 status at baseline (8.4% Dose 1; 16.6% Dose 2).

Table 68. Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose by SARS-CoV-2 Status at Baseline, Participants 2 Through 5 Years of Age, Study P204 Part 2, Solicited Safety Set

Event[a]	Baseline SARS-CoV-2 Negative Dose 1 N=2633	Baseline SARS-CoV-2 Positive Dose 1 N=258	Baseline SARS-CoV-2 Negative Dose 2 N=2617	Baseline SARS-CoV-2 Positive Dose 2 N=256
Any local adverse reaction, n (%)	N1=2632	N1=258	N1=2617	N1=256
Any	1678 (63.8)	154 (59.7)	1932 (73.8)	177 (69.1)
Grade 3	21 (0.8)	2 (0.8)	32 (1.2)	0
Pain at injection site, n (%)	N1=2630	N1=258	N1=2617	N1=256
Any	1630 (62.0)	145 (56.2)	1876 (71.7)	176 (68.8)
Grade 3	3 (0.1)	1 (0.4)	10 (0.4)	0
Erythema (redness), n (%)	N1=2631	N1=258	N1=2617	N1=256
Any	146 (5.5)	9 (3.5)	235 (9.0)	13 (5.1)
Grade 3	11 (0.4)	1 (0.4)	12 (0.5)	0
Swelling (hardness), n (%)	N1=2631	N1=258	N1=2617	N1=256
Any	124 (4.7)	8 (3.1)	217 (8.3)	13 (5.1)
Grade 3	10 (0.4)	0	12 (0.5)	0

Event[a]	Baseline SARS-CoV-2 Negative Dose 1 N=2633	Baseline SARS-CoV-2 Positive Dose 1 N=258	Baseline SARS-CoV-2 Negative Dose 2 N=2617	Baseline SARS-CoV-2 Positive Dose 2 N=256
Axillary/groin swelling/tenderness, n (%)	N1=2630	N1=258	N1=2617	N1=256
Any	171 (6.5)	28 (10.9)	242 (9.2)	19 (7.4)
Grade 3	0	0	1 (<0.1)	0
Any systemic adverse reaction[b], n (%)	N1=2631	N1=258	N1=2617	N1=256
Any	1405 (53.4)	156 (60.5)	1618 (61.8)	156 (60.9)
Grade 3	60 (2.3)	4 (1.6)	108 (4.1)	15 (5.9)
Grade 4	0	1 (0.4)	3 (0.1)	3 (1.2)
Fever[c], n (%)	N1=2631	N1=258	N1=2615	N1=256
Any: ≥38.0°C	221 (8.4)	34 (13.2)	433 (16.6)	53 (20.7)
Grade 1	128 (4.9)	26 (10.1)	222 (8.5)	22 (8.6)
Grade 2	66 (2.5)	6 (2.3)	152 (5.8)	17 (6.6)
Grade 3	25 (1.0)	1 (0.4)	56 (2.1)	11 (4.3)
Grade 4	2 (<0.1)	1 (0.4)	3 (0.1)	3 (1.2)
Headache, n (%)	N1=1801	N1=169	N1=1769	N1=165
Any	206 (11.4)	22 (13.0)	281 (15.9)	19 (11.5)
Grade 3	5 (0.3)	0	8 (0.5)	0
Fatigue, n (%)	N1=1801	N1=169	N1=1769	N1=165
Any	726 (40.3)	67 (39.6)	876 (49.5)	62 (37.6)
Grade 3	19 (1.1)	2 (1.2)	40 (2.3)	3 (1.8)
Myalgia, n (%)	N1=1801	N1=169	N1=1769	N1=165
Any	177 (9.8)	19 (11.2)	283 (16.0)	22 (13.3)
Grade 3	5 (0.3)	0	8 (0.5)	1 (0.6)
Arthralgia, n (%)	N1=5 (0.3)	N1=169	N1=1769	N1=165
Any	110 (6.1)	11 (6.5)	152 (8.6)	13 (7.9)
Grade 3	2 (0.1)	0	3 (0.2)	0
Nausea/vomiting, n (%)	N1=1801	N1=169	N1=1769	N1=165
Any	117 (6.5)	16 (9.5)	170 (9.6)	19 (11.5)
Grade 3	5 (0.3)	2 (1.2)	6 (0.3)	0
Chills, n (%)	N1=1801	N1=169	N1=1769	N1=165
Any	110 (6.1)	15 (8.9)	223 (12.6)	15 (9.1)
Grade 3	1 (<0.1)	0	4 (0.2)	0
Irritability/crying, n (%)	N=829	N=89	N=848	N=91
Any	443 (53.4)	55 (61.8)	461 (54.4)	51 (56.0)
Grade 3	9 (1.1)	2 (2.2)	8 (0.9)	2 (2.2)
Sleepiness, n (%)	N=829	N=89	N=848	N=91
Any	250 (30.2)	31 (34.8)	296 (34.9)	42 (46.2)
Grade 3	2 (0.2)	0	1 (0.1)	0

Event[a]	Baseline SARS-CoV-2 Negative Dose 1 N=2633	Baseline SARS-CoV-2 Positive Dose 1 N=258	Baseline SARS-CoV-2 Negative Dose 2 N=2617	Baseline SARS-CoV-2 Positive Dose 2 N=256
Loss of appetite, n (%)	N=829	N=89	N=848	N=91
Any	199 (24.0)	22 (24.7)	248 (29.2)	37 (40.7)
Grade 3	5 (0.6)	1 (1.1)	7 (0.8)	1 (1.1)

Source: P204 (2-5 years), Table 14.3.1.1.5.1, 14.3.1.1.5.2
Note: Any=Grade 1 or higher.
Abbreviations: n=number of participants with indicated AE; N=number of participants in cohort; N1=number of participants who submitted data
a. Any solicited AR without a row for Grade 4 events indicates there were no Grade 4 solicited ARs reported among mRNA-1273 participants for that event.
b. Solicited systemic ARs collected for participants 2 to <6 years of age were dependent on participant age. Participants 37 months to <6 years of age were assessed for events of fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills. Participants ≤36 months of age were assessed for the solicited systemic ARs of fever, irritability/crying, sleepiness, and loss of appetite. Fever is the only systemic AR assessed in both groups, although the temperature ranges used for toxicity grades differed slightly between the groups.
c. Protocol-defined fever grades in participants aged 37 months to <6 years were the following: grade 1 = 38°C to 38.4°C, grade 2 = 38.5°C to 38.9°C, Grade 3 = 39°C to 40°C, and grade 4 >40° C. Protocol-defined fever grades in participants 2 years to ⩽36 months were the following: grade 1 = 38° C to 38.5° C, grade 2 = 38.6° C to 39.5°C, Grade 3 = 39.6°C to 40°C, and grade 4 >40.0°C
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 3=>100 mm. 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 3=prevents daily activity. Toxicity grade for headache, fatigue, myalgia, arthralgia is defined as Grade 1=no interference with activity, Grade 3=prevents daily activity; Toxicity grade for nausea/vomiting is defined as Grade 1=no interference with activity or 1-2 episodes/24 hours; Grade 3=prevents daily activity; Toxicity grade for chills is defined as Grade 1=no interference with activity; Grade 3=prevents daily activity and requires medical intervention

Unsolicited adverse events

Table 69 below shows rates of unsolicited AEs in Part 2 that occurred within 28 days of vaccination and at rates of ≥1% in any group. Overall, the proportions of participants with unsolicited AEs were 40.0% and 37.5% in the mRNA-1273 and placebo groups, respectively. The rates of unsolicited AEs, including severe events (Grade 3 or higher), were similar across groups except for injection site erythema, which was reported in 1.3% in mRNA-1273 recipients compared to 0.2% of placebo recipients, and COVID-19, which was reported in 5.5% of placebo recipients and 3.1% of mRNA-1273 recipients. The most commonly reported unsolicited AEs among mRNA-1273 recipients and placebo recipients were upper respiratory tract infection (8.1% vs 9.2%), rhinorrhea (3.9% vs 4.2%), and cough (3.6% and 4.4%), respectively.

Table 69. Unsolicited Adverse Events Occurring in ≥1% of Any Treatment Group Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set

Unsolicited Adverse Event	mRNA-1273 25 µg N=3031 Any	Placebo N=1007 Any	mRNA-1273 25 µg N=3031 Severe	Placebo N=1007 Severe
Number of participants reporting unsolicited adverse events, n (%)	1212 (40.0)	378 (37.5)	22 (0.7)	9 (0.9)
Number of unsolicited adverse events, n (%)	2009	677	31	11

Unsolicited Adverse Event	mRNA-1273 25 µg N=3031 Any	Placebo N=1007 Any	mRNA-1273 25 µg N=3031 Severe	Placebo N=1007 Severe
Infections and infestations	707 (23.3)	245 (24.3)	2 (<0.1)	0
Upper respiratory tract infection	244 (8.1)	93 (9.2)	0	0
COVID-19	93 (3.1)	55 (5.5)	0	0
Viral upper respiratory tract infection	55 (1.8)	13 (1.3)	0	0
Ear infection	45 (1.5)	20 (2.0)	0	0
Nasopharyngitis	43 (1.4)	11 (1.1)	0	0
Otitis media	37 (1.2)	12 (1.2)	0	0
Asymptomatic COVID-19	32 (1.1)	13 (1.3)	0	0
Respiratory tract infection viral	31 (1.0)	8 (0.8)	0	0
Metabolism and nutrition disorders, n (%)	40 (1.3)	14 (1.4)	2 (<0.1)	0
Decreased appetite	39 (1.3)	14 (1.4)	2 (<0.1)	0
Psychiatric disorders, n (%)	49 (1.6)	19 (1.9)	1 (<0.1)	2 (0.2)
Irritability	49 (1.6)	16 (1.6)	1 (<0.1)	2 (0.2)
Nervous system disorders, n (%)	32 (1.1)	14 (1.4)	1 (<0.1)	0
Respiratory, thoracic and mediastinal disorders, n (%)	233 (7.7)	84 (8.3)	2 (<0.1)	0
Rhinorrhea	119 (3.9)	42 (4.2)	0	0
Cough	110 (3.6)	44 (4.4)	0	0
Nasal congestion	60 (2.0)	23 (2.3)	0	0
Gastrointestinal disorders, n (%)	133 (4.4)	47 (4.7)	1 (<0.1)	0
Vomiting	55 (1.8)	14 (1.4)	1 (<0.1)	0
Diarrhea	45 (1.5)	19 (1.9)	0	0
Skin and subcutaneous tissue disorders, n (%)	62 (2.0)	14 (1.4)	0	1 (<0.1)
General disorders and administration site conditions, n (%)	248 (8.2)	62 (6.2)	16 (0.5)	6 (0.6)
Pyrexia	95 (3.1)	36 (3.6)	11 (0.4)	4 (0.4)
Fatigue	58 (1.9)	23 (2.3)	4 (0.1)	3 (0.3)
Injection site erythema	38 (1.3)	2 (0.2)	1 (<0.1)	0
Injury, poisoning and procedural complications, n (%)	47 (1.6)	14 (1.4)	0	0

Source: Study P204 (2-5 years) Table 14.3.1.8.1.2, Table 14.3.1.17.2.1.
Abbreviations: COVID-19=coronavirus disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants with indicated AE; N=number of participants in cohort
Note: Percentages are based on the number of safety participants (N). The Safety Set of Part 2 consists of all randomized participants who received any study injection. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. MedDRA version 23.0.

Within 28 days after vaccination, lymphadenopathy-related events were reported by 0.9% of mRNA-1273 recipients and <0.1% of placebo recipients. These events included lymphadenopathy, injection-site lymphadenopathy, and vaccination-site lymphadenopathy which are plausibly related to vaccination. A similar imbalance was observed for solicited axillary (or groin) swelling/tenderness in the injected limb.

Within 28 days after vaccination, some respiratory tract-related infections were reported with greater frequency in the mRNA-1273 group than in the placebo group. Events of pneumonia were reported by 0.3% and 0% of mRNA-1273 and placebo recipients, respectively. Respiratory syncytial virus (RSV) infection was reported by 0.4% and <0.1% of mRNA-1273 and placebo recipients, respectively. There was no pattern concerning time to onset or dose number for these two events. When assessing events reported under other related Preferred Terms (PT), such as Upper Respiratory Tract Infection, there were more events reported in the placebo

group (9.2%) compared to the vaccine group (8.1%). Analyses including all respiratory tract infection-related PTs, with and without COVID-19, showed generally comparable rates between the two groups. Most events were mild to moderate in severity, and the few events which were considered serious (three hospitalizations in the mRNA-1273 group for metapneumovirus infection, adenovirus infection, and viral pneumonia, all with onset within 14 days post-vaccination, and one hospitalization for rhinovirus infection with onset 75 days post-vaccination) are further detailed in the SAE section. All events were assessed as not related to study vaccine by the investigators. FDA agrees with the investigator assessments that there is unlikely to be a causal association between the occurrence of these events and the study vaccine. Imbalances between mRNA-1273 and placebo groups in specific respiratory infections were not observed in older age cohorts, and there is not a clear biological mechanism that would explain a causal association for certain respiratory infections but not others. Overall, the frequency and clinical course for these events do not appear unusual given the age group of the young pediatric study population and the season (fall-winter) during which the study took place, and the observed imbalance could be due to chance. It is also possible that the observed imbalance could be due to an unappreciated bias associated with differences between treatment groups in risk avoidance for viral infections in general, health seeking behaviors, or clinical evaluation of suspected viral illnesses.

Within 28 days after vaccination, events of abdominal pain (including abdominal pain, abdominal pain upper, and abdominal discomfort) were reported by 0.7% (n=21) of mRNA-1273 recipients and 0.4% (n=4) of placebo recipients. All events were mild to moderate in severity. Medically-attended events of abdominal pain were reported by 4 mRNA-1273 recipients and no placebo recipients. The events assessed as related (n=2 in the mRNA-1273 group and n=1 in the placebo group) all occurred within 2 days after vaccination and may represent post-vaccination reactogenicity that are clinically related to solicited adverse reactions of nausea/vomiting and loss of appetite, that were reported in 6.8-9.8% and 23.9-30.5% of mRNA-1273 recipients, respectively, for the 7 day reporting period after each dose in the 2-5 years age cohort (Solicited Systemic AR Tables 65 and 66).

Adverse events of clinical interest
Participants are monitored in the study for AESIs based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (Appendix A).

Blinded Phase (Part 2):
In Part 2 of the study, through data cutoff (February 21, 2022) and after data cutoff, there were 8 AESIs (5 participants) in the mRNA-1273 group (0.2%) and 5 AESIs (2 participants) in the placebo group (<0.1%). Two AESIs in the vaccine group were assessed as related to vaccine by the investigator, and 5 AESIs in the vaccine group were assessed as not related to vaccine by the investigator.

Two AESIs in mRNA-1273 group assessed by PI as related:

- One event of mild (Grade 1) erythema multiforme (described as a rash on both arms) with onset 3 days after Dose 2 in a 3-year-old White, Asian male. The event resolved after 1 day with no treatment. FDA assessed this event as possibly related to study vaccine due to the short time to onset after Dose 2.
- One event of moderate (Grade 2) chest pain (not considered an AESI based on protocol definitions but listed as an AESI in the eCRF) with onset 5 days after Dose 2 in a 4-year-old White male that resolved within 30 minutes (further details and FDA assessment under SMQ *Cardiomyopathy* below).

Six AESIs in the mRNA-1273 group assessed by PI as not related

- Three events of erythema multiforme (EM) in one participant which occurred 3 days after Dose 1 (in the setting of concomitant amoxicillin), 4 weeks after Dose 2, and 6 weeks after Dose 2
- One event of food (egg) allergy
- One serious event of seizure (discussed under SMQ *Convulsions*, below)
- One event of Kawasaki Disease (KD) reported in a 2-year-old Asian male mRNA-1273 recipient (after data cutoff). The participant presented to the emergency department 76 days after Dose 2 with fever, cough, and a rash and tested positive for adenovirus and rhinovirus and negative for COVID-19. He was hospitalized 4 days later (80 days after Dose 2) with a diagnosis of KD based on laboratory results. Chest x-ray, electrocardiogram, and echocardiogram were normal. The participant was treated with IV immunoglobulin and high-dose aspirin and discharged after 3 days. The event was considered not related by the investigator and was ongoing at the time of the writing of this briefing document.

FDA agrees with the investigator assessments that the above 6 events were not related to study vaccine.

There were five AESIs in two placebo recipients. Four AESIs were reported in a 3-year-old female and included the following: Henoch-Schönlein purpura (HSP) 3 days after Dose 2 (assessed as related) that resolved within 7 days; subsequent glycosuria following exogenous steroid treatment (assessed as not related); and ageusia/anosmia with COVID-19 45 days after Dose 2 (assessed as not related). The other placebo recipient was a 2-year-old female placebo recipient with MIS-C 113 days after Dose 2, after being positive for asymptomatic SARS-CoV-2 infection 37 days prior to the onset of MIS-C symptoms (assessed as not related).

FDA agrees with the investigator assessments of these events.

Open Label Phase (Part 1):
One AESI in Part 1 included an event of epilepsy in a 3-year-old White female participant in the 50 µg group, with onset 126 days after Dose 2. FDA agrees with the investigator assessment that this event was unrelated to study vaccine.

FDA Standard MedDRA Queries (Double Blind Part 2 and Open Label Part 1)
FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following Dose 1 through the data cutoff date or unblinding (whichever was earlier). The median duration of blinded follow-up for safety after Dose 2 was 71 days in Part 2 and 231 days in Part 1. SMQs were conducted on AE PTs that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in imbalance between the two treatment groups, and which captured events considered clinically relevant by the FDA, will be discussed.

SMQ *Hypersensitivity*: In Part 2, 151 events were reported in 139 mRNA-1273 recipients (4.6%) compared to 45 events in 39 placebo recipients (3.9%). The most frequently reported events in mRNA-1273 recipients were classified under PTs of conjunctivitis, urticaria, seasonal allergy, and rash. Within 28 days after vaccination, hypersensitivity events were reported by 3.5% of mRNA-1273 recipients and 2.5% of placebo recipients. Within 48 hours after any dose, hypersensitivity events were reported by 0.4% of mRNA-1273 recipients and 0.7% of placebo

recipients. There were no serious or severe hypersensitivity events within 48 hours after any dose. One moderate (Grade 2) event of anaphylaxis (verbatim term: anaphylaxis due to Miralax) was reported in a 3-year-old female mRNA-1273 recipient that occurred 32 days after Dose 1, resolved the same day, and was considered related to study vaccine by the investigator. The participant received a second dose of mRNA-1273, with no reported AEs. In FDA's assessment, given latency of onset and alternative causative agent (Miralax), this event was not related to study vaccine. None of the events yielded by the SMQ *Hypersensitivity* were clinically concerning for severe hypersensitivity. In Part 1, 12 events were reported in 11 mRNA-1273 recipients: 1 participant (1.4%) in the 25 µg group and 10 participants (6.5%) in the 50 µg group. Events were similar in nature to those reported by Part 2 participants.

SMQ *Convulsions:* In Part 2*,* 2 events were reported in 2 mRNA-1273 recipients (<0.1%), and 1 event was reported in 1 placebo recipient (<0.1%). In mRNA-1273 recipients, one event was a Grade 2, non-serious seizure in a 3-year-old female with onset 36 days after Dose 2, and the other event was a Grade 1, serious seizure in a 4-year-old male with onset 22 days after Dose 2. In Part 1, one Grade 1 event of epilepsy was reported in a 3-year-old female participant in the 50 µg group with onset 126 days after Dose 2, and no events were reported in the 25 µg group. FDA agrees with the assessment that all the events under this SMQ were not related to study vaccine.

SMQ *Cardiomyopathy*: In Study P204, scripted safety calls were included in the study design to solicit for symptoms of myocarditis and pericarditis. This resulted in enhanced reporting frequency of associated symptoms in Study P204 compared to those reported (unsolicited) in adults in study P301 and in adolescents in study P203. In Part 2 of P204, 5 participants (0.2%) in the mRNA-1273 group and 2 participants (0.2%) in the placebo group reported PTs included in the SMQ *Cardiomyopathy*. The median time to onset was 5 days (range 1-27 days).

In Part 1, one participant (1.4%) in the 25 µg group and one participant (0.6%) in the 50 µg group reported PTs included in the SMQ *Cardiomyopathy*. All cardiac associated symptoms reported in the blinded and open-label parts of the study are summarized in the table below and include relatedness assessments by the investigator and FDA.

