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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073, Amendments 496, 503
Sponsor	ModernaTX, Inc
Submission Date	August 26, 2022 (EUA request for 12 years of age and older) September 1, 2022 (EUA request for 6 years through 11 years of age)
Receipt Date	August 26, 2022, and September 1, 2022.
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Review Completion Date	October 11, 2022
Established Name/Names used during development	Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Dosage Forms/Strengths and Route of Administration	A 0.25 mL suspension for intramuscular injection (for 6 years through 11 years of age) A 0.5 mL suspension for intramuscular injection (for 12 years through 17 years of age)
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Use: A single booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine
Intended Population	Individuals 6 through 17 years of age

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1 Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be an ongoing global health challenge, and as of October 4, 2022, has led to over 618 million cases of coronavirus disease 2019 (COVID-19), including 6.5 million deaths worldwide.[1] The Moderna COVID-19 Vaccine (also known as mRNA-1273) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral) Wuhan-Hu-1 SARS-CoV-2 strain. The Moderna COVID-19 Vaccine was initially authorized under Emergency Use Authorization (EUA) on December 18, 2020, for primary series vaccination of individuals 18 years of age and older and subsequently authorized for primary series vaccination of individuals 6 months-17 years of age. The vaccine was also previously authorized for booster vaccination of individuals 18 years of age and older; however, following emergence of the Omicron variant and its sublineages (most recently BA.4/BA.5) and observations of decreased vaccine effectiveness against Omicron sublineages compared to the original strain, formulations of the vaccine containing Omicron components were developed to improve vaccine effectiveness. Following a June 28, 2022, meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss potential changes to COVID-19 vaccine strain composition for use in future vaccination campaigns and subsequent discussions with World Health Organization (WHO) and other global regulatory authorities, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use as a booster dose potentially beginning in fall 2022. On August 31, 2022, FDA authorized the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 18 years of age and older, with concurrent revision of the authorization for the original (monovalent) Moderna COVID-19 Vaccine to no longer include use as a booster dose in individuals 18 years of age and older.

Evidence considered by FDA to support the August 31, 2022, authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) included:

- clinical safety and immunogenicity data in individuals ≥18 years of age from a study which evaluated a second booster dose of another bivalent vaccine, mRNA-1273.214, which contains original and Omicron BA.1 mRNA components and is manufactured by the same process as the original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5),
- safety and effectiveness data from clinical trials and observational studies which evaluated primary and booster (homologous and heterologous) vaccination with the original Moderna COVID-19 Vaccine (previously reviewed by FDA),
- post-marketing safety surveillance data with primary series and booster doses of the original Moderna COVID-19 Vaccine, and
- supportive non-clinical immunogenicity data from a study with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

While clinical data for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are not yet available, FDA determined that for purposes of this EUA it is reasonable to assess the effectiveness and the known and potential benefits and risks of this bivalent vaccine based primarily on extrapolation of data from another bivalent vaccine, mRNA-1273.214, manufactured by the same process and containing original and Omicron BA.1 components, and extensive experience to date with the original Moderna COVID-19 Vaccine. This extensive experience with the original vaccine also provides a basis for extrapolation to assess known and potential benefits and risks of Moderna COVID-19 Vaccine, Bivalent (Original

and Omicron BA.4/BA.5) as a booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose of any authorized or approved monovalent COVID-19 vaccine. Furthermore, this extensive experience with the original Moderna COVID-19 Vaccine primary series and booster doses supports extrapolation of clinical data with the bivalent (Original and Omicron BA.1) vaccine in adults ≥18 years of age to inform the effectiveness and benefits and risks of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine for use as a booster dose in younger age groups for which available data would have been sufficient to support authorization of the original Moderna COVID-19 Vaccine for use as a booster dose. In the current EUA request submission, Moderna has provided safety and effectiveness data from evaluation of a booster dose of the original Moderna COVID-19 Vaccine in individuals 6-17 years of age.

Clinical data on a booster dose of the original Moderna COVID-19 Vaccine (mRNA-1273) in individuals 6-17 years consist of safety and immunogenicity data from two ongoing Phase 2/3 studies, in which 1,364 participants 12-17 years of age (in Study P203) received a 50 µg booster dose of mRNA-1273 administered at least 5 months after completion of a 2-dose primary series (100 µg) of mRNA-1273, and 1,294 participants 6-11 years of age (in Study P204) received a 25 µg booster dose of mRNA-1273 administered at least 6 months after completion of a 2-dose primary series (50 µg) of mRNA-1273. Effectiveness of mRNA-1273 as a booster dose was inferred by immunobridging based on a comparison of SARS-CoV-2 neutralizing antibody (nAb) responses against the original (ancestral) strain at 28 days after the booster dose in each age cohort (adolescents 12-17 years and children 6-11 years) to the nAb responses generated after the 2-dose mRNA-1273 primary series in young adults 18-25 years from Study P301, the most clinically relevant population for whom vaccine efficacy was demonstrated in a clinical endpoint efficacy trial. For both pediatric age cohorts, the pre-specified immunobridging success criteria were met for the two co-primary endpoints of the geometric mean concentration (GMC) ratio and difference in seroresponse rates (SRR). Immunogenicity outcomes were generally consistent across demographic subgroups. Participants with evidence of prior SARS-CoV-2 infection pre-booster had numerically higher post-booster nAb GMCs compared to those among participants without evidence of prior SARS-CoV-2 infection pre-boost.