Table 70. Adverse Events Through Data Cutoff of February 21, 2022, Standard MedDRA Query *Cardiomyopathy*, Participants 2 Through 5 Years of Age, Study P204 Blinded Phase Part 2 and Open Label Part 1, Safety Set

Treatment Group	Age/Sex	Preferred Term	Time to Onset after Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
BP Part 2	--	--	--	--		--	--
mRNA-1273 25µg BP Part 2	4 years/ male	Dyspnea	1 day/ Dose 1	Resolved within15 minutes (occurred after vomiting); Concurrent fatigue, vomiting, fever, and loss of consciousness (less than 1 minute); All resolved within 1.5 hours	Resolved	Related	Possibly related
mRNA-1273 25µg BP Part 2	3 years/ female	Dyspnea	22 days/ Dose 1	History of seasonal allergies; Concurrent sore throat and cough (started prior to dyspnea event)	Resolved	Not related	Not related
mRNA-1273 25µg BP Part 2	2 years/ female	Mental status changes	6 days/ Dose 1	History of hypoxemic ischemic encephalopathy (no sequelae); Resolved the same day; No concerns for seizure activity per neurologist; Concurrent oropharyngeal pain and cough; No AEs reported after Dose 2	Resolved	Not related	Not related
mRNA-1273 25µg BP Part 2	3 years/ male	Chest pain	3 days/ Dose 2	Resolved within 15-20 minutes	Resolved	Related	Not related given rapid resolution without intervention
mRNA-1273 25µg BP Part 2	4 years/ male	Chest pain	5 days/ Dose 2	Left sided. Resolved within 30 minutes. Seen by cardiologist. ECG, troponin, and physical exam all within normal levels	Resolved	Related	Not related given rapid resolution without intervention and negative workup
Placebo BP Part 2	2 years/ male	Palpitations	3 days/ Dose 1	History of intermittent lip swelling from 5 days prior to enrollment; Concurrent AE of cyanosis (lip); ED	Resolved	Not related	Not related

Treatment Group	Age/Sex	Preferred Term	Time to Onset after Most Recent Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
				physician treated with prednisone and Zyrtec for an allergic reaction to an unknown source; Resolved the same day			
Placebo BP Part 2	3 years/ female	Dyspnea	27 days/ Dose 1	Concurrent bronchiolitis (started prior to dyspnea) and bilateral ear infection (started during dyspnea event)	Resolved	Not related	Not related
OL Part 1	--	--	--	--		--	--
mRNA-1273 50 µg OL Part 1	5 years/ female	Dyspnea	1 day/ Dose 2	History of asthma; Concurrent urticaria papular and abdominal pain upper; Low grade fever; Treated with asthma meds and acetaminophen	Resolved	Not related	Possibly related (hypersensitivity)
mRNA-1273 25 µg OL Part 1	4 years/ male	Chest pain	5 days/ Dose 1	Resolved the same day; Concurrent back pain; Treated with acetaminophen; 3-mile hike day before; No similar AE post-Dose 2 or booster	Resolved	Related	Possibly related

Source: FDA generated table based on narratives, listings, and dataset submitted to EUA 27073, P204 (2-5 years)
Abbreviations: AE=adverse event; BP=blinded phase; ECG=electrocardiogram; OL=open label; SAE=serious adverse event; ED=emergency department

Additional cardiac-related AEs were queried using PTs suggestive of myocarditis/ pericarditis or associated symptoms/clinical signs not included in the SMQ *Cardiomyopathy.* There were no additional events identified in the 2-5 years cohort that were not already captured in the SMQ *Cardiomyopathy*.

None of the events captured by the SMQ *Cardiomyopathy* met CDC criteria for probable or confirmed cases of acute myocarditis or acute pericarditis[64]

Serious adverse events
In Part 2, from Dose 1 through the data cutoff, SAEs were reported in 9 mRNA-1273 recipients (0.3%) and 2 placebo recipients (0.2%). No SAEs were considered related to the vaccine by the study investigator. FDA agrees with this assessment. No SAEs were reported in Part 1 for the 2-5 years age group.

Table 71.Serious Adverse Events Through Data Cutoff of February 21, 2022, Participants 2 Through 5 Years of Age, Study P204 Part 2, Safety Set

Treatment Group	Age/Sex	SAE Preferred Term	Onset in Days Since Last Dose, Last Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 25 µg	3 years/ female	Metapneumovirus infection	8 days, Dose 1	Ongoing bronchopulmonary dysplasia, asthma; previous episode of RSV bronchiolitis; hospitalized requiring oxygen	Resolved	Not related	Not related
mRNA-1273 25 µg	3 years/ female	Rhinovirus infection	75 days, Dose 2	Hospitalized for bronchiolitis	Resolved	Not related	Not related
mRNA-1273 25 µg	2 years/ male	Adenovirus infection	3 days, Dose 2	Hospitalized	Resolved	Not related	Not related
mRNA-1273 25 µg	3 years/ male	Epstein-Barr virus infection	52 days, Dose 2	Hospitalized for acute EBV, metabolic acidosis, and dehydration; Diagnosed with mild COVID-19 one month prior; Tested positive for SARS-CoV-2 day before admission; Tested positive for EBV and negative for SARS-CoV-2 during hospitalization	Resolved	Not related	Not related
mRNA-1273 25 µg	2 years/ male	Pneumonia viral Bronchial hyperreactivity Respiratory distress	13 days, Dose 1 14 days, Dose 1 14 days, Dose 1	None reported; event started as upper respiratory tract infection, left acute otitis media; hospitalized	Resolved Resolved Resolved	Not related Not related Not related	Not related Not related Not related
mRNA-1273 25 µg	2 years/ female	Urinary tract infection	38 days, Dose 2	Ongoing constipation with fecaloma/colon impaction	Resolved	Not related	Not related
mRNA-1273 25 µg	4 years/ female	Humerus fracture	53 days, Dose 2	Fell while being chased by a dog	Resolved	Not related	Not related
mRNA-1273 25 µg	2 years/ male	Bronchial hyperreactivity	96 days, Dose 2	Hospitalized for 24 hour observation	Resolved	Not related	Not related
mRNA-1273 25 µg	4 years/ male	Seizure	22 days, Dose 2	None reported; Diagnosed with possible atypical seizure	Resolved	Not related	Not related
Placebo	2 years/ female	Rhinovirus infection Asthma	83 days, Dose 2 83 days, Dose 2	Ongoing allergic rhinitis; attending daycare; family history of asthma; hospitalized on oxygen	Resolved with sequelae (mild intermittent asthma)	Not related Not related	Not related Not related

Treatment Group	Age/Sex	SAE Preferred Term	Onset in Days Since Last Dose, Last Dose	Risk Factors, Pertinent Details	Resolution	Investigator Assessment	FDA Assessment
Placebo	2 years/ male	Abdominal wall abscess	28 days, Dose 2	Had recently undergone planned incisional hernia repair, orchidopexy, and bronchoscopy; Ongoing bronchopulmonary dysplasia; Chronic inhaled corticosteroid use	Resolved	Not related	Not related

Source: FDA generated table based on narratives, Listing 16.2.7.5.1, Listing 16.2.7.5.2, and dataset submitted to EUA 27073 P204 (2-5 years)
Abbreviations: COVID-19=coronavirus disease-2019; RSV=respiratory syncytial virus; SAE=sersious adverse event

Adverse events leading to discontinuation from study vaccination or study participation
AEs leading to discontinuation from study vaccination after Dose 1 and before Dose 2 were reported by 1 mRNA-1273 recipient who also discontinued from study participation. This participant was a 4-year-old White male with no reported medical history who experienced a nonserious, mild (Grade 1) AE of urticaria (urticaria on torso and wrists) on the same day as Dose 1 of mRNA-1273, leading to discontinuation from study vaccination. Treatment included levocetirizine and ibuprofen. The event resolved 2 days later and was considered related to the study vaccine by the study investigator. The participant was discontinued from the study 5 days later. FDA agrees with the investigator's assessment that this event was related to study vaccine. There were no placebo recipients in Part 2 and no participants in Part 1 who were discontinued from study vaccination or study participation due to an AE.

4.4.3.5 Summary for Participants 2 Through 5 Years of Age

The comparison of immune response between children 2-5 years of age in Study P204 and young adults in Study P301 provided the primary evidence to support effectiveness of the vaccine. The study met the pre-specified success criteria for the two co-primary endpoints of GMC ratio and difference in SRRs. The GMC ratio (children 2-5 years to young adults) was 1.0 (95% CI 0.9, 1.2) which met the pre-specified success criterion of a LL of the 95% CI ≥0.67 and a point estimate of ≥0.8. The difference in SRRs (children 2-5 years minus young adults) was −0.4% (95% CI −2.7, 1.5) which met the pre-specified success criterion of a LL of the 95% CI >−10% and an SRR difference point estimate >−5%.

The immunogenicity data across demographic subgroups were generally consistent with those observed in the overall study population, though interpretability of subgroup-specific effectiveness results is limited by the small number of participants in certain subgroups. The majority of participants 2-5 years of age were SARS-CoV-2 negative at baseline; however, subgroup analyses demonstrated that baseline positive mRNA-1273 recipients had numerically higher GMCs (with non-overlapping CIs) at Day 57 compared to those who were baseline negative.

Descriptive analyses of VE in children 2-5 years of age further supported and provided direct evidence of vaccine effectiveness. The observed VE against COVID-19 starting 14 days after Dose 2 was 46.4% (95% CI 19.8, 63.8) when using the COVID-19 case definition used in Study P301, and 36.8% (95% CI 12.5, 54.0) when using the broader CDC case definition. Efficacy was evaluated during the time period in which the Omicron variant was the predominant circulating strain. Estimates of vaccine efficacy among participants 2-5 years appear consistent with the VE estimates observed in adults during Omicron, based on observational studies. Across demographic subgroups, vaccine efficacy was generally consistent with the results obtained based on the general study population, though interpretability of subgroup specific VE is limited by the small number of participants in certain subgroups. There were too few COVID-19 cases in participants who were SARS-CoV-2 seropositive at baseline to draw firm conclusions. There were no reports of severe COVID-19.

The most common solicited adverse reactions after any dose of mRNA-1273 were pain at the injection site (81.5%), irritability/crying (71.0%), sleepiness (49.7%), and loss of appetite (42.4%) among participants 23-36 months of age, and fatigue (61.9%) among participants 37 months through 5 years of age. Solicited local and systemic adverse reactions in the 2-5 years age group generally occurred more frequently and were more severe after Dose 2 compared to Dose 1. Most local and systemic reactions were mild to moderate in severity, with onset 1-2 days post-vaccination, and resolved within 2 days after onset. Fever was the only Grade 4

solicited adverse reaction reported among participants and was uncommon. Overall, rates of solicited adverse reactions were similar between participants with positive versus negative SARS-CoV-2 status at baseline, with the exception of fever which was reported more commonly among baseline-positive participants.

In general, unsolicited AEs reported within 28 days after vaccination were reported by a similar percentage of mRNA-1273 recipients (40.0%) compared to placebo recipients (37.5%). Within 28 days after vaccination, hypersensitivity-related events were reported by 3.5% of mRNA-1273 recipients and 2.5% of placebo recipients. None of the events were clinically concerning for anaphylaxis. Lymphadenopathy-related events were reported by 0.9% of mRNA-1273 recipients and <0.1% of placebo recipients and were plausibly related to vaccination. There was an imbalance observed in events of abdominal pain (including abdominal pain, abdominal pain upper, and abdominal discomfort), which were reported by 0.7% of mRNA-1273 recipients and 0.4% of placebo recipients. Currently available information is insufficient to determine a causal relationship with the vaccine.

In Part 2, the frequency of reported PTs included in the SMQ *Cardiomyopathy* was the same in the vaccine and placebo groups (0.2% in each group). All of the events were mild to moderate and most resolved the same day. Only one case involved a cardiac workup with ECG, troponin, and physical exam, none of which showed any abnormalities. No events of myocarditis or pericarditis were reported in Part 1 or Part 2 in the 2-5 years age cohort through the time of data cutoff. However, cases of myocarditis/pericarditis have been reported following the authorization of mRNA-1273 in adults ≥18 years of age with routine pharmacovigilance/safety surveillance by the CDC and FDA, as discussed in Section 2.3.2.

No deaths were reported in participants 2-5 years in the study. SAEs were infrequent and occurred at a similar rate among mRNA-1273 and placebo recipients (0.3% and 0.2%, respectively). Available evidence does not suggest a causal relationship between these SAEs and the vaccine.

4.4.4 Participants 6 through 23 Months of Age

Participants 6 through 23 months of age began enrollment into Study P204 Part 1 on May 20, 2021, and Part 2 on October 18, 2021. As of the February 21, 2022, data cutoff for this EUA amendment, safety data were available from a total of 2,500 children 6 through 23 months of age (1,911 in the mRNA-1273 group and 589 in the placebo group) enrolled in Part 1 and Part 2 who received at least one dose. The data cutoff was triggered when a minimum of 1,000 mRNA-1273 recipients included in Part 2 had received two doses (25 µg each, 28 days apart) and had ≥2 months of follow-up after Dose 2.

4.4.4.1 Part 1: Dose-Finding and 25 µg Dose Selection

The open-label, dose-finding phase (Part 1) of Study P204 in participants 6-23 months included a total of 150 participants who received a 25 µg dose level of mRNA-1273. Per recommendation of the internal safety team, no children were enrolled in the 50 µg study arm in the 6-23 months age cohort based on the high rate of solicited adverse reactions in the 2-5 years age cohort for this dose.

A protocol-specified assessment of immunogenicity as measured by PsVNA ID50 in participants 6-23 months of age was compared to results from a subset of participants 18-25 years from Study P301, for whom clinical efficacy had been demonstrated. Results of the analysis for participants 6-23 months (n=98) demonstrated a GMT ratio of 1.4 (95% CI 1.1, 1.7) and a

difference in SRRs of 1.0% (95% CI −2.8%, 3.0%). Based on these results, along with the tolerable safety profile of the 25-µg dose, the DSMB recommended selection of the 25-µg dose level for advancement into Part 2 for the 6-23 months age cohort.

Analyses of solicited adverse reactions after Dose 1 and Dose 2 were reviewed, and the tolerability profile of the 25-µg dose was considered acceptable for advancement into Part 2 with a larger cohort of 6-23 months of age participants. The most frequently reported solicited local AR after any dose was injection site pain (49.3%), and the most frequently reported solicited systemic AR after any dose was irritability/crying (77.3%). The majority of solicited ARs were Grade 1 or 2 with no Grade 4 solicited ARs reported in Part 1. Most solicited ARs occurred within 2 days after each dose and persisted for a median of 2-3 days.

In Part 1, 53.3% of participants reported unsolicited AEs up to 28 days after any dose. Overall, unsolicited AEs were either typical for the 6-23 months of age population (background events unrelated to vaccination) or generally consistent with the known reactogenicity profile of mRNA-1273 (adverse reactions). In the mRNA-1273 group, the rates of unsolicited AEs within 28 days in Part 1 were similar to those in Part 2 (49.3%) and will not be discussed in detail. SAEs and AEs of clinical interest from Part 1 are presented in the Part 2 safety section, below. The median duration of follow-up for Part 1 participants from Dose 2 through the data cutoff date of February 21, 2022, was 233.5 days.

4.4.4.2 Part 2: Blinded, Placebo-Controlled Phase

Participant disposition and inclusion in analysis populations
Disposition tables for the blinded, placebo-controlled phase of the study (Part 2) are presented below in Table 72 (immunogenicity populations), Table 73 (efficacy populations) and Table 74 (safety population).

For immunobridging, a random sample of 274 participants 6-23 months of age from Study P204 Part 2 was selected for inclusion in the Immunogenicity Subset and compared with 340 young adult participants 18-25 years who received mRNA-1273 (100 µg) in Study P301. The PP Immunogenicity Subset, used for the primary immunogenicity analyses, consisted of 230 participants 6-23 months of age and 295 young adult participants. Among participants ages 6-23 months, the majority of exclusions from the PP Immunogenicity Subset were due to lack of immunogenicity data at Day 57 (9.1%) followed by positive SARS-CoV-2 status at baseline (5.5%). Among young adults, the most common reasons for exclusion from the PP Immunogenicity Subset were positive SARS-CoV-2 status at baseline (5.0%) and not receiving Dose 2 per schedule (4.7%).

Table 72. Disposition of Participants 6 Through 23 Months of Age, Study P204 Part 2, Immunogenicity Populations

Disposition	6-23 Months RNA-1273 25 µg	18-25 Years RNA-1273 100 µg
Immunogenicity Subset[a]	N=274	N=340
PP Immunogenicity Subset[b]	N=230 (83.9)	N=295 (86.8)
Excluded from PP Immunogenicity Subset[c], n (%)	44 (16.1)	45 (13.2)
Reason for exclusion, n (%)	--	--
Positive baseline SARS-CoV-2 status[d]	15 (5.5)	17 (5.0)
Did not receive Dose 2 per schedule	0	16 (4.7)
Received Dose 2 out of window	2 (0.7)	2 (0.6)
No immunogenicity data at Day 57	25 (9.1)	9 (2.6)
Other major protocol deviations	0	0
HIV infection	0	1 (0.3)
Age outside randomized age group	2 (0.7)	0

Source: Study P204 (6-23 months) Table 14.1.2.3.2
a. The Immunogenicity Subset consists of participants in the Full Analysis Set (FAS) who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
b. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.
c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.
d. Adapted from EUA 27073. Am 399, dated 4May2022; response to information request: Five participants 18 to 25 years of age in P301 who had positive baseline SARS-CoV-2 Status and did not receive Dose 2 were counted in the category of positive baseline SARS-CoV-2 status.

In the populations used to assess the efficacy endpoints, dispositions were overall similar between the mRNA-1273 and placebo groups. There was a higher percentage of participants in the mRNA-1273 group compared to the placebo group excluded from the PP Set for Efficacy due to receiving Dose 2 outside the allowable window (2.1% compared to 0.8%, respectively) and a higher percentage of participants in the placebo group compared to the mRNA-1273 group excluded from the PP Set for Efficacy due to randomized but not dosed (0.5% compared to 0.1%, respectively) and discontinued study treatment or participation without receiving Dose 2 (0.8% compared to 0.2%, respectively).

Table 73. Disposition of Participants 6 Through 23 Months of Age, Study P204 Part 2, Efficacy Populations

Disposition	mRNA-1273 25 µg	Placebo
Randomized	N=1762	N=593
Full Analysis Set[a]	N=1760 (99.9)	N=590 (99.5)
mITT Set[b]	N=1574 (89.3)	N=531 (89.5)
mITT1 Set[c]	N=1574 (89.3)	N=530 (89.4)

Disposition	mRNA-1273 25 µg	Placebo
PP Set for Efficacy[d]	N=1511 (85.8)	N=513 (86.5)
Excluded from PP Set for Efficacy, n (%)	251 (14.2)	80 (13.5)
Reason for exclusion, n (%)	--	--
Randomized but not dosed	2 (0.1)	3 (0.5)
Positive or missing baseline SARS-CoV-2 status	186 (10.6)	59 (9.9)
Discontinued study treatment or participation without receiving Dose 2	4 (0.2)	5 (0.8)
Did not receive Dose 2 and passed window of +14 days	21 (1.2)	7 (1.2)
Received incorrect vaccination	0	1 (0.2)
Received Dose 2 out of window	37 (2.1)	5 (0.8)
Had other major protocol deviations	1 (<0.1)	0

Source: Study P204 (6-23 months) Tables 14.1.2.1.2.1, 14.1.2.3.2, 14.1.2.5
a. The FAS consists of all randomized participants who received at least one dose of IP. Numbers are based on planned treatment group.
b. The mITT Set consists of all participants in the FAS who had 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) before the first dose of IP, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.
c. The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (i.e., at least 1 dose received that is not as randomized or planned). Numbers are based on planned treatment group.
Percentages are based on the number of participants randomized.
d. The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group. Percentages are based on the number of participants randomized.

Table 74 provides the disposition of participants from the study who contributed to the assessment of safety. Most study participants from both the mRNA-1273 group (90.8%) and the placebo group (89.2%) completed both doses of study vaccine. The rate of discontinuation from study vaccination was low overall (<1.0%) with 0.8% of participants in the placebo group discontinuing as compared to 0.2% of the mRNA-1273 group. There was a slightly higher rate of discontinuation from study participation in the placebo group (2.5%) as compared to the mRNA-1273 group (1.1%). The most common reason to discontinue study participation in both groups was withdrawal of consent (1.7% in the placebo group and 0.5% in the mRNA-1273 group). One participant (0.2%) in the placebo group discontinued from study vaccination and study participation due to an AE of COVID-19 infection, and one participant in the mRNA-1273 group discontinued from study vaccination and study participation due to an AE of urticaria (discussed on page 135, above).

Table 74. Disposition of Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Populations

Disposition	mRNA-1273 25 µg	Placebo
Randomized	N=1762	N=593
Completed one dose, n (%)	1760 (99.9)	590 (99.5)
Completed two doses, n (%)	1600 (90.8)	529 (89.2)
Discontinued from study vaccination[a], n (%)	4 (0.2)	5 (0.8)
Reason for discontinuation, n (%)	--	--
Adverse event	0	1 (0.2)
Withdrawal of consent	1 (<0.1)	3 (0.5)
Participant entered open-label or crossover phase[d]	1 (<0.1)	0
Lost to follow-up	0	0
Other	1 (<0.1)	0
Missing	1 (<0.1)	1 (0.2)

Disposition	mRNA-1273 25 µg	Placebo
Discontinued from study participation, n (%)	19 (1.1)	15 (2.5)
Reason for discontinuation, n (%)	--	--
Adverse event [e]	1 (<0.1)	1 (0.2)
Withdrawal of consent	8 (0.5)	10 (1.7)
Lost to follow-up	5 (0.3)	1 (0.2)
Protocol deviation	0	0
Physician decision	1 (<0.1)	0
Other	2 (0.1)	2 (0.3)
Missing	2 (0.1)	1 (0.2)
Safety Set[b]	N=1761	N=589
Solicited Safety Set[c]	N=1758	N=585
First Injection Solicited Safety Set, n (%)	1746 (99.1)	582 (98.8)
Second Injection Solicited Safety Set, n (%)	1596 (90.6)	526 (89.3)
Number of participants unblinded, n (%)	1 (<0.1)	1 (0.2)
Received first injection in open-label phase	0	0

Source: Study P204 (6-23 months) Table 14.1.1.1.2, Table 14.1.2.1.2.1, Listing 16.2.7.7.2, and Listing 16.2.7.8.2
Percentages based on participants randomized
a. Study Vaccine Discontinuation is defined as a subject who received the first injection but didn't receive the second injection.
b. The Safety Set consists of all randomized participants who received at least one dose.
c. The Solicited Safety Set consists of all participants who were randomized and received at least one dose and contributed any solicited AR data (i.e., had at least 1 post-baseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.
d. One mRNA-1273 recipient was unblinded due to the SAE of febrile seizure (discussed in Section 4.4.3.4 below) and remained in the study in the open-label phase.
e. The one mRNA-1273 recipient shown as discontinued from study participation was also discontinued from study vaccine, but the this information was missing at the time of data cutoff. His discontinuation from study participation was entered in electronic data capture on March 1, 2022, after data cutoff date of February 21, 2022 (discussed in Section 4.4.3.4 below).

Table 75. Duration of Follow-Up After Dose 2 Through Data Cutoff of February 21, 2022, Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Set

Duration of Follow-Up	mRNA-1273 25 µg N=1761	Placebo N=589	Total N=2350
Blinded follow-up	--	--	--
≥28 days since Dose 2, n (%)	1470 (83.5)	482 (81.8)	1952 (83.1)
≥56 days since Dose 2, n (%)	1138 (64.6)	368 (62.5)	1506 (64.1)
Median follow-up from Dose 2, days (min, max)	68 (0, 99)	68 (0, 99)	68 (0, 99)

Source: P204 (6-23 months) Tables 14.1.5.2

Demographic and baseline characteristics

The PP Immunogenicity Subset, which contributed to the co-primary endpoints for the study, consisted of 230 vaccinated participants 6-23 months of age from Part 2 and was compared to 295 vaccinated young adult participants 18-25 years of age from Study P301 (Table 76). Compared to the young adult population, the 6-23 months old population included a lower percentage of Asian participants (5.2% compared to 10.2% in the young adult population) and Black participants (5.2% compared to 9.8%) but a higher percentage of multiracial participants (10.4% compared to 4.7%). Similar to the groups of participants ages 2-5 years and 6-11 years, a lower percentage of participants self-identified as Hispanic in the 6-23 months group (17.0%) compared to the young adult group (26.4%). Those participants 6-23 months of age also had a lower percentage of participants who were obese at baseline (BMI >95th percentile) than young adults (BMI >30 kg/m^2), reported in 18.3% of 6-23 months of age participants compared to 23.1% of young adult participants.

Table 76. Demographics and Other Baseline Characteristics, Participants 6 Through 23 Months of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

Characteristic	6-23 Months mRNA-1273 25 µg N=230	18-25 Years mRNA-1273 100 µg N=295
Sex, n (%)	--	--
Female	120 (52.2)	153 (51.9)
Male	110 (47.8)	142 (48.1)
Age	--	--
≥6 months and <1 year, n (%)	42 (18.3)	--
≥1 year and <2 years, n (%)	188 (81.7)	--
Race, n (%)	--	--
American Indian or Alaska Native	1 (0.4)	3 (1.0)
Asian	12 (5.2)	30 (10.2)
Black	12 (5.2)	29 (9.8)
Native Hawaiian or other Pacific Islander	0	2 (0.7)
White	173 (75.2)	206 (69.8)
Other	8 (3.5)	8 (2.7)
Multiracial	24 (10.4)	14 (4.7)
Not reported	0	3 (1.0)
Unknown	0	0
Ethnicity, n (%)	--	--
Hispanic or Latino	39 (17.0)	78 (26.4)
Not Hispanic or Latino	189 (82.2)	215 (72.9)
Not reported	2 (0.9)	0
Unknown	0	2 (0.7)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	143 (62.2)	145 (49.2)
Communities of Color	87 (37.8)	150 (50.8)
Country, n (%)	--	--
US	230 (100)	295 (100)
Canada	0	0
Obesity Status[b], n (%)	--	--
Obese	42 (18.3)	68 (23.1)
Non-obese	188 (81.7)	226 (76.6)
Missing	0	1 (0.3)

Source: Study P204 (6-23 months) Table 14.1.3.3.2
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. Obesity is defined as BMI >95th percentile of the WHO growth reference data for P204 and BMI >30 kg/m2 for P301

In the Safety Set, the demographics characteristics were similar between the mRNA-1273 and placebo groups (Table 77). The demographic characteristics of the PP Set for Efficacy in participants 6-23 months of age (data not shown) that included 1,511 vaccine recipients and 513 placebo group were similar to the baseline characteristics of the Safety Set.

Table 77. Demographic and Baseline Characteristics, Participants 6 Through 23 Months, Study P204 Part 2, Safety Set

Characteristic	mRNA-1273 25 µg N=1761	Placebo N=589
Sex, n (%)	--	--
Female	851 (48.3)	299 (50.8)
Male	910 (51.7)	290 (49.2)

Characteristic	mRNA-1273 25 µg N=1761	Placebo N=589
Age	--	--
≥6 months and <1 year, n (%)	375 (21.3)	124 (21.1)
≥1 year and <2 years, n (%)	1373 (78.0)	462 (78.4)
≥2 years[a], n (%)	13 (0.7)	3 (0.5)
Mean (SD), months	15.8 (5.01)	15.9 (4.86)
Median, months	16.0	17.0
Race, n (%)	--	--
White	1390 (78.9)	466 (79.1)
Black	57 (3.2)	16 (2.7)
Asian	79 (4.5)	35 (5.9)
American Indian or Alaska Native	4 (0.2)	0
Native Hawaiian or other Pacific Islander	0	0
Multiracial	186 (10.6)	64 (10.9)
Other	31 (1.8)	5 (0.8)
Not reported	9 (0.5)	2 (0.3)
Unknown	5 (0.3)	1 (0.2)
Ethnicity, n (%)	--	--
Hispanic or Latino	227 (12.9)	84 (14.3)
Not Hispanic or Latino	1517 (86.1)	498 (84.6)
Not reported	15 (0.9)	6 (1.0)
Unknown	2 (0.1)	1 (0.2)
Race and ethnicity group[b], n (%)	--	--
White non-Hispanic	1221 (69.3)	393 (66.7)
Communities of color	538 (30.6)	194 (32.9)
Missing	2 (0.1)	2 (0.3)
Country	--	--
US	1657 (94.1)	555 (94.2)
Canada	104 (5.9)	34 (5.8)
Obesity status[c]	--	--
Obese	381 (21.6)	127 (21.6)
Non-obese	1378 (78.3)	460 (78.1)
Missing	2 (0.1)	2 (0.3)
Baseline SARS-CoV-2 status[d], n (%)	--	--
Positive	106 (6.0)	38 (6.5)
Negative	1575 (89.4)	530 (90.0)
Missing	80 (4.5)	21 (3.6)

Source: Study P204 (6-23 months) Table 14.1.3.2 (dated 9June2022)
Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.
a. Some participants ≥ 2 years were included in the 6 months to <2 years subgroup, likely because of coincident enrollment of both age groups, entry errors at the time of randomization and other limitations of the IRT system.
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. Obesity is defined as BMI >95th percentile of the WHO growth reference data.
d. Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result on Day 1. Negative is defined as a negative RT-PCR test and negative Elecsys result on Day 1.

Comorbidities at baseline

Participants with stable chronic medical conditions were included in the study. Comorbidities which may lead to increased risk of severe COVID-19 include obesity, chronic lung disease (including asthma), clinically significant cardiac disorders, diabetes mellitus, and HIV infection. In Part 2, 23.0% of mRNA-1273 recipients and 22.1% of placebo recipients 6-23 months of age

had at least one of the comorbidities listed above. Obesity was the most common baseline comorbidity, reported by 21.6% of both mRNA-1273 recipients and placebo recipients.

Table 78. Baseline comorbidities, Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Set

Comorbidity	mRNA-1273 25 µg N=1761	Placebo N=589
Any of the following comorbidities, n (%)	405 (23.0)	130 (22.1)
Obesity[a]	381 (21.6)	127 (21.6)
Chronic lung disease (including asthma)[b]	27 (1.5)	2 (0.3)
Asthma[c]	22 (1.2)	2 (0.3)
Clinically significant cardiac disorders[d]	6 (0.3)	1 (0.2)
Diabetes mellitus	0	0
HIV	0	0

Source: P204 (6-23 months) Table 14.1.3.2, 14.1.4.1.2.1.2, 14.1.4.1.2.2.2, 14.1.4.1.2.3.2, 14.1.4.1.2.4.2, 14.1.4.1.2.5.2
a. BMI ≥ 95th percentile for age and gender (WHO definition)
b. Includes sleep apnea, wheezing, bronchospasm, bronchopulmonary dysplasia, pulmonary fibrosis, asthma, and cystic fibrosis
c. Includes bronchial hyperreactivity
d. Includes Aortic dilatation, Aortic dissection, Arterial switch operation, Atrioventricular block first degree, Bicuspid aortic valve, Cardiac ablation, Cardiac operation, Coarctation of the aorta, Double outlet right ventricle, Extrasystoles, Fallots tetralogy, Heart block congenital, Heart disease congenital, Hypertrophic cardiomyopathy, Hypoplastic left heart syndrome, Palpitations, Patent ductus arteriosus, Pulmonary valve disease, Pulmonary valve stenosis, Supraventricular tachycardia, Systemic-pulmonary artery shunt, Transposition of the great vessels, Ventricular extrasystoles, Ventricular septal defect, Ventricular septal defect repair, and Wolff-Parkinson-White syndrome

4.4.4.3 Vaccine Effectiveness

Primary immunogenicity endpoint

Vaccine effectiveness in participants ages 6-23 months was inferred through immunobridging to the young adult data in Study P301 using the co-primary endpoints of GMC ratio and difference in SRRs at 28 days post-Dose 2 (Day 57). Results for the co-primary endpoint of GMC ratio (6-23 months to 18-25 years) are displayed below in Table 79. GMCs were based on neutralizing antibody concentrations measured by (b) (4) PsVNA assay one month after Dose 2 (Day 57) in participants in both groups (6-23 months to 18-25 years) in the PP Immunogenicity Subset. The GMC ratio was 1.3 (95% CI 1.1, 1.5) which met the pre-specified success criterion of a lower limit (LL) of the 95% CI ≥0.67 and a point estimate of GMC ratio ≥0.8.

Table 79. Geometric Mean Antibody Concentration as Measured by Pseudovirus nAb Assay at Day 57, Participants 6 Through 23 Months of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

6-23 Months GMC (95% CI) N1=230	18-25 Years GMC (95% CI) N1=291	GMC Ratio[a,b] (6-23 Months/18-25 Years) (95% CI)	Met Success Criterion[b]
1780.7(1606.4, 1973.8)	1390.8 (1269.1, 1524.2)	1.3 (1.1, 1.5)	Yes

Source: Study P204 (6-23 months) Tables 14.2.1.1.3.1.3
LLOQ: 10
N1 = Number of participants with non-missing data at baseline and the corresponding timepoint.
Based on pseudovirus nAb assay by (b) (4). Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
GMC is estimated by geometric least square (LS) means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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. The noninferiority of GM value will be considered demonstrated if the lower bound of the 95% CI of the GMR is ≥ 0.67 based on the noninferiority margin of 1.5 and the GMR point estimate ≥ 0.8 (minimum threshold).

Results for the co-primary endpoint of difference in SRRs between participants 6-23 months and young adults are displayed below in Table 80. The difference in SRRs was 0.7% (95% CI −1.0, 2.5) which met the pre-specified success criterion of a LL of the 95% CI greater than −10% and a point estimate greater than −5%. All participants in the 6-23 months age group met the seroresponse definition.

Table 80. Seroresponse Rates as Measured by Pseudovirus nAb Assay at Day 57, Participants 6 Through 23 Months of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subset

6-23 Months Seroresponse[a] n (%) (95% CI)[b] N1=230	18-25 Years Seroresponse[a] n (%) (95% CI)[b] N1=291	Difference in Seroresponse Rate % (6-23 Months−18-25 Years) (95% CI)[c]	Met Success Criterion[d]
230 (100) (98.4, 100)	289 (99.3) (97.5, 99.9)	0.7 (−1.0, 2.5)	Yes

Source: Study P204 (6-23 months) Table 14.2.3.1.1.3, 14.2.1.2.3.1.3
LLOQ: 10
Based on pseudovirus nAb assay by (b) (4).
N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint.
a. 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 N1.
b. 95% CI is calculated using the Clopper-Pearson method.
c. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
d. The noninferiority of difference in seroresponse rate will be considered demonstrated if the lower bound of the 95% CI of the seroresponse rate difference is ≥ -10% and the point estimate of seroresponse rate difference ≥ -5% (minimum threshold).

Subgroup analyses of primary immunogenicity endpoint

The GMC ratio and difference in SRRs across demographic subgroups were consistent with the results obtained based on the general study population, though some subgroup analyses were limited by small sample size. The majority of participants in both comparator groups included in the PP Immunogenicity Subset were SARS-CoV-2 negative at baseline, however subgroup analyses based on status at baseline demonstrated numerically higher GMCs (with non-overlapping CIs) at Day 57 in baseline positive participants compared to baseline negative participants.

Table 81. Subgroup Analyses of GMC Ratio and Difference in Seroresponse Rate as Measured by Pseudovirus nAb Assay at Day 57, Participants 6 Through 23 Months of Age, Study P204 Part 2, and 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subsets

Characteristic	6-23 Months N=230 GMC (95% CI)	18-25 Years N=295 GMC (95% CI)	GMC Ratio[a] (95% CI)	6-23 Months N=230 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponse Rate, % (95% CI)[d]
Sex	--	--	--	--	--	--
Male	n=110 1810.2 (1561.0, 2099.2)	n=141 1407.3 (1234.7, 1604.0)	1.3 (1.1, 1.6)	n=110 110 (100) (96.7, 100.0)	n=141 140 (99.3) (96.1, >99.9)	0.7 (-2.7, 3.9)
Female	n=120 1754.0 (1518.0, 2026.6)	n=150 1375.4 (1208.7, 1565.1)	1.3 (1.1, 1.5)	n=120 120 (100) (97.0, 100.0)	n=150 149 (99.3) (96.3, >99.9)	0.7 (-2.5, 3.7)
Race	--	--	--	--	--	--
Black or African American	n=12 3156.6 (1956.4, 5092.9)	n=29 1706.7 (1254.6, 2321.6)	1.9 (1.0, 3.3)	n=12 12 (100) (73.5, 100.0)	n=29 29 (100) (88.1, 100.0)	NE (NE, NE)
White	n=173 1735.9 (1550.1, 1944.0)	n=203 1378.0 (1241.3, 1529.8)	1.3 (1.0, 1.5)	n=173 173 (100) (97.9, 100.0)	n=203 202 (99.5) (97.3, >99.9)	0.5 (-1.7, 2.7)
Other	n=45 1685.8 (1293.6, 2196.8)	n=59 1298.2 (1030.2, 1635.9)	1.3 (0.9, 1.8)	n=45 45 (100) (92.1, 100.0)	n=59 58 (98.3) (90.9, >99.9)	1.7 (-6.3, 9.1)
Ethnicity	--	--	--	--	--	--
Hispanic or Latino	n=39 1617.3 (1291.2, 2025.7)	n=75 1586.2 (1348.4, 1865.8)	1.0 (0.8, 1.3)	n=39 39 (100) (91.0, 100.0)	n=75 75 (100) (95.2, 100.0)	NE (NE, NE)
Not Hispanic or Latino or Missing	n=191 1816.0 (1617.0, 2039.4)	n=216 1328.7 (1191.4, 1481.9)	1.4 (1.2, 1.6)	n=191 191 (100) (98.1, 100.0)	n=216 214 (99.1) (96.7, 99.9)	0.9 (-1.1, 3.3)
Race and ethnicity group	--	--	--	--	--	--
White non-Hispanic	n=143 1758.6 (1551.3, 1993.6)	n=144 1292.4 (1140.6, 1464.5)	1.361 (1.1, 1.6)	n=143 143 (100) (97.5, 100.0)	n=144 143 (99.3) (96.2, >99.9)	0.7 (-1.9, 3.8)
Communities of Color	n=87 1817.5 (1524.2, 2167.2)	n=147 1494.4 (1305.1, 1711.0)	1.216 (1.0, 1.5)	n=87 87 (100) (95.8, 100.0)	n=147 146 (99.3) (96.3, >99.9)	0.7 (-3.6, 3.8)

Characteristic	6-23 Months N=230 GMC (95% CI)	18-25 Years N=295 GMC (95% CI)	GMC Ratio[a] (95% CI)	6-23 Months N=230 Seroresponse[b], n (%) (95% CI)[c]	18-25 Years N=295 Seroresponse[b], n (%) (95% CI)[c]	Difference in Seroresponse Rate, % (95% CI)[d]
Obesity Status	--	--	--	--	--	--
Obese[e]	n=42 1541.6 (1079.7, 2201.2)	n=65 1655.4 (1243.2, 2204.1)	0.9 (0.6, 1.5)	n=42 42 (100) (91.6, 100.0)	n=65 63 (96.9) (89.3, 99.6)	3.1 (-5.5, 10.6)
Non-obese	n=188 1838.9 (1671.6, 2023.0)	n=225 1326.3 (1215.6, 1447.2)	1.4 (1.2, 1.6)	N=188 188 (100) (98.1, 100.0)	n=225 225 (100) (98.4, 100.0)	NE (NE, NE)
Baseline SARS-CoV-2 status	--	--	--	--	--	--
Negative[f,h]	n=234 1760.8 (1585.7, 1955.2)	n=296 1358.7 (1237.9, 1491.3)	1.296 (1.1, 1.5)	n=234 234 (100) (98.4, 100.0)	n=296 293 (99.0) (97.1, 99.8)	1.0 (-0.6, 2.9)
Positive[f,g]	n=12 6733.8 (3222.5, 14070.9)	n=15 3850.1 (2019.1, 7341.2)	1.749 (0.6, 5.1)	n=12 12 (100) (73.5, 100.0)	n=15 14 (93.3) (68.1, 99.8)	6.7 (-19.1, 30.4)

Source: Study P204 (6-23 months) Table 14.2.1.1.3.3.3, 14.2.1.1.3.8.3, 14.2.1.1.3.2.3, 14.2.1.2.3.3.3, 14.2.1.2.3.8.3, 14.2.1.2.3.2.3
LLOQ: 10
NE = not evaluable
n = Number of subjects in subgroup with non-missing data at baseline and the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
GMC is estimated by geometric least square (LS) means
a. The log-transformed antibody levels are analyzed using an analysis of covariance (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.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
e. Obesity is defined as BMI >= 95th percentile of the WHO growth reference data for P204 and BMI >=30 kg/m2 for P301
f. Results by baseline SARS-CoV-2 status were based on the Immunogenicity Subset which included for 6-23 months N= 274 and for 18-25 years N=340. Total Ns include participants for whom baseline SARS-CoV-2 status are missing. The Immunogenicity Subset consists of participants in the Full Analysis Set who have baseline (Day 1) SARS-CoV-2 status available and have baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
g. 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.
h. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Exploratory immunogenicity analyses against variants
Immunogenicity against variants of concern based on neutralizing antibodies have not been assessed for this age cohort.

Efficacy evaluation
Vaccine efficacy (VE) was descriptively analyzed as a secondary endpoint in the study, with the data cutoff date of February 21, 2022. The median duration of follow-up after Dose 2 was 68 days. The study evaluated the first occurrence of symptomatic COVID-19, in participants without evidence of previous SARS-CoV-2 at baseline, using two different case definitions—the CDC case definition and the P301 COVID-19 definition. Using the CDC case definition, there were 51 cases among 1,511 mRNA-1273 recipients and 34 cases among 513 placebo recipients, for an estimated VE of 50.6% (95% CI 21.4, 68.6). Using the P301 definition, there were 37 cases in the mRNA-1273 group and 18 cases in the placebo group, for an estimated VE of 31.5% (95% CI -27.7, 62.0).

Table 82. COVID-19 Incidence Starting 14 Days after Dose 2, Participants 6 Through 23 Months of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Disease/Infection	mRNA-1273 25 µg N=1511 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=513 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
COVID-19 based on CDC definition[d]	51 (3.4) 368.9 138.2 (102.9, 181.8)	34 (6.6) 121.5 279.8 (193.8, 391.0)	50.6% (21.4, 68.6)
COVID-19 based on P301 definition[e]	37 (2.4) 370.1 100.0 (70.4, 137.8)	18 (3.5) 123.3 146.0 (86.6, 230.8)	31.5% (-27.7, 62.0)

Sources: P204 (6 to 23 months) Table 14.2.7.1.1.2.1, 14.2.8.1.1.2.1
N = Included 15 individuals aged 2 to 4 years randomized in the 6 through 23 months of age group stratum (12 in the Moderna COVID-19 Vaccine group and 3 in the placebo group), and none of them had a COVID-19 case starting 14 days after Dose 2.
a. Person-years is defined as the total years from randomization date to the first date of COVID-19 (P301 primary definition or CDC definition, as applicable), 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
d. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.
e. COVID-19 (P301 primary definition) is at least 2 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF), 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; AND at least 1 positive RT-PCR test for SARS-CoV-2.

The date of first enrollment of the blinded phase of the study was October 18, 2021, and the data cutoff was February 21, 2022. Thus, the evaluation of efficacy (starting 14 days after Dose 2) coincided with the emergence and rapid surge of the Omicron variant in the US. Among the 85 CDC-defined cases of COVID-19 in the PP Set for Efficacy, there were 44 participants (28 in the mRNA-1273 group and 16 in the placebo group) with SARS-CoV-2 sequencing data available. All 44 cases were sequenced to be the Omicron variant from BA.1 and BA.1.1 lineages (cases occurring December 2021 through February 2022). Vaccine efficacy against symptomatic COVID-19 observed in this study appears consistent with the vaccine efficacy observed among adults during the Omicron surge, based on observational studies in the US.[65]

For additional discussion of clinical efficacy below, including subgroup analyses, cumulative incidence, and efficacy by time period, the broader CDC definition of COVID-19 will be used to maximize the number of cases and the precision of the estimate.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of vaccine efficacy against COVID-19, per the CDC case definition, starting 14 days after Dose 2 are displayed below in Table 83. In general, VE estimates by subgroup were similar to that obtained for the overall study population. Notable exceptions are the lower VE estimates for Black or African American participants (13.8%, with a case split of 6 cases in the mRNA-1273 group and 2 cases in the placebo group) and for obese participants (-5.6%, with a case split of 13 cases in the mRNA-1273 group and 4 cases in the placebo group), although the small number of participants in these subgroups resulted in VE estimates with wide 95% CIs, thus limiting the interpretation of these results.

Table 83. Subgroup Analysis, Participants 6 Through 23 Months of Age With COVID-19 (CDC Case Definition) Starting 14 Days After Dose 2, Study P204 Part 2, PP Set for Efficacy

Characteristic	mRNA-1273 25 µg Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Placebo Cases/N (%) Incidence Rate per 1,000 Person-Years[a] (95% CI)	Vaccine Efficacy[b] (95% CI)
Sex	--	--	--
Male	22/780 (2.8) 115.8 (72.5, 175.3)	15/256 (5.9) 244.959 (137.102, 404.022)	52.7% (2.1, 76.6)
Female	29/731 (4.0) 162.1 (108.6, 232.8)	19/257 (7.4) 315.2 (189.8, 492.3)	48.6% (2.9, 72.1)
Race	--	--	--
Black or African American	6/49 (12.2) 470.4 (172.6, 1023.8)	2/13 (15.4) 545.6 (66.1, 1970.7)	13.8% (-773.5, 84.6)
White	42/1189 (3.5) 146.0 (105.2, 197.3)	28/408 (6.9) 291.9 (194.0, 421.9)	50.0% (16.2, 69.7)
Other	3/273 (1.1) 43.8 (9.0, 128.1)	4/92 (4.3) 182.4 (49.7, 467.1)	76.0% (-42.0, 96.5)
Ethnicity	--	--	--
Hispanic or Latino	9/188 (4.8) 186.3 (85.2, 353.7)	6/70 (8.6) 339.0 (124.4, 737.9)	45.0% (-87.7, 81.3)
Not Hispanic or Latino	42/1323 (3.2) 131.0 (94.4, 177.1)	28/443 (6.3) 269.7 (179.2, 389.8)	51.4% (18.6, 70.6)
Race and ethnicity group	--	--	--
White non-Hispanic	34/1051 (3.2) 134.7 (93.3, 188.3)	24/348 (6.9) 298.4 (191.2, 444.1)	54.9% (20.4, 74.0)
Communities of Color	17/458 (3.7) 146.4 (85.3, 234.4)	10/164 (6.1) 245.4 (117.7, 451.3)	40.3% (-45.8, 74.2)
Obesity status	--	--	--
Obese	13/330 (3.9) 160.5 (85.4, 274.4)	4/118 (3.4) 151.9 (41.4, 388.9)	-5.6% (-344.8, 67.4)
Non-obese	38/1179 (3.2) 132.2 (93.6, 181.5)	30/394 (7.6) 316.2 (213.3, 451.4)	58.2% (30.1, 74.8)

Source: P204 (6-23 months) 14.2.8.1.1.3.1
NE=not evaluable
Obesity is defined as BMI >= 95th percentile of the WHO growth reference data.
a. 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.
b. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

There were too few COVID-19 cases among participants with evidence of prior SARS-CoV-2 infection at baseline to reliably estimate vaccine efficacy in this subgroup. Starting 14 days after Dose 2, among the 88 participants in the Full Analysis Set who developed COVID-19 per CDC definition, no participants in the mRNA-1273 group and 1 participant in the placebo group had evidence of prior SARS-CoV-2 infection at baseline. The remaining 85 participants (51 in the mRNA-1273 group compared to 34 in the placebo group) had no evidence of prior SARS-CoV-2 infection at baseline.

Vaccine efficacy: including participants with prior SARS-CoV-2 infection
The VE estimate using the CDC case definition of COVID-19 was similar to the protocol-specified efficacy analysis when assessed in a population of participants both with and without evidence of prior SARS-CoV-2 infection (or unknown) at baseline (FAS), with a VE estimate of 52.1% (95% CI 24.3, 69.3) starting 14 days after Dose 2.

SARS-CoV-2 infection
Efficacy was also evaluated against SARS-CoV-2 infection regardless of symptoms (including both COVID-19 cases and cases of asymptomatic infection), as well as against asymptomatic SARS-CoV-2 infection. Results for these analyses are shown below in Table 84. Definition for asymptomatic infection and the collection time points for RT-PCR for SARS-CoV-2 and N-serology are the same as those in the 2-5 years cohort (Section 4.4.3.3 SARS-CoV-2 infection). As RT-PCR for SARS-CoV-2 and N-serology were assessed at limited time points during the study, it is likely that not all cases of asymptomatic infection were captured in these analyses.

VE against SARS-CoV-2 infections regardless of symptoms included more COVID-19 symptomatic cases than asymptomatic cases in both groups, but with symptomatic COVID-19 making up a smaller proportion of the total cases in the mRNA-1273 group (60.5%) than in the placebo group (75.6%).

VE against asymptomatic infection starting at least 14 days after Dose 2 was estimated as 3.8% (95% CI −111.5%, 52.8%). As noted, the 95% CI includes zero, making it difficult to draw conclusions regarding efficacy against asymptomatic infection.

Table 84. Incidence of SARS-CoV-2 Infection Starting 14 Days after Dose 2, Participants 6 Through 23 Months of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Disease/Infection	mRNA-1273 25 µg N=1511 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=513 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
SARS-CoV-2 infection[d] (regardless of symptoms)	81 (5.4) 363.5 222.8 (177.0, 276.9)	45 (8.8) 120.2 374.4 (273.1, 501.0)	40.5% (12.3%, 59.2%)
Asymptomatic SARS-CoV-2 infection[e]	32 (2.1) 363.7 88.0 (60.2, 124.2)	11 (2.1) 120.2 91.5 (45.7, 163.7)	3.8% (-111.5%, 52.8%)

Sources: P204 (6-23 months) Table 14.2.5.1.1.2.1, Table 14.2.6.1.1.2.1.1

a. Person-years is defined as the total years from randomization date to the first date of SARS-CoV-2 infection, or asymptomatic SARS-CoV-2 infection, as applicable, to the last date of study participation, 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. Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 versus placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

d. SARS-CoV-2 infection (regardless of symptoms) is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline. Participants have 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) or positive RT-PCR post-baseline

e. Asymptomatic infection is identified by the absence of symptoms and the presence of infection as detected by RT-PCR or serology tests for participants with negative SARS-CoV-2 status at baseline. Specifically, the absence of COVID-19 symptoms and at least one of the following: 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.

Severe COVID-19 cases

There were no reports of severe COVID-19 cases in participants 6-23 months of age in this study as of the data cutoff.

COVID-19 cases by time period

Additional analyses of the efficacy endpoint were conducted to evaluate VE against COVID-19, based on the CDC case definition, by time period (Table 85). VE for the prevention of COVID-19 starting any time after Dose 1 was 43.3% (95% CI 16.7%, 61.1%). Although these data suggest some protection against COVID-19 following one dose, the follow-up time after one dose was limited in study participants, as almost all study participants went on to receive a second dose. In addition, the small number of COVID-19 cases and wide CI that includes zero in the time period after Dose 1 to before Dose 2 makes it difficult to reach a conclusion on vaccine efficacy during that time. These data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

VE estimates from analyses any time after Dose 1 and any time after Dose 2 were overall similar to the protocol-specified efficacy analysis against COVID-19 starting 14 days after Dose 2 (50.6% [21.4%, 68.6%]).

Table 85. Incidence of COVID-19 (CDC Case Definition) by Time Period, Participants 6 Through 23 Months of Age, Study P204 Part 2, mITT1 Set

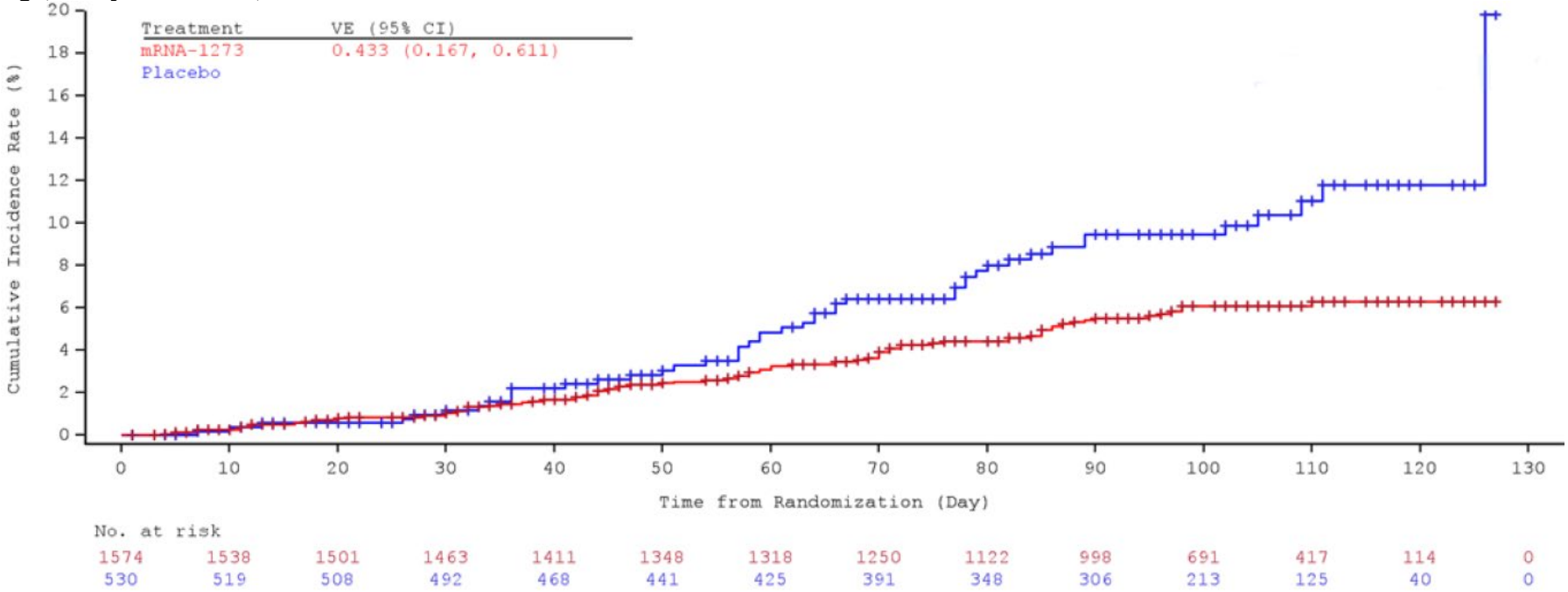
First COVID-19[d] Occurrence	mRNA-1273 25 µg N=1574 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=530 Cases/N1 (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
Any time after Dose 1	80/1574 (5.1) 380.5 210.2 (166.7, 261.7)	46/530 (8.7) 124.0 371.1 (271.7, 495.0)	43.3% (16.7%, 61.1%)
Any time after Dose 1 to before Dose 2	18/1574 (1.1) 127.9 140.8 (83.4, 222.5)	6/530 (1.1) 42.9 139.7 (51.3, 304.1)	-0.7% (-210.0%, 61.7%)
Any time after Dose 2	62/1439 (4.3) 251.4 246.6 (189.1, 316.2)	40/480 (8.3) 80.5 497.0 (355.1, 676.8)	50.4% (24.2%, 67.2%)

Source: P204 (6-23 months) Table 14.2.8.4.1.2.1
N1 is the number of participants at risk. Percentages are based on N1.
a. COVID-19 (CDC definition) is at least 1 of the following systemic symptoms: fever (temperature ≥38ºC/≥100.4ºF) 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 or vomiting, or poor appetite/poor feeding; OR at least 1 of the following respiratory signs/symptoms: cough (of any duration, including ≤48 hours), shortness of breath or difficulty breathing (of any duration, including ≤48 hours); AND a positive test for SARS-CoV-2 by RT-PCR.
b. Person-years for each time period is defined as the total years from the start of each time period to the date of CDC case definition of COVID-19, the end of each time period, last date of study participation, efficacy data cutoff date, whichever is earliest.
c. Incidence rate for each time period is defined as the number of participants with an event during the time period divided by the number of participants at risk at the beginning of each time period 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.
d. Vaccine efficacy is 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 for the time period.

Cumulative incidence curves

The cumulative incidence curve for COVID-19 based on the CDC case definition starting after randomization (same day as Dose 1), in the mITT1 Set shows that cases of COVID-19 remained similarly low in both the mRNA-1273 and placebo groups until approximately 1 week after Dose 2, at which time point the curve starts to diverge, with more cases accumulating in the placebo group than in the mRNA-1273 group (Figure 4).Figure 1

Figure 4. Cumulative Incidence Curve of CDC Case Definition of COVID-19 Starting After Randomization, Participants 6 Through 23 Months of Age, Study P204 Part 2, mITT1 Set



Source: P204 (6-23 months) Figure 14.2.5.2.3.2.1

Sensitivity analysis accounting for different COVID-19 testing methods during the Omicron surge

During the Omicron surge, in-person illness visits and protocol-specified RT-PCR confirmatory testing were not always possible due to COVID-19 restrictions. During this time, data were collected for COVID-19 cases based on RT-PCR testing (performed at CLIA-certified central or local laboratory), home testing, and where test modality was not identified. A sensitivity analysis of VE was performed to include all reported cases of COVID-19 and SARS-CoV-2 infection irrespective of test modality (Table 86, below). As expected with a broader allowance for test results, the number of COVID-19 cases and SARS-CoV-2 infections was higher in the sensitivity analysis compared to the main analysis. The VE point estimate of 53.5% for the CDC definition of COVID-19 based on this sensitivity analysis was comparable to the VE point estimate of 50.6% in protocol-specified analysis which included only centrally confirmed RT-PCR results.

Table 86. Sensitivity Analysis of All Reported Cases Irrespective of Testing Method and Location* Starting 14 Days after Dose 2, Participants 6 Through 23 Months of Age, Study P204 Part 2, Per-Protocol Set for Efficacy

Disease/Infection	mRNA-1273 25 µg N=1511 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Placebo N=513 Cases (%) Person-Years[a] Incidence Rate per 1,000 Person-Years[b] (95% CI)	Vaccine Efficacy[c] (95% CI)
CDC case definition of COVID-19	74 (4.9); 367.1 201.6 (158.3, 253.066)	52 (10.1); 119.8 433.9 (324.0, 569.0)	53.5% (32.4%, 67.8%)
P301 case definition of COVID-19	51 (3.4); 369.0 138.2 (102.9, 181.7)	30 (5.8); 122.1 245.7 (165.7, 350.7)	43.7% (8.5%, 64.8%)

Source: Study P204 (6-23 months) Table 14.2.7.1.1.2, Table 14.2.8.1.1.2

*Testing Method and Location could include RT-PCR performed at a CLIA-certified central laboratory, RT-PCR performed at a local laboratory, home testing, and unknown testing modality

a. Person-years is defined as the total years from the randomization date to the date of event (CDC case definition of COVID-19, P301 case definition of COVID-19, 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 is 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.

4.4.4.4 Safety

Overview of adverse events

Safety analyses presented in this section of the review focus on data from the blinded phase of the study (Part 2) through the cutoff date of February 21, 2022, with a median duration of blinded follow-up of 68 days post Dose 2. From the open-label portion of the study (Part 1), only the analyses of SAEs and unsolicited AEs of clinical interest are presented.

The table below summarizes AEs in participants 6-23 months of age from Part 2 of Study P204. Overall, the proportions of MAAEs were balanced between vaccine and placebo groups. SAEs were uncommon in general (0.9% for the mRNA-1273 groups and 0.2% for the placebo group), with 2 SAEs (0.1%) in the mRNA-1273 group assessed as related to vaccination by the investigator (discussed in detail later in this section) and none in the placebo group. No deaths were reported in either group. The rate of unsolicited AEs within 28 days after vaccination, including related unsolicited AEs, was similar in both groups. As compared to the placebo group, a greater percentage of participants in the vaccine group experienced local and systemic solicited adverse reactions (ARs).

Table 87. Safety Overview, Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Set, Solicited Safety Set

Adverse Event	mRNA-1273 25 µg	Placebo
Solicited adverse reactions within 7 days	n/N1 (%)	n/N1 (%)
Solicited local adverse reaction (any dose)	1148/1758 (65.3)	261/585 (44.6)
Dose 1	775/1746 (44.4)	193/582 (33.2)
Dose 2	868/1596 (54.4)	159/526 (30.2)
Grade 3 or 4 solicited local adverse reaction (any dose)	30/1758 (1.7)	2/585 (0.3)
Solicited systemic adverse reaction (any dose)	1555/1758 (88.5)	494/585 (84.4)
Dose 1	1334/1746 (76.4)	421/582 (72.3)
Dose 2	1174/1596 (73.6)	350/526 (66.5)
Grade 3 or 4 systemic adverse reaction (any dose)	89/1758 (5.1)	22/585 (3.8)
Immediate[a] unsolicited adverse events after vaccination	n/N (%)	n/N (%)
After any dose	5/1761 (0.3)	4/589 (0.7)
Dose 1	1/1761 (<0.1)	3/589 (0.5)
Dose 2	4/1601 (0.2)	1/528 (0.2)
Unsolicited adverse events	n/N (%)	n/N (%)
Unsolicited TEAE within 28 days after any injection	869/1761 (49.3)	284/589 (48.2)
Non-serious unsolicited TEAE	868/1761 (49.3)	284/589 (48.2)
Related non-serious unsolicited TEAE	292/1761 (16.6)	71/589 (12.1)
Severe non-serious unsolicited TEAE	18/1761 (1.0)	4/589 (0.7)
Related severe non-serious unsolicited TEAE	13/1761 (0.7)	3/589 (0.5)
Medically attended adverse event (MAAE)[b]	678/1761 (38.5)	242/589 (41.1)
Related MAAE [b]	26/1761 (1.5)	5/589 (0.8)
SAE[b]	15/1761 (0.9)	1/589 (0.2)
Related SAE [b]	2/1761 (0.1)	0
AEs of special interest (AESI) [b]	4/1761 (0.2)	1/589 (0.2)
Deaths [b]	0	0
TEAE leading to discontinuation of study vaccine [b]	1/1761 (<0.1)	1/589 (0.2)
TEAE leading to discontinuation from study participation [b, c]	0	1/589 (0.2)

Sources: P204 (6-23 months) Table 14.3.1.1.1.2.1, 14.3.1.1.2.2.1, 14.3.1.1.3.2.1, 14.3.1.7.1.2, 14.3.1.7.2.2
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.
a. Within 30 minutes after vaccination
b. Events during entire blinded study period
c. The TEAE in the mRNA-1273 recipient that led to discontinuation of study vaccine also led to discontinuation from study participation after the data cutoff date of February 21, 2022.

Table 88 summarizes safety by baseline SARS-CoV-2 status in the mRNA-1273 group. In the Safety Set, approximately 6.0% of mRNA-1273 recipients had evidence of prior SARS-CoV-2 infection at baseline. Overall, rates of AEs after any dose based on baseline SARS-CoV-2 status were similar between participants with negative SARS-CoV-2 status at baseline (94.1%) and those with positive SARS-CoV-2 status at baseline (93.4%).

Table 88. Safety Overview by Baseline SARS-CoV-2 Status, Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Set, Solicited Safety Set

Adverse Event	Baseline SARS-CoV-2 Negative	Baseline SARS-CoV-2 Positive
Solicited adverse reactions within 7 days	n/N1 (%)	n/N1 (%)
Solicited local adverse reaction (any dose)	1022/1572 (65.0)	72/106 (67.9)
Dose 1	687/1560 (44.0)	47/105 (44.8)
Dose 2	779/1438 (54.2)	54/92 (58.7)
Grade 3 or 4 local adverse reaction (any dose)	27/1572 (1.7)	1/106 (0.9)
Solicited systemic adverse reaction (any dose)	1391/1572 (88.5)	92/106 (86.8)
Dose 1	1188/1560 (76.2)	83/105 (79.0)
Dose 2	1064/1438 (74.0)	61/92 (66.3)
Grade 3 or 4 systemic adverse reaction (any dose)	79/1572 (5.0)	9/106 (8.5)
Unsolicited adverse events within 28 days	n/N (%)	n/N (%)
Unsolicited AE (any dose)	791/1575 (50.2)	44/106 (41.5)
Non-serious unsolicited AE (any dose)	790/1575 (50.2)	44/106 (41.5)
Severe non-serious unsolicited AE (any dose)	17/1575 (1.1)	1/106 (0.9)
MAAE within 28 days after any injection (any dose)	442/1575 (28.1)	27/106 (25.5)
SAE within 28 days after any injection (any dose)	7/1575 (0.4)	0

Sources: P204 (6-23 months) Table 14.3.1.1.5.1, 14.3.1.1.5.2, 14.3.1.1.5.3, 14.3.1.7.1.4.2.1
Note: Solicited AR percentages are based on the number of exposed participants who submitted any data for the event (N1). Unsolicited AE percentages are based on the number of safety participants (N). A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. The Safety Set of Part 1 consists of all enrolled participants and Part 2 consists of all randomized participants who received any study injection. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

Immediate adverse events

Immediate unsolicited AEs occurring within 30 minutes of vaccination were infrequent and occurred in 5 mRNA-1273 recipients (0.3%) and 4 placebo recipients (0.6%). Of these, 1 in the mRNA-1273 group (<0.1%) and 3 in the placebo group (0.5%) occurred after Dose 1, and 4 in the mRNA-1273 group (0.2%) and 1 in the placebo group (0.2%) occurred after Dose 2. The immediate AEs in the mRNA-1273 were irritability (3 participants) and injection site injury (scratch in 2 participants). There were no events clinically concerning for anaphylaxis.

Solicited adverse reactions

The frequency of solicited local adverse reactions in the 6-23 months age group were slightly higher after dose 2 compared to Dose 1, while systemic adverse reactions were generally comparable across doses. The adverse reactions in participants 6 through 23 months of age after any dose were irritability/crying (81.5%), pain at the injection site (56.2%), sleepiness (51.1%), loss of appetite (45.7%), fever (21.8%), swelling at the injection site (18.4%), erythema at the injection site (17.9%), and axillary swelling/tenderness (12.2%).

Solicited local adverse reactions were more common in the mRNA-1273 group than in the placebo group. Solicited local ARs generally occurred more frequently and were more severe after Dose 2 compared to Dose 1 in the mRNA-1273 group. The most common solicited local AR was injection site pain, which was reported by 37.4% of mRNA-1273 recipients after Dose 1 and 46.2% of mRNA-1273 recipients after Dose 2. In mRNA-1273 recipients, injection site erythema, injection site swelling, and axillary (or groin) swelling/tenderness were reported by 5.9%-8.6% of participants after Dose 1 and 9.3%-15.3% of participants after Dose 2. Grade 3 (severe) solicited local ARs were reported by 0.5% of mRNA-1273 recipients after Dose 1 and by 1.4% of mRNA-1273 recipients after Dose 2. There were no Grade 3 reported events of injection site pain or axillary (or groin) swelling or tenderness and no Grade 4 solicited local ARs. The frequencies and characteristics of local adverse

reactions within 7 days after each vaccination in Part 2 study participants 6 months-23 months of age are summarized in Table 89.

Table 89. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Participants 6 Through 23 Months of Age, Study P204 Part 2, Solicited Safety Set

Event	mRNA-1273 25 µg Dose 1 N=1746	Placebo Dose 1 N=582	mRNA-1273 25 µg Dose 2 N=1596	Placebo Dose 2 N=526
Any local adverse reaction, n (%)	N1=1745	N1=582	N1=1596	N1=526
Any	775 (44.4)	193 (33.2)	868 (54.4)	159 (30.2)
Grade 1	701 (40.2)	187 (32.1)	720 (45.1)	152 (28.9)
Grade 2	65 (3.7)	4 (0.7)	125 (7.8)	7 (1.3)
Grade 3	9 (0.5)	2 (0.3)	23 (1.4)	0
Pain/tenderness at injection site, n (%)	N1=1744	N1=582	N1=1596	N1=526
Any	652 (37.4)	175 (30.1)	738 (46.2)	135 (25.7)
Grade 1	636 (36.5)	174 (29.9)	701 (43.9)	132 (25.1)
Grade 2	16 (0.9)	1 (0.2)	37 (2.3)	3 (0.6)
Grade 3	0	0	0	0
Erythema (redness), n (%)	N1=1744	N1=582	N1=1596	N1=526
Any	150 (8.6)	24 (4.1)	216 (13.5)	20 (3.8)
Grade 1	110 (6.3)	19 (3.3)	137 (8.6)	16 (3.0)
Grade 2	35 (2.0)	3 (0.5)	65 (4.1)	4 (0.8)
Grade 3	5 (0.3)	2 (0.3)	14(0.9)	0
Swelling (hardness), n (%)	N1=1744	N1=582	N1=1596	N1=526
Any	146 (8.4)	15 (2.6)	244(15.3)	11 (2.1)
Grade 1	113 (6.5)	15 (2.6)	168 (10.5)	10 (1.9)
Grade 2	28 (1.6)	0	62 (3.9)	1 (0.2)
Grade 3	5 (0.3)	0	14 (0.9)	0
Axillary/groin swelling/tenderness, n (%)	N1=1743	N1=582	N1=1596	N1=526
Any	102 (5.9)	26 (4.5)	148 (9.3)	28 (5.3)
Grade 1	101 (5.8)	26 (4.5)	146 (9.1)	28 (5.3)
Grade 2	1 (<0.1)	0	2 (0.1)	0
Grade 3	0	0	0	0

Source: EUA 27073 Am 430, P204 (6-23 months), Table 14.3.1.1.1.2.1.2, Table 14.3.1.1.2.2.1.2.
Note: Any=Grade 1 or higher. There were no Grade 4 solicited local ARs reported.
N = Included 16 individuals aged 2 to 4 years randomized in the 6 through 23 months of age group stratum (13 in the mRNA-1273 group and 3 in the placebo group).
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=5-20mm (participants aged 6 to ≤36 months); Grade 2=>20-50mm (participants aged 6 to ≤36 months); Grade 3=>50mm (participants aged 6 to ≤36 months). Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=some swelling or tenderness but no interference with normal daily activities for participants aged 6 to ≤36; Grade 2=swelling or tenderness that interferes with normal daily activities for participants aged 6 to ≤36 months; Grade 3=swelling or tenderness that prevents normal daily activities for participants aged 6 to ≤36.

The incidence of solicited systemic ARs was generally similar after Dose 1 and Dose 2 in the mRNA-1273 group (76.4% and 73.6%, respectively). Most solicited systemic reactions were Grade 1 and Grade 2 in severity. The most common solicited systemic AR reported by mRNA-1273 recipients was irritability/crying, reported by 67.6% of participants after Dose 1 and by 64.3% of participants after Dose 2. Fever was reported by 11.0% of mRNA-1273 recipients after Dose 1 and by 14.6% of mRNA-1273 recipients after Dose 2.

Grade 3 and Grade 4 solicited systemic ARs in mRNA-1273 recipients were reported by 2.6% and <0.1% (n=1) of participants after Dose 1 and by 2.8% and 0.2% (n=3) of participants after Dose 2, respectively. The most common Grade 3 event in mRNA-1273 recipients was irritability/fussiness reported in 1.4% of participants after Dose 1 and 1.6% of participants after Dose 2. Grade 3 fever

(temperature 39.6-40.0°C) was reported by 0.6% and 0.4% of mRNA-1273 recipients after Dose 1 and Dose 2, respectively. The only Grade 4 events were fever (temperature >40.0°C) and included 1 event after mRNA-1273 Dose 1, 3 events after mRNA-1273 Dose 2, and 1 event after placebo Dose 1. The frequencies of systemic adverse reactions within 7 days after each vaccination in Part 2 study participants 6 months-23 months of age are summarized in Table 90.

Table 90. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 6 Through 23 Months of Age, Study P204 Part 2, Solicited Safety Set

Event	mRNA-1273 25 µg Dose 1 N=1745	Placebo Dose 1 N=582	mRNA-1273 25 µg Dose 2 N=1596	Placebo Dose 2 N=526
Any systemic adverse reaction, n (%)	N1=1745	N1=582	N1=1596	N1=526
Any	1334 (76.4)	421 (72.3)	1174 (73.6)	350 (66.5)
Grade 1	891 (51.1)	288 (49.5)	711 (44.5)	238 (45.2)
Grade 2	397 (22.8)	122 (21.0)	416 (26.1)	100 (19.0)
Grade 3	45 (2.6)	10 (1.7)	44 (2.8)	12 (2.3)
Grade 4	1 (<0.1)	1 (0.2)	3 (0.2)	0
Fever, n (%)	N1=1743	N1=582	N1=1594	N1=526
Any: ≥38.0°C	191 (11.0)	49 (8.4)	232 (14.6)	44 (8.4)
Grade 1: 38.0°C to 38.4°C	96 (5.5)	27 (4.6)	122 (7.7)	19 (3.6)
Grade 2: 38.5°C to 39.5°C	83 (4.8)	18 (3.1)	100 (6.3)	19 (3.6)
Grade 3: 39.6°C to 40.0°C	11 (0.6)	3 (0.5)	7 (0.4)	6 (1.1)
Grade 4: >40.0°C	1 (<0.1)	1 (0.2)	3 (0.2)	0
Irritability/crying, n (%)	N1=1737	N1=581	N1=1589	N1=525
Any	1175 (67.6)	361 (62.1)	1021 (64.3)	307 (58.5)
Grade 1	815 (46.9)	248 (42.7)	647 (40.7)	214 (40.8)
Grade 2	336 (19.3)	107 (18.4)	349 (22.0)	88 (16.8)
Grade 3	24 (1.4)	6 (1.0)	25 (1.6)	5 (1.0)
Grade 4	0	0	0	0
Sleepiness, n (%)	N1=1739	N1=581	N1=1589	N1=525
Any	645 (37.1)	217 (37.3)	558 (35.1)	175 (33.3)
Grade 1	624 (35.9)	211 (36.3)	546 (34.4)	168 (32.0)
Grade 2	17 (1.0)	5 (0.9)	11 (0.7)	6 (1.1)
Grade 3	4 (0.2)	1 (0.2)	1 (<0.1)	1 (0.2)
Grade 4	0	0	0	0
Loss of appetite, n (%)	N1=1737	N1=581	N1=1589	N1=525
Any	524 (30.2)	152 (26.2)	510 (32.1)	132 (25.1)
Grade 1	456 (26.3)	135 (23.2)	438 (27.6)	116 (22.1)
Grade 2	58 (3.3)	16 (2.8)	56 (3.5)	14 (2.7)
Grade 3	10 (0.6)	1 (0.2)	16 (1.0)	2 (0.4)
Grade 4	0	0	0	0
Use of antipyretic/pain medication, n (%)	N=1746	N=582	N=1596	N=526
Any	482 (27.6)	141 (24.2)	543 (34.0)	111 (21.1)

Source: P204 (6-23 months); Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1, Table 14.1.8.1.2, Table 14.1.8.2.2.
Note: Any=Grade 1 or higher.
N = Included 16 individuals aged 2 to 4 years randomized in the 6 through 23 months of age group stratum (13 in mRNA-1273 group and 3 in the placebo group).
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for irritability/crying, sleepiness, and loss of appetite 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. Medications were collected on an eDiary.

Duration/Onset of Adverse Reactions

Most local and systemic reactions were mild to moderate in severity and resolved within 2-3 days. In the mRNA-1273 group, time to onset of most solicited local reactions was within 1-2 days after any dose, and time to onset of most solicited systemic reactions was within 1-3 days after any dose.

Solicited local ARs persisting beyond 7 days after any dose were reported more frequently in the mRNA-1273 group (2.0%) compared to the placebo group (0.3%). The majority of events were mild (Grade 1). Among mRNA-1273 recipients, axillary (or groin) swelling/tenderness was the local AR most frequently reported as persisting (0.8% and 1.0% after Dose 1 and Dose 2, respectively). Solicited systemic ARs persisting beyond 7 days after any dose were reported in similar proportions in both groups (12.6% mRNA-1273 vs 11.5% placebo). The majority of events were mild (Grade 1) or moderate (Grade 2). Overall, 8.0% and 6.0% of mRNA-1273 recipients reported solicited systemic ARs that persisted beyond the 7-day reporting period following Dose 1 and Dose 2, respectively. Irritability/crying was the most frequently reported persisting systemic AR (6.0% post-Dose 1 and 4.3% post-Dose 2).

Delayed solicited injection site reactions, defined as beginning after 7 days post-vaccination, were reported by 1.2% of mRNA-1273 recipients after Dose 1 and none after Dose 2. None of these delayed local reactions were medically attended and none were considered severe. The most common delayed local reaction after any dose was erythema (0.9%).

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing mRNA-1273 and placebo groups by sex, race, ethnicity, and SARS-CoV-2 status at baseline. No notable differences were observed among the demographic subgroups. Solicited local and systemic reactions after vaccination among mRNA-1273 recipients by baseline SARS-CoV-2 status are shown in Table 91. Overall, the frequencies of solicited local and systemic ARs were similar irrespective of SARS-CoV-2 status at baseline, except for fever which was reported more frequently after each dose in baseline positive participants (17.3% Dose 1; 20.7% Dose 2) compared to those who were negative at baseline (10.3% Dose 1; 14.1% Dose 2).

Table 91. Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose by Baseline SARS-CoV-2 Status, Participants 6 Through 23 Months of Age, Study P204 Part 2, Solicited Safety Set

Event[a]	Baseline SARS-CoV-2 Negative Dose 1 N=1561	Baseline SARS-CoV-2 Positive Dose 1 N=105	Baseline SARS-CoV-2 Negative Dose 2 N=1438	Baseline SARS-CoV-2 Positive Dose 2 N=92
Any local adverse reaction, n (%)	N1=1560	N1=105	N1=1438	N1=92
Any	687 (44.0)	47 (44.8)	779 (54.2)	54 (58.7)
Grade 3	8 (0.5)	1 (1.0)	20 (1.4)	0
Pain at injection site, n (%)	N1=1559	N1=105	N1=1438	N1=92
Any	579 (37.1)	43 (41.0)	659 (45.8)	48 (52.2)
Grade 3	0	0	0	0
Erythema (redness), n (%)	N1=1560	N1=104	N1=1438	N1=92
Any	130 (8.3)	10 (9.6)	194 (13.5)	9 (9.8)
Grade 3	4 (0.3)	1 (1.0)	11 (0.8)	0
Swelling (hardness), n (%)	N1=1559	N1=105	N1=1438	N1=92
Any	124 (8.0)	11 (10.5)	223 (15.5)	9 (9.8)
Grade 3	5 (0.3)	0	14 (1.0)	0
Axillary (or groin) swelling or tenderness, n (%)	N1=1559	N1=104	N1=1438	N1=92
Any	87 (5.6)	8 (7.7)	136 (9.5)	9 (9.8)
Grade 3	0	0	0	0

Event[a]	Baseline SARS-CoV-2 Negative Dose 1 N=1561	Baseline SARS-CoV-2 Positive Dose 1 N=105	Baseline SARS-CoV-2 Negative Dose 2 N=1438	Baseline SARS-CoV-2 Positive Dose 2 N=92
Any systemic adverse reaction[b], n (%)	N1=1560	N1=105	N1=1438	N1=92
Any	1188 (76.2)	83 (79.0)	1064 (74.0)	61 (66.3)
Grade 3	41 (2.6)	4 (3.8)	38 (2.6)	5 (5.4)
Grade 4	1 (<0.1)	0	3 (0.2)	0
Fever, n (%)	N1=1559	N1=104	N1=1437	N1=92
Any: ≥38.0°C	160 (10.3)	18 (17.3)	203 (14.1)	19 (20.7)
Grade 1: 38.0-38.4°C	78 (5.0)	8 (7.7)	110 (7.7)	9 (9.8)
Grade 2: 38.5-39.5°C	71 (4.6)	9 (8.7)	84 (5.8)	9 (9.8)
Grade 3: 39.6-40.0°C	10 (0.6)	1 (1.0)	6 (0.4)	1 (1.1)
Grade 4: >40.0°C	1 (<0.1)	0	3 (0.2)	0
Irritability/crying, n (%)	N=1553	N=104	N=1431	N=92
Any	1045 (67.3)	77 (74.0)	924 (64.6)	56 (60.9)
Grade 3	22 (1.4)	2 (1.9)	22 (1.5)	2 (2.2)
Sleepiness, n (%)	N=1554	N=105	N=1431	N=92
Any	571 (36.7)	40 (38.1)	506 (35.4)	30 (32.6)
Grade 3	3 (0.2)	1 (1.0)	1 (<0.1)	0
Loss of appetite, n (%)	N=1553	N=104	N=1431	N=92
Any	469 (30.2)	30 (28.8)	462 (32.3)	23 (25.0)
Grade 3	10 (0.6)	0	14 (1.0)	2 (2.2)

Source: P204 (6-23 months), Table 14.3.1.1.5.1, 14.3.1.1.5.2
Note: Any=Grade 1 or higher.
a. Any solicited AR without a row for Grade 4 events indicates there were no Grade 4 solicited ARs reported among mRNA-1273 participants for that event.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Pain is injection site pain or tenderness/injection site pain.
Toxicity grade for Injection site erythema (redness) or swelling (hardness) is defined as: G1 = 5 — 20 mm; G3 = >50 mm
Toxicity grade for groin or underarm swelling or tenderness is defined as: G1 = Some swelling or tenderness but no interference with normal daily activities/No interference with activity; G3 = Swelling or tenderness that prevents normal daily activities/Prevents daily activity

Unsolicited adverse events

The table below shows rates of unsolicited AEs in Part 2 that occurred within 28 days of vaccination and at rates of ≥1% in any group. Overall, rates of unsolicited AEs were similar between the mRNA-1273 group (49.3%) and the placebo group (48.2%). Exceptions were events classified under System Organ Class (SOC) *General disorders and administration site conditions*, specifically injection site lymphadenopathy and injection site erythema. The most commonly reported unsolicited AEs among mRNA-1273 participants were upper respiratory tract infection (10.3%), irritability (8.6%), fever (5.1%), and teething (4.7%).

Table 92. Unsolicited Adverse Events Occurring in ≥1% of Any Treatment Group Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Participants 6 Through 23 Months of Age, Study P204 Part 2, Safety Set

Unsolicited AE	mRNA-1273 25 µg N=1761 Any	Placebo N=589 Any	mRNA-1273 25 µg N=1761 Severe	Placebo N=589 Severe
Number of participants reporting unsolicited adverse events, n (%)	869 (49.3)	284 (48.2)	21 (1.2)	4 (0.7)
Number of unsolicited adverse events	1711	572	25	6
Infections and infestations, n (%)	526 (29.9)	183 (31.1)	7 (0.4)	1 (0.2)
Upper respiratory tract infection	182 (10.3)	72 (12.2)	0	0
Ear infection	66 (3.7)	18 (3.1)	0	0
COVID-19	62 (3.5)	29 (4.9)	0	0
Otitis media	46 (2.6)	22 (3.7)	0	0
Hand-foot-and-mouth disease	27 (1.5)	9 (1.5)	0	1 (0.2)
Viral upper respiratory tract infection	27 (1.5)	7 (1.2)	0	0
Respiratory tract infection viral	24 (1.4)	8 (1.4)	1 (<0.1)	1 (0.2)
Otitis media acute	25 (1.4)	4 (0.7)	0	0
Croup infectious	23 (1.3)	2 (0.3)	0	0
Nasopharyngitis	20 (1.1)	8 (1.4)	0	0
Immune system disorders, n (%)	8 (0.5)	8 (1.4)	1 (<0.1)	0
Metabolism and nutrition disorders, n (%)	71 (4.0)	26 (4.4)	4 (0.2)	1 (0.2)
Decreased appetite	68 (3.9)	26 (4.4)	3 (0.2)	1 (0.2)
Psychiatric disorders, n (%)	152 (8.6)	48 (8.1)	8 (0.5)	1 (0.2)
Irritability	151 (8.6)	47 (8.0)	8 (0.5)	1 (0.2)
Nervous system disorders, n (%)	38 (2.2)	15 (2.5)	2 (0.1)	0
Somnolence	33 (1.9)	15 (2.5)	0	0
Respiratory, thoracic and mediastinal disorders, n (%)	143 (8.1)	46 (7.8)	0	0
Rhinorrhea	76 (4.3)	27 (4.6)	0	0
Cough	74 (4.2)	21 (3.6)	0	0
Nasal congestion	37 (2.1)	14 (2.4)	0	0
Gastrointestinal disorders, n (%)	170 (9.7)	60 (10.2)	0	0
Teething	83 (4.7)	31 (5.3)	0	0
Diarrhea	57 (3.2)	13 (2.2)	0	0
Vomiting	33 (1.9)	13 (2.2)	0	0
Skin and subcutaneous tissue disorders, n (%)	52 (3.0)	21 (3.6)	1 (<0.1)	0
General disorders and administration site conditions, n (%)	147 (8.3)	37 (6.3)	1 (<0.1)	2 (0.3)
Pyrexia	90 (5.1)	31 (5.3)	1 (<0.1)	2 (0.3)
Injection site lymphadenopathy	25 (1.4)	1 (0.2)	0	0
Injection site erythema	20 (1.1)	1 (0.2)	0	0
Injury, poisoning and procedural complications, n (%)	30 (1.7)	10 (1.7)	1 (<0.1)	0

Source: P204 (6-23 months) Table 14.3.1.8.1.2, Table 14.3.1.17.2.1.
Note: Percentages are based on the number of safety participants (N). The Safety Set of Part 2 consists of all randomized participants who received any study injection. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. MedDRA version 23.0.

During the 28-day follow-up period following any dose, lymphadenopathy-related events were reported by 1.5% of mRNA-1273 recipients and 0.2% of placebo recipients. These events included lymphadenopathy, injection-site lymphadenopathy, and vaccination-site lymphadenopathy which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary (or groin) swelling/tenderness in the injected limb.

Within 28 days after vaccination, some respiratory tract-related infections were reported with greater frequency in the mRNA-1273 group compared to the placebo group, including croup, respiratory syncytial virus (RSV), and pneumonia. Events of croup were reported by 1.3% of mRNA-1273 recipients and 0.3% of placebo recipients, RSV by 0.8% of mRNA-1273 recipients and 0.5% of placebo recipients, and pneumonia by 0.2% of mRNA-1273 recipients and no placebo recipients. There was no pattern concerning time to onset or dose number for these three events. When assessing events reported under other related Preferred Terms (PT), such as Upper Respiratory Tract Infection, there were more events reported in the placebo group (12.2%) compared to the vaccine group (10.3%). An analysis including all respiratory-tract infection related PTs, with and without COVID-19, showed no imbalance between the two groups, and most events were mild to moderate in severity. The few events which were considered serious are further detailed in the section on SAEs: 4 hospitalizations with onset within 28 days post-vaccination in the mRNA-1273 group for metapneumovirus infection, electrolyte imbalance secondary to RSV infection, rhinovirus infection, and bronchiolitis; and 3 hospitalizations with onset >28 days post-vaccination for adenovirus, asthma, and croup. All events were assessed as not related to study vaccine by the investigators. FDA agrees with the investigator assessments that there is unlikely to be a causal association between the occurrence of these events and the study vaccine. Imbalances between mRNA-1273 and placebo groups in RSV and pneumonia were also observed in the 2-5 years age cohort but not in older age cohorts, and there is not a clear biological mechanism that would explain a causal association for certain respiratory infections but not others. Overall, the frequency and clinical course for these events do not appear unusual given the age group of the study population and the season (fall-winter) during which the study took place, and the observed imbalance could be due to chance. It is also possible that the observed imbalance could be due to an unappreciated bias associated with differences between treatment groups in risk avoidance for viral infections in general, health seeking behaviors, or clinical evaluation of suspected viral illnesses.

Adverse events of clinical interest
Participants are monitored in the study for AESIs based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (Appendix A).

Double Blind Phase (Part 2)
In Part 2 of the study, through the data cutoff of February 21, 2022, with a median duration of follow-up of 68 days post Dose 2, there were 4 AESIs among 4 participants in the mRNA-1273 group (0.2%) and 1 AESI in a participant in the placebo group (0.2%). The 2 events assessed by the investigator as related in the mRNA-1273 group are as follows:

- One serious event of febrile convulsion with onset 1 day after Dose 1 in a 1-year-old female. Further details on the event and FDA assessment can be found below under SAEs.
- One mild (Grade 1) event of liver injury (elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) with onset 2 days after Dose 2 in a 9-month-old female. The laboratory findings were reported due to routine laboratory monitoring for potential exposure to maternal cystic fibrosis medication during breastfeeding. There were no concurrent symptoms in the participant, who previously had elevated AST at one month and elevated ALT and AST at 3.5 months of age (prior to study vaccinations). Subsequently, it was reported that the participant had stopped breast feeding 3 months prior to the onset of the AE, and that she had experienced a viral gastroenteritis-type illness one week prior to the associated blood collection. In FDA assessment, this event was possibly related given temporality to vaccination, though the preceding viral gastroenteritis event is a plausible alternative etiology.

The remaining AESIs, assessed as not related to investigational product by the investigator, are listed below. These events were all considered serious and further details, including FDA assessment, can be found in the below in the section on SAEs.

- One event of febrile convulsion with onset 21 days after Dose 1 of mRNA-1273 in a 1-year-old male with a documented history of intermittent fevers who underwent evaluation by infectious disease and rheumatology and was diagnosed with Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome.
- One event of erythema multiforme with onset 35 days after Dose 1 of mRNA-1273 in a 1-year-old male, in setting of recent exposure to peanut and amoxicillin.
- Events of acute respiratory failure, bronchiolitis, and rhinovirus infection with onset 29 days after Dose 1 of placebo in a 1-year-old male.

Open-label Phase (Part 1)
One AESI was reported in Part 1, in a 1-year-old male participant in the mRNA-1273 25 µg group who experienced a febrile convulsion that started 10 days after Dose 2 and resolved the same day. It was preceded by an event of maculo-papular rash 2 days prior. This event of febrile convulsion was considered an SAE as the participant was hospitalized, which included electroencephalogram (EEG) evaluation that was assessed as normal. Based on the interval between vaccination and the event, and preceding rash suggestive of a viral exanthem, FDA agrees with the investigator's assessment that the event was not related to study vaccine.

FDA Standard MedDRA Queries (Double Blind Part 2 and Open Label Part 1)
FDA conducted Standard MedDRA Queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited AEs with onset following Dose 1 through the data cutoff date or unblinding (whichever was earlier). The median duration of blinded follow-up for safety was 68 days after Dose 2 in Part 2 of the study and 233.5 days after Dose 2 in Part 1 of the study. SMQs were conducted on AE PTs that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which resulted in imbalance between the two treatment groups, and which captured events considered clinically relevant by the FDA will be discussed.

For the SMQ *Hypersensitivity*, in Part 2, 110 events were reported in 101 mRNA-1273 recipients (5.7%) compared to 47 events in 41 placebo recipients (7.0%). The most frequently reported events in mRNA-1273 recipients were classified under PTs of conjunctivitis, rash, and urticaria. Within the first 28 days after vaccination, hypersensitivity events were reported by 3.9% of mRNA-1273 recipients and 5.3% of placebo recipients. Within the first 48 hours after any dose, hypersensitivity events were reported by 0.5% of mRNA-1273 recipients and 0.7% of placebo recipients. Most events reported in under PTs in this SMQ were mild and assessed as not related to study vaccine. There were 2 hypersensitivity-related SAEs in mRNA-1273 recipients (asthma and erythema multiforme), both assessed as not related, which are detailed below under SAEs in Table 93. There were 2 AEs of anaphylactic reaction in the mRNA-1273 group, both with onset greater than 2 weeks after vaccination, and both attributable to sources other than vaccine (exposure to egg product, exposure to smoothie). In Part 1, 20 events in this SMQ were reported in 15 mRNA-1273 participants (10.0%). Events were similar in nature to those reported by Part 2 mRNA-1273 recipients and included a 7-month-old male participant who experienced severe (Grade 3) SAEs of urticaria, wheezing, and cough attributed to egg product (details below under SAEs).

In Part 2, for the SMQ *Convulsions*, 3 events were reported in 3 mRNA-1273 recipients (0.2%), and no events were reported in placebo recipients. In Part 1, there was 1 reported event. All events were under the PT febrile convulsion and were considered SAEs. Further details for these cases are included under SAEs.

In Study P204, scripted safety calls were included in the study design to solicit for symptoms of myocarditis and pericarditis. This resulted in enhanced reporting frequency of associated symptoms in Study P204 compared to those reported (unsolicited) in adults from Study P301 and adolescents from study P203. In Part 2 of P204, no participants (mRNA-1273 or placebo) experienced an event included within the SMQ *Cardiomyopathy*. In Part 1, one participant reported a PT of dyspnea described as follows:

- An 8-month-old male in the mRNA-1273 group with recent otitis media acute and upper respiratory tract infection experienced an event of dyspnea 27 days after Dose 1 which was attributed to nasal congestion. Concurrent symptoms included fever, fatigue, nasal congestion, rhinorrhea, decreased appetite, cough, and diarrhea. The event of dyspnea resolved within 6 days. The event was considered not related to the vaccine by the investigator. FDA agrees with the assessment.

The dataset was also queried for additional PTs, not included in the SMQ *Cardiomyopathy*, which could represent potentially cardiac related clinical AEs. Two PTs of irritability and vomiting, reported by a single participant, were identified in the safety database.

- A 1-year-old female in the mRNA-1273 group in Part 2, with no reported past medical history, reported concurrent mild AEs of irritability, vomiting, and fever 22 days after Dose 2. These AEs were assessed by the investigator as not related to study vaccine. FDA agrees with the assessment.

None of the events captured by the SMQ *Cardiomyopathy* or in the additional analysis met CDC criteria for probable or confirmed myocarditis or pericarditis.[66]

Serious adverse events
In Part 2, from Dose 1 through the data cutoff, SAEs were reported in 15 mRNA-1273 recipients (0.9%) and 1 placebo recipient (0.2%). Twelve SAEs were assessed by the study investigator as not related to investigational product, and 4 SAEs in 2 mRNA-1273 recipients were assessed by the study investigator as related. The Sponsor assessed all SAEs as not related to the study vaccine. The differences between the investigator and Sponsor assessments were as follows:

- A 1-year-old female with a family history of type 1 diabetes mellitus and a recent upper respiratory infection experienced an event of diabetic ketoacidosis (DKA) 37 days after Dose 2 (resolved 7 days later) and was diagnosed with type 1 diabetes mellitus. The investigator assessed both events as potentially related to mRNA-1273 but noted the events were more likely caused by genetic factors and/or the preceding viral upper respiratory tract infection. The Sponsor considered the events as not related to the study vaccine. FDA agrees with the Sponsor that the events of DKA and type 1 diabetes were not related to study vaccine and were more likely caused by genetic factors and/or a precipitating infection.
- A 1-year-old female in the mRNA-1273 group experienced an event of pyrexia (temperature of 103.1°F) approximately 6 hours after Dose 1. One day after Dose 1, based on the description given by the parent of the participant having been limp, not making any purposeful movement, and alert but not tracking (possible post-ictal state), she was diagnosed in the emergency department as having experienced an event of febrile convulsion. Seizure activity was not witnessed, and no other AEs were reported at the time. Three days after onset of fever and 2 days after the febrile seizure, the participant was reported to have a maculo-papular rash on the trunk. The investigator considered the events related to the study vaccine. The Sponsor assessed the events as not related to the

vaccine due to the short time to onset of the fever after vaccination and the onset of the rash after resolution of the fever, which the Sponsor concluded was suggestive of a viral illness as a more plausible explanation for the occurrence of the reported events. In FDA assessment, these AEs reported within 3 days following Dose 1 are potentially related to study vaccination; however, an alternate etiology of viral illness is possible given the associated rash onset upon defervescence (as seen with HHV-6 infection). Following data cutoff, the child experienced a second febrile seizure 7 weeks later that was witnessed and reported to be brief, not requiring medical attention. This event was assessed by the investigator and Sponsor as not related to study vaccine. Three weeks later, the participant received mRNA-1273 Dose 2, with medication to prevent fever, with no reported AEs. FDA agrees with the investigator and Sponsor assessments for the second event of febrile seizure.

Additionally, in Part 1, five SAEs were reported by 3 participants in the mRNA-1273 group. None of the events were assessed as related by the investigator. FDA agrees with the investigator assessments. The following table provides an overview of SAEs reported through data cutoff in Part 2 (blinded phase) and Part 1 (open label phase).

Table 93. Serious Adverse Events Through Data Cutoff of February 21, 2022, Participants 6 Through 23 Months of Age, Study P204 Blinded Phase Part 2 and Open Label Part 1, Safety Set

Treatment Group	Age*/Sex	SAE Preferred Term	Time to Onset after Most Recent Dose	Risk factors/pertinent details	Resolution	Investigator Assessment	FDA Assessment
Part 2 Blinded							
mRNA-1273 25 µg	17 months/F	Pyrexia Febrile convulsion	Day of Dose 1 1 day after Dose 1	Fever onset 6 hours post-vaccination; unwitnessed febrile convulsion 1 day after; rash developed 3 days after fever (see narrative above)	Resolved Resolved	Related Related	Possibly related Possibly related
mRNA-1273 25 µg	18 months/M	Mastoiditis	3 days after Dose 1	Intermittent fevers 2 months prior to event onset; History of otitis media; Tested positive for adenovirus during hospitalization	Resolved	Not related	Not related
mRNA-1273 25 µg	12 months/F	Metapneumovirus infection	4 days after Dose 1	Hospitalized in intensive care unit for 3 days	Resolved	Not related	Not related
mRNA-1273 25 µg	12 months/F	Electrolyte imbalance	8 days after Dose 1	Hospitalized; concurrent RSV infection with respiratory distress and dehydration	Resolved	Not related	Not related
mRNA-1273 25 µg	12 months/F	Rhinovirus infection	8 days after Dose 1	Hospitalized for 1 day. Reported by mother to have fever of 106^{o} F.	Resolved	Not related	Not related
mRNA-1273 25 µg	23 months/F	Foreign body in respiratory tract	15 days after Dose 1	Unspecified foreign body in respiratory tract, required bronchoscopy assisted removal	Resolved	Not related	Not related
mRNA-1273 25 µg	19 months/F	Bronchiolitis	17 days after Dose 1	Food allergy (nuts), eczema; hospitalized on high-flow nasal cannula; viral panel negative	Resolved	Not related	Not related
mRNA-1273 25 µg	19 months/M	Febrile convulsion	21 days after Dose 1	Medical history of intermittent fevers with rash; Fever for previous 2 days; Infectious disease and rheumatology diagnosed with PFAPA^{+}; Received Dose 2 with no associated AEs	Resolved	Not related	Not related
mRNA-1273 25 µg	11 months/M	Erythema multiforme	35 days after Dose 1	History of eczema and peanut allergy; exposed to peanut butter and amoxicillin (day 8 at onset of symptoms of EM)	Resolved	Not related	Not related

Treatment Group	Age*/Sex	SAE Preferred Term	Time to Onset after Most Recent Dose	Risk factors/pertinent details	Resolution	Investigator Assessment	FDA Assessment
mRNA-1273 25 µg	20 months/M	Adenovirus infection	35 days after Dose 1	Hospitalized due to concern for MIS-C vs Kawasaki Disease (KD). Found to be positive for adenovirus on PCR. SARS-CoV-2 negative; KD diagnosis excluded	Resolved	Not related	Not related
mRNA-1273 25 µg	14 months/M	Asthma	31 days after Dose 2	Prodromal URI symptoms, temperature of 100.3°F, diagnosis of pneumonia at urgent care and started on amoxicillin; hospitalized 4 days later for respiratory distress requiring high-flow nasal cannula, CXR at hospital: viral or reactive airway disease; viral panel negative	Resolved with sequelae: ongoing diagnosis of asthma	Not related	Not related
mRNA-1273 25 µg	15 months/F	Diabetic ketoacidosis Type 1 diabetes mellitus	37 days after Dose 2	Family history of type 1 diabetes (see narrative above)	Resolved Resolved with sequelae: diagnosis of type 1 diabetes	Related Related	Not related Not related
mRNA-1273 25 µg	22 months/F	Croup infectious	43 days after Dose 2	Inflammation of upper respiratory tract after recent adenoidectomy and turbinate reduction	Resolved	Not related	Not related
mRNA-1273 25 µg	18 months/M	Gastroenteritis viral	43 days after Dose 2	Hospitalized (2 days)	Resolved	Not related	Not related
mRNA-1273 25 µg	17 months/F	Febrile convulsion	66 days after Dose 2	Daycare reported possible seizure and tactile fever after a nap; fever 101.5 and normal exam in ED	Resolved	Not related	Not related
Placebo	15 months/M	Bronchiolitis; Rhinovirus infection; Acute respiratory failure	29 days after Dose 1	Hospitalized on high flow nasal cannula	Resolved	Not related	Not related

Treatment Group	Age*/Sex	SAE Preferred Term	Time to Onset after Most Recent Dose	Risk factors/pertinent details	Resolution	Investigator Assessment	FDA Assessment
OL Part 1							
mRNA-1273 25 µg	16 months/M	Febrile convulsion	10 days after Dose 2	Preceding maculo-papular rash and fever suggested associated viral illness	Resolved	Not related	Not related
mRNA-1273 25 µg	7 months/M	Cough; Wheezing; Urticaria	21 days after Dose 2	Hypersensitivity to egg exposure	Resolved	Not related	Not related
mRNA-1273 25 µg	22 months/F	Rhinovirus infection	149 days after Dose 2	Hospitalized (2 days) for respiratory distress, also found to have otitis media, re-admitted 2 days after discharge for continued respiratory distress requiring oxygen (2 days)	Resolved	Not related	Not related

Source: FDA generated table based on case narratives, listings, and dataset submitted to EUA 27073, P204 (6-23 months)
[+]PFAPA= Periodic fever, aphthous stomatitis, pharyngitis, and adenitis; ED=Emergency Department
*Age = age at enrollment

Adverse events leading to discontinuation from study vaccination or study participation
AEs leading to discontinuation from study vaccination after Dose 1 and before Dose 2, and AEs leading to discontinuation from study participation, were reported by 1 mRNA-1273 recipient (urticaria) and 1 placebo recipient (COVID-19) in Part 2, as described below. There were no participants from Part 1 who were discontinued from study vaccination or study participation due to an AE.

- A 1-year-old White male participant in the mRNA-1273 group experienced a mild AE of urticaria that started the same day as Dose 1 and resolved after 1 day. The investigator assessed the event as related to mRNA-1273.
- A 7-month-old White female participant in the placebo group experienced a mild AE of COVID-19 leading to discontinuation from study vaccination and from study participation. The event started 10 days after Dose 1 and resolved in 10 days. The investigator assessed the event as not related to the study investigational product.

FDA agrees with the investigator's assessment of relatedness to study vaccine for each of the reported AEs described above.

4.4.4.5 Summary for Participants 6 Through 23 Months of Age

The comparison of immune response between children 6-23 months of age in Study P204 and young adults in Study P301 provided the primary evidence to support effectiveness of the vaccine. The study met the pre-specified success criteria for the two co-primary endpoints of GMC ratio and difference in SRRs. The GMC ratio (children 6-23 months to young adults) was 1.3 (95% CI 1.1, 1.5) which met the pre-specified success criterion of a LL of the 95% CI ≥0.67 and a point estimate of ≥0.8. The difference in SRRs (children 6-23 months minus young adults) was 0.7 (95% CI -1.0, 2.5) which met the pre-specified success criterion of a LL of the 95% CI >-10% and an SRR difference point estimate >-5%.

The immunogenicity data across demographic subgroups were generally consistent with those observed in the overall study population, though subgroup-specific analyses are limited by the small number of participants in certain subgroups. As observed in older pediatric age cohorts, the majority of participants were SARS CoV-2 seronegative; however, subgroup analyses of those seropositive at baseline (N=12) demonstrated numerically higher GMCs (with non-overlapping CIs) at Day 57 compared to those who were seronegative at baseline.

Descriptive analyses of VE in children 6-23 months of age further supported and provided direct evidence of vaccine effectiveness. The observed VE against COVID-19 starting 14 days after Dose 2 was 31.5% (95% CI -27.7%, 62.0%) when using the COVID-19 case definition used in Study P301, and 50.6% (95% CI 21.4%, 68.6%) when using the broader CDC case definition. Efficacy was evaluated during the time period in which the Omicron variant was the predominant circulating strain. Estimates of vaccine efficacy among participants 6 -23 months appear consistent with VE estimates observed in adults during Omicron[67], based on observational studies. Across demographic subgroups, vaccine efficacy was consistent with the results obtained based on the general study population, though interpretability of subgroup-specific VE is limited by the small number of participants in certain subgroups. There were too few COVID-19 cases in participants who were SARS-CoV-2 seropositive at baseline to draw any firm conclusions about VE in this subgroup. There were no reports of severe COVID-19 in this age group.

The most common solicited adverse reactions after any dose of mRNA-1273 were irritability/crying (81.5%), pain at the injection site (56.2%), sleepiness (51.1%), loss of appetite

(45.7%), fever (21.8%), swelling at the injection site (18.4%), erythema at the injections site (17.9%), and axillary (or groin) swelling/tenderness (12.2%). In general, solicited local adverse reactions occurred more frequently and were more severe after Dose 2 compared to Dose 1, while the frequency and severity of solicited systemic adverse reactions were more balanced between Dose 1 and Dose 2. Most local and systemic reactions were mild to moderate in severity, with onset 1-2 days post-vaccination, and resolved within 2 to 3 days after onset. Fever was the only Grade 4 solicited adverse reaction reported among participants and was uncommon. Overall, the frequencies of solicited local and systemic ARs were similar between the participants with and without evidence of prior SARS-CoV-2 infection at baseline, except for fever which was reported in a greater proportion of participants with positive than negative SARS-CoV-2 status at baseline after each dose. Local adverse reactions in participants 6-23 months were generally reported less frequently compared to older children, adolescents, and young adults. The solicited systemic adverse reaction terms differed in the 6-23 months age cohort compared to the terms in age cohorts 37 months and older, with the exception of fever. Fever was generally reported more frequently in the 6-23 months age cohort compared to the older age cohorts after vaccination.

In general, unsolicited AEs reported within 28 days after vaccination occurred with similar frequencies in mRNA-1273 recipients (49.3%) and placebo recipients (48.2%). Exceptions were a higher incidence of events related to injection site reactions and vaccine reactogenicity, including lymphadenopathy-related events which were reported by 1.5% of mRNA-1273 recipients and 0.2% of placebo recipients. Some respiratory tract-related infections, such as croup, were reported with greater frequency in the vaccine group compared to the placebo group, but these events were typical of normal childhood illnesses, clinical course, and seasonal pattern for this age. Within 28 days after vaccination, hypersensitivity-related events were reported by 3.9% of mRNA-1273 recipients and 5.3% of placebo recipients. There were no events assessed as related to study vaccine that were clinically concerning for anaphylaxis. Altogether, in Part 1 and Part 2 of the study, there were 4 events of febrile convulsion, only one of which (an SAE) was assessed as related by the investigator.

In this age cohort, few participants reported events under the SMQ *Cardiomyopathy,* and none were assessed as related to study vaccine. No events of probable or confirmed myocarditis or pericarditis were reported in the study through the time of data cutoff. However, suspected cases of myocarditis has been reported in 2 adolescent participants in study P203 and cases of myocarditis/pericarditis have been reported following the authorization of mRNA-1273 in adults ≥18 years of age with routine pharmacovigilance/safety surveillance by the CDC and FDA, as discussed in Section 2.3.2.

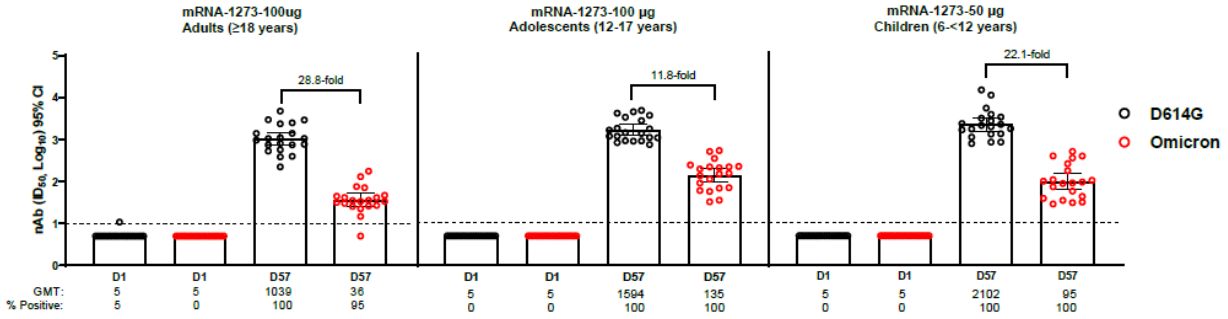
No deaths were reported in participants 6-23 months in the study. SAEs were infrequent and occurred in 0.9% of mRNA-1273 recipients and 0.2% of placebo recipients. Only the SAEs of pyrexia and febrile convulsion, which occurred in a single participant 1 and 2 days, respectively, after Dose 1 of mRNA-1273 were considered possibly related to study vaccine.

4.5 Immunogenicity Against Omicron Variant

In a study published by the Sponsor, immunogenicity against the B.1.1.529 (Omicron) variant was assessed by neutralizing antibody ID50 GMT using a non-validated lentivirus-based PsVNA assay at Day 1 and Day 57 (4 weeks) following Dose 2 of mRNA-1273 in a subgroup of adults ≥18 years from P301, adolescents 12-17 years from P203, and children 6-11 years from P204. Neutralizing antibody titers against the Omicron variant were compared to neutralizing antibody titers against the ancestral strain (D614G) measured using a validated PsVNA assay.[68] Twenty

participants from each age group were included in this analysis. At 4 weeks post Dose 2, compared to GMTs against D614G, neutralizing antibody GMTs against Omicron were 28.8-fold lower in adults ≥18 years, 11.8-fold lower in adolescents 12-17 years, and 22.1-fold lower in children 6-11 years. Although these results indicate neutralizing antibodies against Omicron were reduced less in adolescents and children 6-17 years compared to adults, it is unknown whether these results translate to differences in clinical efficacy against Omicron between adults and pediatric populations. Data from this study was not independently verified by the FDA.

Figure 5. Neutralization of D614G and Omicron SARS-CoV-2 Pseudoviruses by Sera From mRNA-1273 Primary Vaccination Recipients After Dose 2



Source: Girard B, Tomassini JE, Deng W, et al. mRNA-1273 Vaccine-elicited Neutralization of SARS-CoV-2 Omicron in Adolescents and Children. medRxiv 2022.01.24.22269666.

4.6 Third Primary Series Dose in Individuals 6 Months Through 17 Years of Age With Certain Kinds of Immunocompromise

The Moderna COVID-19 Vaccine was initially authorized under EUA for use as a 2-dose primary series in individuals 18 years of age and older. On August 12, 2021, FDA expanded the Moderna COVID-19 Vaccine EUA to include use of a third primary series dose, administered at least 28 days after the second dose, in individuals 18 years of age and older with certain kinds of immunocompromise (i.e., individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise). Evidence to support the need for and safety and effectiveness of a third primary series dose in such individuals was provided by peer-reviewed, published studies of mRNA-1273 and BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) in solid organ transplant recipients. Data presented in these publications supported that a third primary series dose resulted in modest enhancement of anti-SARS-CoV-2 antibodies compared to those elicited by the second primary series dose, and no safety concerns were identified. Additional details are provided in FDA's August 12, 2021 Decision Memorandum.

No data are available to directly inform safety and effectiveness of mRNA-1273 in children who have undergone solid organ transplant or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. However, it is reasonable to extrapolate that children with these certain kinds of immunocompromise would have a similar need for and benefit from a third primary series dose as adults 18 years of age and older, and it is reasonable to extrapolate benefit of a third primary series dose in children with certain kinds of immunocompromise based on effectiveness data in adults. Additionally, based on available safety data for first and second primary series doses of mRNA-1273 in children, and available safety data from post-authorization experience with third primary series doses of Moderna COVID-19 Vaccine in immunocompromised adults, it is reasonable to extrapolate to conclude a

favorable benefit-risk balance for use of a third primary series dose, administered at least 28 days after the second dose, in individuals 6 months through 17 years of age with certain kinds of immunocompromise.

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

5.1 Inspections of Clinical Study Sites

Bioresearch Monitoring inspections were conducted at four domestic clinical investigator sites participating in the conduct of study mRNA-1273-P203 in participants 12 through 17 years of age and at six domestic clinical investigator sites participating in the conduct of study mRNA-1273-P204 in participants 6 months through 11 years of age. The inspections did not reveal problems impacting the data submitted in support of this EUA amendment.

5.2 Chemistry, Manufacturing, and Control (CMC) Information

The CMC information to support the presentations of the Moderna COVID-19 Vaccine (mRNA-1273) proposed for use in the 6 months through 5 years and 6 years through 11 years age groups was based in part on data that supported the March 29, 2022 authorization of the additional presentation of the Moderna COVID-19 Vaccine containing 50 µg mRNA per 0.5 mL supplied in a vial with a dark blue cap and a label with a purple border that states “BOOSTER DOSES ONLY” (see Letter of Authorization, March 29, 2022). That presentation, as well as the presentations labeled for use in individuals 6 months through 5 years of age and 6 years through 11 years of age, have the same ingredients and the same concentration of ingredients.

The Moderna COVID-19 Vaccine (mRNA-1273) drug product for use in individuals 6 months to 5 years of age is supplied as a multiple-dose ready-to-use vial with a dark blue cap and a label with a magenta border.

The Moderna COVID-19 Vaccine (mRNA-1273) drug product for use in individuals 6 years to 11 years of age is supplied in multiple-dose ready-to-use vials with: (1) a dark blue cap and a label with a teal border (currently not available); and (2) a dark blue cap and a label with a purple border (the cartons and vial labels of the presentation supplied in a multiple-dose vial with a dark blue cap and a label with a purple border state “BOOSTER DOSES ONLY”, but this presentation will also be authorized to provide primary series doses to individuals 6 years through 11 years of age). For the presentation supplied in a multiple-dose vial with a dark blue cap and a label with a teal border, the cartons state, “For age 6 years through 11 years” and the vial labels state “Age 6 y through 11 y.” Because this presentation is not currently available, FDA will authorize the use of the presentation with a dark blue cap and a label with a purple border that states “BOOSTER DOSES ONLY” for use in individuals 6 years through 11 years of age. Both presentations are appropriate for use in the age group, as both presentations have the same ingredients and the same concentration of ingredients and both presentations are authorized to provide a 0.5 mL dose containing 50 µg of mRNA-1273. The multiple-dose vials with dark blue caps and labels with a purple border presentation was already authorized for use as a booster dose in individuals 18 years of age and older (see Letter of Authorization, March 29, 2022).

The multiple-dose vial presentations for use in individuals 6 months to 5 years of age and individuals 6 years to 11 years of age contain 0.10 mg/mL mRNA and a 3.2-mL target fill volume (nominal 2.5 mL volume). Each vial of 0.10 mg/mL mRNA-1273 DP contains (b) (4) mg of mRNA encapsulated in (b) (4) mg of SM-102 lipid nanoparticle (LNP) as a white to off-white dispersion in

a preservative-free buffer containing 20 mM tromethamine (Tris), (b) (4) mM acetate, 87 g/L sucrose at pH 7.5. The 0.10 mg/mL mRNA-1273 drug product composition unit formula per 1 mL, 0.25 mL dose, and 0.5 mL dose is presented in the table below.

Table 94. Drug Product Composition of 0.10 mg/mL mRNA-1273 for Use in Individuals 6 Months to 5 Years of Age (0.25 mL dose) and Individuals 6 Years to 11 Years of Age (0.5 mL dose)

Component	Unit Formula (mg/mL)	Unit Formula (mg/dose) (0.25 mL dose)	Unit Formula (mg/dose) (0.50 mL dose)
CX-024414	0.10	0.025	0.050
SM-102 LNP	--	--	--
SM-102	(b) (4)	(b) (4)	(b) (4)
Cholesterol			
DSPC			
PEG2000-DMG			
Total LNP content	2.0	0.50	1.01
Tromethamine (Tris)	0.50	0.13	0.25
Tromethamine-HCl (Tris-HCl)	2.5	0.62	1.2
Acetic acid (Glacial)	0.042	0.011	0.021
Sodium acetate trihydrate	0.20	0.049	0.10
Sucrose	87	21.8	43.5
Water for injection	q.s. 1.0 mL	q.s. 0.25 mL	q.s. 0.50 mL

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; LNP = lipid nanoparticle; N/A = not applicable; q.s. = quantum sufficit

Human Factors Study

The number of 0.25 mL doses that could be withdrawn from the multiple-dose vials filled with the target 3.2 mL volume was evaluated in a human factors study. The results presented in the table below support withdrawal, with 100% probability, of up to 12 doses of 0.25 mL using an 11-µL low dead-volume syringe/needle combination and up to 9 doses of 0.25 mL when an 80-µL high dead-volume syringe/needle combination is used.

Table 95. Results of Human Factors Study of Extraction of 0.25 mL Doses from Vials with a 3.2-mL Fill Volume Using Syringe/Needle Combinations of Varying Dead-Volumes

Syringe/Needle Type	Syringe/Needle Dead-Volume (µL)	Probability to Withdraw as Predicted by Model (%)	Actual Doses Extracted (n Vials/Total Vials; % Outcome)	Residual Volume in Vial (mL) Average	Residual Volume in Vial (mL) STDEV
(b) (4) 1 mL TB, Fixed 25G x 1”	11	100% for 10 doses	12 (n=10/10; 100%)	0.1765	0.0265
(b) (4) 1-mL Tuberculin Slip Tip, BD 25G x 1.5" (b) (4)	80	0.04% for 10 doses	10 (n=1/10; 10%)	0.1459	N/A
(b) (4) 1-mL Tuberculin Slip Tip, BD 25G x 1.5" (b) (4)	80	95.7% for 9 doses	9 (n=9/10; 90%)	0.2509	0.0764

Therefore, for the presentation of Moderna COVID-19 Vaccine supplied in a multiple-dose ready-to-use vial with a dark blue cap and a label with a magenta border for use in individuals 6 months through 5 years of age, the fact sheets will state:

- Each multiple-dose vial with a dark blue cap and a label with a magenta border contains 10 primary series doses of 0.25 mL each; low dead-volume syringes and/or needles can

be used to extract 10 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.25 mL of vaccine;
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.25 mL, discard the vial and content;
- Do not pool excess vaccine from multiple vials.

5.3 Clinical Assays

Pseudotype Virus Neutralizing Antibody Assay from Duke University, North Carolina
The post vaccination serology samples for participants 12-17 years of age (Study P203), 6-11 years of age (Study P204 Part 1 and Part 2) and 6 months through 5 years of age (Study P204 Part 1) were tested using the pseudotype virus neutralization assay used to assess the immunogenicity of Moderna's mRNA vaccine in that age group. The assay was validated at Duke University. The assay measures neutralizing antibodies using a pseudotype lentivirus expressing SARS-CoV-2 Spike protein and 293T cells expressing high levels of ACE2 (293T/ACE2 cells) in a 96 well plate format. The pseudotype lentivirus particle expresses the SARS-CoV-2 Spike protein (D614G form of the USA-WA1/2020 Wuhan strain) and a firefly luciferase reporter gene. Infected cells express luciferase, and luciferase activity is quantified by relative light units (RLU) of luminescence. Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) and 80% (ID80) relative to mean RLU in virus-control wells. The assay was validated using both convalescent serum samples and clinical samples from individuals who received Moderna's mRNA-1273 vaccine. The assay-validation study evaluated Accuracy, Precision, Limit of Detection, Lower and Upper Limits of Quantification, Dilutional Linearity, Specificity and Robustness. The validation results met the pre-established acceptance criteria and support the suitability of the assay to accurately quantify neutralizing antibodies in human serum samples.

The pseudotype virus neutralization assay was modified to measure neutralizing antibodies against the SARS-CoV-2 Delta variant, using a pseudotype virus expressing Spike protein from the Delta strain. The Delta modified assay was validated using Moderna's clinical samples from individuals who received two doses of the prototype vaccine (Wuhan Strain) and who had high neutralizing antibodies against the Delta variant. After the emergence of Omicron variant, there was a need to modify the assay to measure the neutralizing antibodies against that variant of concern and currently the assay specific for Omicron is being validated using serum samples from people who received the prototype vaccine and also were infected with the Omicron variant virus and therefore contain a high titer of Omicron-specific antibodies

Reporter Virus based Microneutralization Assay from (b) (4)

The 6 months through 5 years pediatric group post vaccination serology samples from Part 2 of Study P204 and a subset of samples from the 18 to 25 years old comparator group (Study P301) were tested using a Reporter virus Microneutralization Assay validated at (b) (4) Similar to the assay developed at Duke University, this is also a cell-based assay that measures the ability of SARS CoV-2 neutralizing antibodies to inhibit the infection of 293T-ACE2 cells by SARS CoV-2 Reporter Virus Particles (RVP) that express (b) (4) test serum samples, reference standard and controls are (b) (4) with a known quantity of SARS CoV-2-GFP for (b) (4) prior to infection of 293T-ACE2 cells. Post infection, the cells are (b) (4)

(b) (4)

The serum antibody concentration per test sample is determined by interpolating the mean of the replicate Foci Forming Units (FFU) values off the fitted reference standard curve. The reference standard was calibrated to the first WHO International Antibody Standard for SARS CoV-2 Lot 20/136. The interpolated antibody concentrations are then dilution corrected. The final concentration is the antibody concentration associated with the lowest dilution with an antibody concentration within the quantifiable range of the assay. The results are reported in final Geometric Mean Antibody Concentration (GMC) in AU/mL. The assay-validation study evaluated Precision and Ruggedness, Relative Accuracy, Selectivity, Dilutional Linearity, LLOQ, ULOQ and Specificity.

5.4 Planned Pharmacovigilance Activities

ModernaTX, Inc. submitted a revised PVP to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor includes anaphylaxis, myocarditis, and pericarditis as Important Identified Risks, and vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation, long term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects, in subjects with unstable health conditions and comorbidities, and in subjects with autoimmune or inflammatory disorders are areas the Sponsor identified as missing information.

Division of Pharmacovigilance recommendations are as follows:

1. Reporting to VAERS and Moderna

Providers administering the Moderna COVID-19 Vaccine must report to VAERS and to the extent feasible, report to Moderna, the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an AE
- SAEs (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

2. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
    - SAEs (irrespective of attribution to vaccination)
    - Cases of MIS-C in children and adults
    - Cases of COVID-19 that result in hospitalization or death

3. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports in accordance with a reporting interval and due date agreed upon by CBER's Office of Biostatistics and Pharmacovigilance. Each periodic safety report is required to contain descriptive information which includes:
    - A narrative summary and analysis of AEs submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and AESIs
    - A narrative summary and analysis of vaccine administration errors, whether or not associated with an AE, that were identified since the last reporting interval

- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Fact Sheet for Vaccination Providers, changes made to studies, studies initiated)

4. The Sponsor will conduct post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine and a pre-specified list of AESIs, including myocarditis and pericarditis, along with deaths and hospitalizations and severe COVID-19. The study population should include individuals administered the authorized Moderna COVID-19 Vaccine in the general US population (6 months of age and older), individuals who receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities.

5. This condition of authorization under the EUA, to conduct post-authorization observational studies will encompass the evaluation of individuals 6 months through 17 years of age in the following studies, which are also existing post-marketing requirements or commitments (PMRs/PMCs) for safety-related studies, that were previously identified in the January 31, 2022, approval letter for Spikevax/Moderna Covid-19 Vaccine, BLA 125752/0:

    - Study mRNA-1273-P903, entitled “Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity”, to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
    - Study mRNA-1273-P904, entitled “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe,” to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.
    - Study mRNA-1273-P911, entitled “Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273),” to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.
    - Study mRNA-1273-P901, entitled “Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine.”

Additionally, Moderna will conduct the following clinical trials to assess the risk of subclinical myocarditis (these are postmarketing requirements listed in BL 125752/0 approval letter, dated January 31, 2022):

- Study mRNA-1273-P301, substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older.
- Study mRNA-1273-P203 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 years through <18 years of age.
- Study mRNA-1273-P204 substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months through <12 years of age.

Additional VAERS reporting
An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with mRNA-1273 recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) AEs. Responses where the participant received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate. v-safe may be modified to allow adolescents to self-register and report to v-safe, and a pathway created for a parent/guardian to report on behalf of younger children.

5.5 EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6 Benefit-Risk Assessment in the Context of Proposed EUA for Moderna COVID-19 Vaccine in Children 6 Months through 17 Years of Age

6.1 Known and Potential Benefits

Available data support the effectiveness of the Moderna COVID-19 Vaccine in preventing symptomatic COVID-19 in pediatric age groups from 6 months through 17 years of age. For each of four distinct age cohorts (12-17 years, 6-11 years, 2-5 years, and 6-23 months), vaccine effectiveness was inferred by immunobridging, based on a comparison of neutralizing antibody responses with formal hypothesis testing, to a young adult age group (18-25 years) for whom VE had been demonstrated in a Phase 3 efficacy trial. Additionally, descriptive efficacy analyses for each age cohort provide VE estimates that are consistent with VE estimates from observational studies in adults from the corresponding time periods[69], supporting robust effectiveness against COVID-19 caused by the ancestral strain, Alpha, and Delta variants and more modest effectiveness against COVID-19 caused by the Omicron variant (corresponding to lower neutralizing antibody titers against Omicron as compared to the ancestral strain). In addition, a study conducted in the US on the Pfizer COVID-19 Vaccine (another mRNA COVID-19 vaccine) indicates vaccine effectiveness was similar between the 5-11- and 12-15-year-old age groups and adults during the Omicron wave in the US.[70]

For most demographic subgroups evaluated, results were consistent with the protocol-specified efficacy analyses; however, a small sample size in some subgroup analyses limited the interpretability of the respective VE estimates.

While no severe COVID-19 cases were reported among participants 6 months through 17 years in clinical studies, vaccine efficacy against severe disease and hospitalizations (including for multisystem inflammatory syndrome) is expected to be higher compared to vaccine efficacy against non-severe COVID-19 as observed in the adult clinical trial (see FDA approval memo) and in real-world studies.[71]

6.2 Uncertainties Related to Benefits

Uncertainties related to benefits of the Moderna COVID-19 Vaccine when used in individuals 6 months through 17 years of age include the following:

- Duration of vaccine effectiveness: the blinded, placebo-controlled evaluation period for descriptive efficacy analyses was limited to several months, and waning of protection following a primary series has been observed in adult recipients of the Moderna COVID-19 Vaccine and in pediatric recipients of the Pfizer-BioNTech COVID-19 Vaccine
- Need for a booster dose: based on experience with adults, it is likely that a booster dose will be needed to increase robustness, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants. A booster dose could be considered for authorization with submission of supportive data in a future amendment to the EUA.
- Effectiveness in certain populations at high risk of severe COVID-19, including immunocompromised individuals: such individuals may benefit from an additional (third) primary series dose.
- Benefits in individuals previously infected with SARS-CoV-2: descriptive efficacy analyses included relatively few COVID-19 cases in previously infected participants. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity.[72] Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.
- Effectiveness in preventing post-acute sequelae of COVID-19: available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.
- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants: the continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.
- Vaccine effectiveness against asymptomatic infection and transmission of SARS-CoV-2: Available data from the pediatric clinical trials of mRNA-1273 suggests variable levels of short-term effectiveness against asymptomatic infection across different age cohorts, and available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections.

6.3 Known and Potential Risks

Overall rates of solicited local and systemic adverse reactions (ARs) among adolescents 12-17 years of age were similar to those reported among young adults. In children 6 months through

11 years of age, rates of solicited local and systemic adverse reactions were generally lower compared to those observed in adolescents and in previous clinical trials with young adults, with the exception of fever which was reported more frequently in the younger age groups compared to adolescents and adults. Rates of fever after vaccination in the 6 months through 5 years age cohort were not substantially different compared to rates observed in this age group after other routine childhood vaccines. The overall lower reactogenicity after vaccination in the younger age cohorts likely reflects the lower vaccine mRNA content evaluated in children 6 months through 5 years (25 µg) and 6-11 years (50 µg) compared to adolescent and adults (100 µg). Among 6-17 year-old vaccine recipients with evidence of prior SARS-CoV-2 infection, rates of some solicited ARs were higher after Dose 1 compared to vaccine recipients without evidence of prior infection, but rates of solicited ARs were generally similar between these two populations after Dose 2. Among vaccine recipients 6 months through 5 years of age with evidence of prior SARS-CoV-2 infection, rates of fever after Dose 1 and Dose 2 were higher compared to vaccine recipients without evidence of prior infection, but rates of other solicited ARs after Dose 1 and Dose 2 were similar between the two populations.

Across the 6 months through 17 years age cohorts, in analyses of unsolicited AEs within 28 days following vaccination, imbalances between mRNA-1273 and placebo recipients were found for lymphadenopathy and hypersensitivity-related events at the injection site, which are likely attributable to the vaccine. More events of abdominal pain were observed in mRNA-1273 recipients compared to the placebo recipients among the 6-11 years and 2-5 years age cohorts. There is insufficient information at this time to conclude on causal relationship between these events and the vaccine.

No deaths were reported among participants 6 months through 17 years. SAEs were infrequent and occurred at similar rates among mRNA-1273 and placebo recipients. Available evidence does not suggest a causal relationship between these SAEs and the vaccine.

Anaphylaxis has been identified as an important risk after vaccination, primarily among individuals with a history of severe allergic reactions to other medications or foods. The occurrence of anaphylaxis after receipt of the Moderna COVID-19 Vaccine (or Spikevax) in post-authorization/post-marketing surveillance is comparable with those reported after receipt of other licensed preventative vaccines.[73] Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the PVP for the vaccine.

Myocarditis/pericarditis

Myocarditis/pericarditis, in particular in the first week following Dose 2, is a known risk associated with the Moderna COVID-19 Vaccine, with the highest reported rate in males 18-24 years. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, most affected individuals had resolution of symptoms with conservative management. The pediatric clinical trial safety database for mRNA-1273 is not large enough to quantify the frequency of this uncommon AE in pediatric age groups.

For individuals 12-17 years, the real-world data from Australia, Canada, and France, where the mRNA-1273 vaccine has been authorized for use among this age group, indicated a similar myocarditis/pericarditis risk compared to ages 18-24 years (Figure 7, Appendix C). In the quantitative risk assessment model of the Sponsor-sourced myocarditis case data from the

Moderna Post-Authorization Study (PASS) in the US with 50,000 children and adolescents vaccinated with mRNA-1273 (off-label use), the Sponsor's estimated number of myocarditis cases per 1 million 2nd doses of mRNA-1273 among adolescents is 46 (male and female combined) in the 12-17 years old age group. The data from FDA BEST for the Pfizer COVID-19 Vaccine indicates a risk for males 12-17 years comparable to the risk in males 18-25 years. However, the meta-analysis of BEST data for the Pfizer COVID-19 Vaccine reports excess cases per one million 2nd doses for 12–15-year-old males as 132.2 (95%CI: 92.0-189.6), and for 16-17-year-old males as 159.9 (95%CI: 59.9-414.3), while 95.6 (95%CI: 61.0-147.4) for 18-25-year-old males, which is higher than what was reported in Moderna's US PASS study.

For individuals 6-11 years, there is limited real-world data for mRNA-1273 vaccine from the US or non-US countries. Data from Israel (Israeli MOH) for the Pfizer COVID-19 Vaccine indicates a negligible risk as no cases were reported among 121,915 second doses administered in 5-11-year-olds compared to 59.0, 145.2, and 103.7 cases per one million doses among males ages 12-15 years, 16-19 years, and 20-24 years, respectively, within a 30-day risk window. US VAERS data (US-VAERS) for Pfizer COVID-19 Vaccine also suggests a similar pattern of lower myocarditis/pericarditis risk among 5-11 year-olds with 2.7 cases reported within a 0-7 days risk window per one million second doses administered, whereas 48.1, 74.2, 35.3 cases were reported per one million second doses in the 12-15 years, 16-27 years, and 18-24 years age groups, respectively. No myocarditis cases have been observed in children <12 years in the US PASS study.

For individuals 6 months through 5 years, there is limited real-world data for any mRNA COVID-19 vaccine from either US or non-US countries.

FDA and CDC have been continuously monitoring myocarditis/pericarditis risk through BEST, VSD and VAERS. Some evidence indicated potentially higher risk of myocarditis/pericarditis associated with the Moderna COVID-19 Vaccine compared to the Pfizer COVID-19 Vaccine among young adult males. Recent review of the available US and non-US data is inconclusive for evidence of risk difference for myocarditis between the two vaccines (Figure 6, Appendix C).

Risk of myocarditis/pericarditis is described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of myocarditis/pericarditis will be further evaluated as part of the PVP for the vaccine.

6.4 Uncertainties Related to Risks

Safety in certain subpopulations
There are currently insufficient data to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised individuals 6 months through 17 years. Safety data in children and adolescents previously infected with SARS-CoV-2 are limited; however, while available data indicate higher rates of some common adverse reactions, no safety concerns have been identified that would result in unfavorable benefit-risk in previously infected individuals.

Myocarditis/pericarditis
The risk of vaccine-associated myocarditis/pericarditis in individuals 6 months through 17 years, is described in Section 6.3 above. Remaining uncertainties related to vaccine-associated myocarditis/pericarditis include:

- Incidence in the age group of 6 months through 4 years, for which there is no real-world data available for any mRNA COVID-19 vaccine, and risk specific to mRNA-1273 in ages 5-11 years
- Risk after additional primary series or booster doses of the vaccine
- Long-term sequelae and outcomes in affected individuals
- Whether and to what extent subclinical cases might occur, and if so, the long-term outcomes
- Mechanism of pathogenesis of vaccine-associated myocarditis/pericarditis
- Individual factors conferring increased risk for vaccine-associated myocarditis/pericarditis.

Adverse events that are very uncommon or that require longer follow-up to be detected
Following authorization of the vaccine, use in large numbers of individuals 6 months through 17 years of age may reveal additional, potentially less frequent and/or more serious AEs not detected in the trial safety population of approximately 11,500 participants in pediatric age groups. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

7 VRBPAC Meeting Summary

The 174th meeting of the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) was held on June 14-15, 2022, to consider Moderna's requests to expand the authorization of the EUA for the Moderna COVID-19 Vaccine to include the pediatric age groups of 12 through 17 years, 6 through 11 years, and 6 months through 5 years. The first day of the meeting included presentations by staff from the Centers for Disease Control and Prevention on the current epidemiology of SARS-CoV-2 and COVID-19 in the United States, the efficacy of the current COVID-19 vaccines, and the safety of the currently authorized mRNA COVID-19 vaccines from active and passive surveillance in VSD and VAERS, respectively. FDA then presented an update on active surveillance data from the Biologics Effectiveness and Safety (BEST) System for myocarditis/pericarditis and other events of interest among individuals vaccinated with the mRNA COVID-19 vaccines. Subsequently, Moderna presented data from their ongoing pediatric studies in support of their EUA requests (age groups 12 through 17 years and 6 through 11 years on the first day and 6 months through 5 years on the second day), followed on each respective day by FDA's independent assessment of the data and a period for questions from committee members. Both meeting days included an Open Public Hearing.

In their discussions, committee members noted the limitations of clinical endpoint efficacy data for the two older age groups in that efficacy was assessed prior to emergence of the Omicron variant but generally agreed that the immunobridging data for each age group, along with available supportive efficacy data and post-authorization effectiveness data in adults, supported the benefits of the vaccine in pediatric populations. Committee members acknowledged that seroprevalence studies indicate prior infection in up to approximately 80% of individuals living in the US but also acknowledged available data indicating that vaccination following natural infection may improve protection against subsequent infection and serious outcomes. Committee members stressed the importance of data to support authorization of a third (booster) dose of Moderna COVID-19 Vaccine for pediatric age groups in the near future, based on available data overwhelmingly indicating the need for three doses of available mRNA vaccines to achieve more optimal protection against COVID-19 and serious outcomes caused by the Omicron variant. Committee members stressed the importance of post-authorization assessments of vaccine effectiveness in the setting of continually evolving epidemiology of the COVID-19 pandemic. Committee members also generally agreed that available safety data was

clearly favorable to support EUA in pediatric age groups but stressed the importance of continued post-authorization safety surveillance, in particular for myocarditis/pericarditis and for certain respiratory infections (RSV and pneumonia) in the youngest age group, for which imbalances of uncertain clinical significance were observed in the clinical trial, and febrile seizures given the rates of fever observed in the youngest age group. Some committee members encouraged Moderna to continue pediatric development of the vaccine with assessment of alternative dose levels or dosing intervals that could improve upon effectiveness or decrease the risk of myocarditis. Committee members also stressed the importance of generating data to inform the safety and effectiveness of concomitant use of the vaccine with other routine childhood vaccinations and expressed concern that the current lack of such data would be a barrier to successful vaccination campaigns.

Many committee members opined that authorization of the vaccine in pediatric age groups, supported by available data, would be important to providing patients and their caregivers choices in how to best protect themselves from COVID-19. Some committee members also expressed the importance of accurately communicating the relative risks of COVID-19 and expected benefits of vaccination for the age groups where risk of serious outcomes from COVID-19 is lower, while some committee members encouraged vaccination of all eligible children consistent with use of other preventive vaccines for diseases that cause similar morbidity and mortality as COVID-19, others felt strongly that use of COVID-19 vaccines should not be mandated for the youngest age group.

Following the committee discussion on the first day, the VRBPAC voted 22-0 in each of two separate votes in favor of determinations that the known and potential benefits of the Moderna COVID-19 Vaccine, when administered as a 2-dose series, outweighed the known and potential risks for use in adolescents 12 through 17 years of age and in children 6 through 11 years of age. Following the committee discussion on the second day, the VRBPAC voted 21-0 in favor of a determination that the known and potential benefits of the Moderna COVID-19 Vaccine, when administered as a 2-dose series, outweighed the known and potential risks for use in infants and children 6 months through 5 years of age.

8 Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the June 14-15, 2022 meeting, the review team concludes that:

- As summarized in Section 3 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, the Moderna COVID-19 vaccine, when administered as a 2-dose primary series to adolescents 12-17 years (100 µg each dose), children 6-11 years (50 µg each dose), and infants and children 6 months through 5 years (further divided into 6-23 months and 2-5 years; 25 µg each dose), may be effective in preventing serious or life-threatening disease or condition that can be caused by SARS-CoV-2. Vaccine effectiveness for all four pediatric age cohorts was inferred by immunobridging based on a comparison of SARS-CoV-2 neutralizing antibody (nAb) responses at 1 month after Dose 2 in participants in each age cohort (12-

17 years, 6-11 years, 2-5 years, 6-23 months) to the nAb responses generated by young adults 18-25 years of age, the most clinically relevant subgroup of the adult study population for whom vaccine efficacy was demonstrated in a clinical endpoint efficacy trial. Immunobridging success criteria were met for all four pediatric age cohorts. Immunogenicity outcomes were consistent across demographic subgroups, excepting higher post-vaccination neutralizing antibody titers among participants with evidence of prior SARS-CoV-2 infection. Additionally, descriptive analyses of VE against COVID-19 were assessed in all age cohorts. Using the CDC definition for the protocol-specified VE endpoint of COVID-19 cases starting 14 days after Dose 2, VE was 93.3% (95% CI 47.9, 99.9) for participants 12-17 years of age during an evaluation period when the ancestral strain (with D614G mutation), and then Alpha variant were predominant, 76.8% (95% CI -37.3, 96.6) for participants 6-11 years of age during an evaluation period when the Delta variant was predominant, and 36.8% (95% CI 12.5, 54.0) and 50.6% (95% CI 21.4, 68.6) for participants 2-5 years of age and 6-23 months of age, respectively, during an evaluation period when the Omicron variant was predominant. Estimates of VE for each age cohort were generally consistent with VE estimates from observational studies of a Moderna COVID-19 Vaccine two-dose primary series in adults during the same time periods.[74] Effectiveness of a third primary series dose in individuals 6 months through 17 years of age with certain kinds of immunocompromise is extrapolated from data in adults.

- Based on the data summarized in Section 4 and summary of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 17 years. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and expected reduction in the risk of severe COVID-19. Uncertainties related to benefits include the durability of effectiveness, effectiveness against newly emerging variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known risks include common local and systemic adverse reactions, notably injection site reactions and fever among all age cohorts, irritability/crying and sleepiness among participants 6-36 months and fatigue and headache among participants 37 months through 17 years, which were mostly mild to moderate and generally of short duration. Less common risks include lymphadenopathy, hypersensitivity reactions, and abdominal pain (in individuals 2-11 years). Although not reported in the clinical studies, events of vaccine-associated myocarditis/pericarditis and anaphylaxis are also known risks, with the expectation based on available data with mRNA COVID-19 vaccines that the risk of myocarditis will be highest in older adolescents but lower in younger adolescents and substantially lower in pre-adolescents. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up. A favorable benefit-risk balance for use of a third primary series dose in individuals 6 months through 17 years of age with certain kinds of immunocompromise is extrapolated from data in adults.

- As summarized in Section 2.2, Spikevax is FDA approved for active immunization for prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Comirnaty is the only FDA approved COVID-19 vaccine for use in individuals 16-17 years of age, and the Pfizer-BioNTech COVID-19 vaccine is authorized under EUA

but not yet approved for use in children and adolescents 5-15 years of age. No COVID-19 vaccine is currently available for use in infants and children below 5 years of age.

Based on the considerations outlined above, the review team therefore recommends issuance of an amendment to the EUA of the Moderna COVID-19 Vaccine to include use of a 2-dose primary series, administered 1 month apart, for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 17 years, as follows:

- 100 µg each dose for individuals 12 years through 17 years of age;
- 50 µg each dose for individuals 6 years through 11 years of age; and
- 25 µg each dose for individuals 6 months through 5 years of age.

The review team also recommends authorization of a third primary series dose, at the age-appropriate dose level as specified above and administered at least 4 weeks after the second primary series dose, for use in individuals 6 months through 17 years of age with certain kinds of immunocompromise (solid organ transplant recipients or individuals with conditions causing an equivalent level of immunocompromise).
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9 Appendix A. Adverse Events of Special Interest

Table 96. 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

Adverse Event	Additional Notes
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 Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/L) within 48 hours; OR Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR 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 3-fold elevation above the upper normal limit for ALT or AST OR >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 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 Multisystem inflammatory syndrome in children 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 (e.g., gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	Including but not limited to: Guillain-Barre syndrome Acute disseminated encephalomyelitis Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/encephalomyelitis Aseptic meningitis Febrile seizures Generalized seizures/convulsions Stroke (hemorrhagic and non-hemorrhagic) Narcolepsy
Anaphylaxis	Anaphylaxis as defined per protocol. Follow reporting procedures in protocol Section 7.4.5

Adverse Event	Additional Notes
Other syndromes	Fibromyalgia Postural orthostatic tachycardia syndrome Chronic fatigue syndrome (includes myalgic encephalomyelitis and post viral fatigue syndrome) Myasthenia gravis

10 Appendix B: COVID-19 Case Definitions

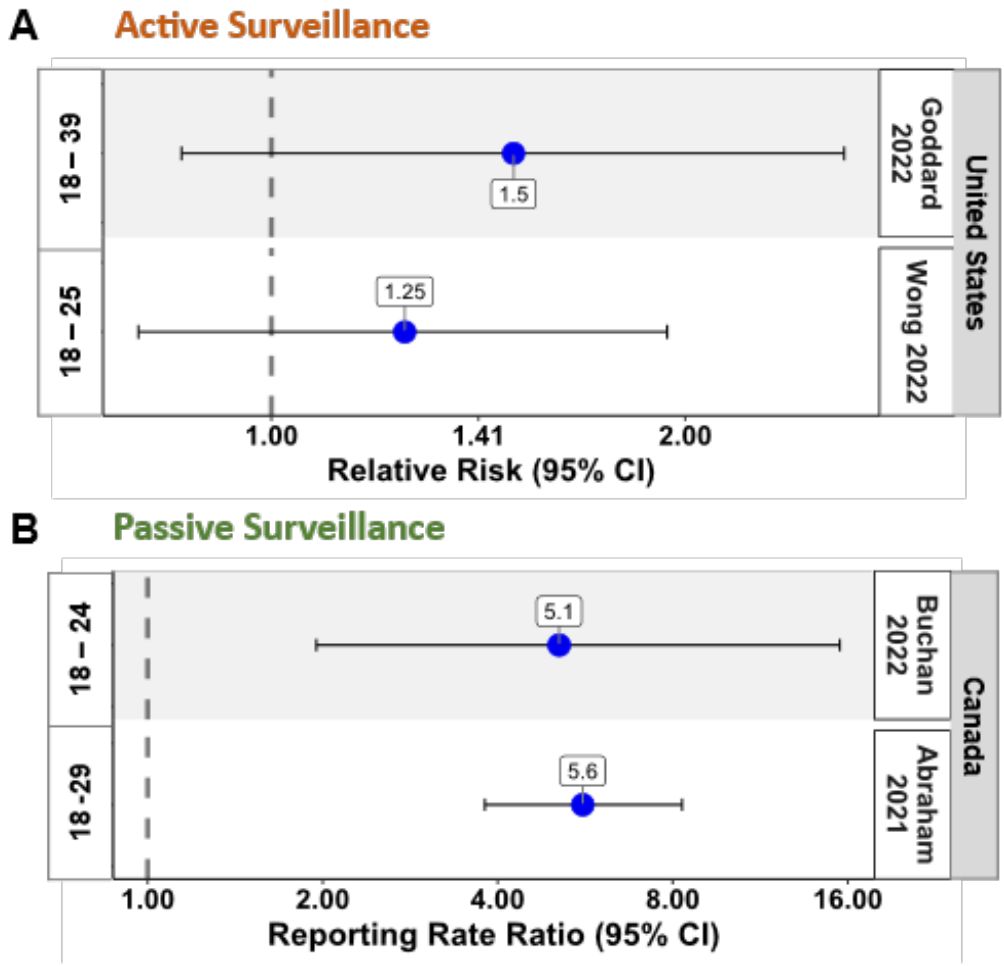
Table 97. COVID-19 and SARS-CoV-2 Infection Case Definitions in Study mRNA-1273-P204

Endpoint	Definition
COVID-19 based on CDC case definition	At least one of the following systemic symptoms post-baseline, starting 14 days after the first and second dose of IP: fever (temperature >38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours), cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (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 or vomiting, poor appetite or poor feeding, **AND** at least 1 nasal swab (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR
COVID-19 based on P301 case definition	A positive RT-PCR test result (by NP swab, nasal swab, or saliva sample [or respiratory sample, if hospitalized]) post-baseline, starting 14 days after the first and second dose of IP, together with eligible symptoms as follows: 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 ONE 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, starting 14 days after both the first and second dose of IP: bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by *Roche Elecsys*) post baseline, **OR** Positive RT-PCR post-baseline.
Asymptomatic SARS-CoV-2 infection	For participants with negative SARS-CoV-2 status at baseline, starting 14 days after both the first and second dose of IP: Absence of any COVID-19 symptoms, **AND** bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, **AND/OR** Positive RT-PCR test at scheduled or unscheduled/illness visits.

Source: Study P204 protocol amendment 7
Abbreviations: bAb=binding antibody; CDC=Centers for Disease Control and Prevention; IP=investigational product; NP=nasopharyngeal; RT-PCR=reverse-transcriptase polymerase chain reaction; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

11 Appendix C: Myocarditis Risk Assessment

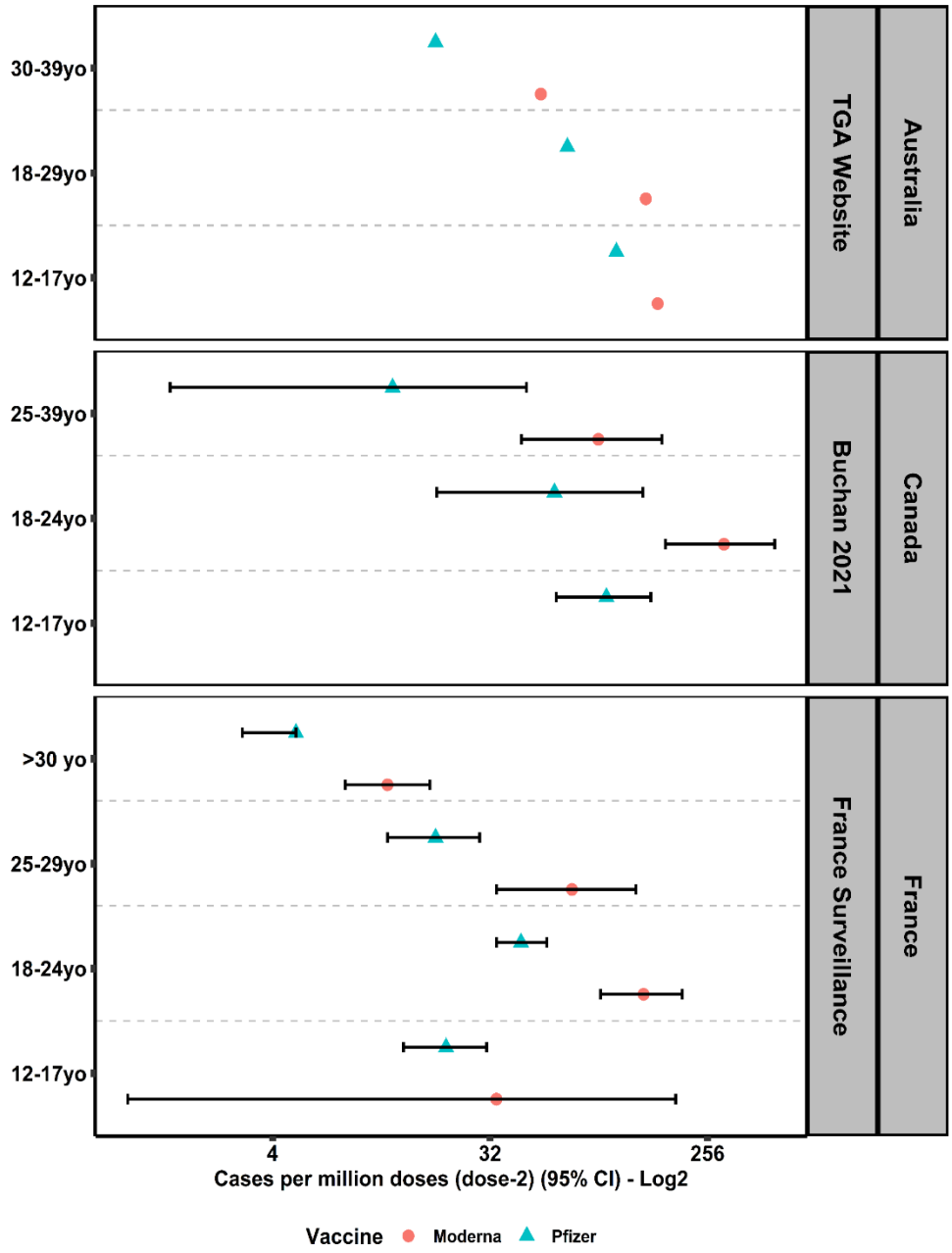
Figure 6. Risk of Myocarditis in Males After a Second Dose of Moderna vs Pfizer COVID-19 Vaccines



Source: FDA reviewer figure
Notes: Risk windows: Goddard et al. 0-7 days; Wong 1-7 days; Abraham 1-7 days; Buchan included all events reported following vaccination

Abraham N, et al. Myocarditis and/or pericarditis risk after mRNA COVID-19 vaccination: a Canadian head to head comparison of BNT162b2 and mRNA-1273 vaccines. *Vaccine* 2022 May 25.
Buchan SA., et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. *medRxiv* 2021 Jan 1.
Goddard K, et al. Risk of Myocarditis and Pericarditis Following BNT162b2 and mRNA-1273 COVID-19 Vaccination. (preprint) retrieved from https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4059218.
Wong HL, et al. Risk of Myocarditis/Pericarditis Following COVID-19 mRNA Vaccination in the United States.

Figure 7. Risk of Myocarditis in Males After a Second Dose of Moderna or Pfizer COVID-19 Vaccine, by Age Group



Source: FDA reviewer figure
Note: Cases include all reports following Dose 2, regardless of time since vaccination
Australia: Therapeutic Goods Administation (Australian Government). https://www.health.gov.au/sites/default/files/documents/2022/05/covid-19-vaccination-guidance-on-myocarditis-and-pericarditis-after-mrna-covid-19-vaccines.pdf
Canada: Buchan SA., et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. medRxiv 2021 Jan 1.
France: The National Agency for the Safety of Medicines and Health Products. https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf

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