An analysis of the safety data for the 12-17 years age group (a median duration of follow-up of 116 days post-booster dose through the data cutoff of May 16, 2022) and for the 6-11 years age group (a median duration of follow-up of 29 days post-booster dose through the data cutoff of May 23, 2022) revealed no new safety concerns. Solicited local and systemic reactions among booster dose recipients 6-17 years were mostly mild to moderate in severity and generally of short duration. The most common solicited adverse reactions after a booster dose in both pediatric age cohorts were pain at the injection site (90.1%-91.2%), fatigue (48.9%-58.7%), and headache (38.2%-57.1%). Numerically, a lower proportion of participants with evidence of prior SARS-CoV-2 infection pre-booster reported solicited local and systemic adverse reactions compared to participants without evidence of prior SARS-CoV-2 infection pre-booster. As of the data cutoffs, there were no cases of myocarditis or pericarditis reported among booster recipients in either age cohort. Among booster recipients 6-17 years, there was one serious event of abdominal pain occurring 16 days post-booster dose in a 7-year-old that FDA considers potentially related to study vaccination, though a plausible alternative etiology exists.

Post-marketing safety data for the original Moderna COVID-19 Vaccine are relevant to the safety evaluation of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) because the vaccines are manufactured using the same process. As of September 14, 2022, more than 230 million doses of the original Moderna COVID-19 Vaccine have been

administered in the US, including 46,056,042 first booster doses and 11,441,286 second booster doses. Of the total doses given in the US, 322,368 have been administered to individuals 6 through 17 years of age. There have been 618,265 doses of Moderna COVID-19, Bivalent administered to adults age 18 years and older (data lock point September 14, 2022). In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain. For important risks identified in the pharmacovigilance plan for Moderna COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis remain identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/post-marketing studies for the original Moderna COVID-19 Vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor will also conduct planned post-authorization studies to evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in all ages in the general US population.

The totality of scientific evidence available at this time supports the conclusion that a booster dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6-17 years of age, when administered at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine, may be effective and that the known and potential benefits outweigh the known and potential risks. Therefore, the review team recommends authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use in individuals 6-17 years of age as a single booster dose (12-17 years: 50 µg; 6-11 years: 25 µg) administered at least 2 months after either completion of a primary series or previous booster dose with an authorized or approved monovalent COVID-19 Vaccine.

2 Background

2.1 SARS-CoV-2 Virus and COVID-19

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 variable respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions,[2] may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome, leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks but symptoms may persist for months in some individuals.[3] 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.[4,5] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[4] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.[6,7] However, COVID-19-associated hospitalizations and deaths have occurred in individuals 17 years of age and younger, and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 4, 2022, has led to over 618 million cases of COVID-19 and 6.5 million deaths worldwide.[1] In the US, more than 96 million cases and 1 million deaths have been reported to

the Centers for Disease Control and Prevention (CDC).[8] Approximately 14% of cases occurred in children and adolescents 5 through 17 years of age.[9]

Since the start of the pandemic caused by the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as the ancestral, original, or reference strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron (B.1.1.529). The Omicron variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including the recent BA.4 and BA.5 sublineages, which account for nearly all reported COVID-19 cases in the US currently, that have been associated with recent increases in COVID-19 case rates.[10] In addition, population-level evidence suggests an increased reinfection risk associated with the Omicron variant and its sublineages compared to earlier SARS-CoV-2 variants.[11] Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see Section 3.1 below). Consequently, a booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages is an important public health need.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, and/or BA.5 lineage, as specified.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1 Spikevax, Moderna COVID-19 Vaccine, and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-dose primary series 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 (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a: 2-dose primary series for individuals 6 months of age and older, and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 18 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years old and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 18 years of age and older is 50 µg in 0.5 mL. Safety

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

2.2.2 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine, and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: 3-dose primary series for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, and a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. The Pfizer-BioNTech COVID-19 vaccine is also authorized as a first booster dose in individuals 5-11 years of age and older, to be administered at least 5 months after completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 12 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series and booster doses is specified for the age group in which the vaccine is being administered: 3 µg in 0.2 mL (primary series only) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 11 years of age, and 30 µg in 0.3 mL for 12 years of age and older. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are detailed in the decision memoranda available on the FDA website.

2.2.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to prevent COVID-19 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). The safety and effectiveness data supporting authorization for the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the FDA website.

2.2.4 Novavax COVID-19 Vaccine

The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.5 Therapies for COVID-19

The antiviral Veklury (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.

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 include the following:

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.

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 extracorporeal membrane oxygenation (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 COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

3 Rationale for Bivalent Booster Doses

3.1 Post-authorization Effectiveness Data Against Clinically Relevant SARS CoV-2 Variants

While the currently authorized and approved COVID-19 vaccines in the US are based on the original SARS-CoV-2 strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.[12,13,14,15,16,17,18,19,20,21,22]

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness

against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.[12,13,14] Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[12,13,14,15] observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization[12,16,17,18] and lower effectiveness among the immunocompromised individuals.[20] In Israeli experience with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older, a second booster dose improved VE overall (including a reduction in mortality), although effectiveness against mild disease decreased during a 10-week follow-up period.[21,22]

3.2 June 28th VRBPAC and Subsequent Regulatory Discussions

On June 28, 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see FDA website for background materials). The committee heard presentations on the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants in the United States and COVID-19 vaccine effectiveness (CDC) and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition were also presented (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the US. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

Following the VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and to discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see ICMR website for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as it is currently unknown which strains will be circulating in the future.

On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent booster vaccine (Original and Omicron BA.4/BA.5) to improve protection during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent (Original and Omicron BA.4/BA.5) vaccine in relevant populations. FDA recognized that data in trial participants who would receive the bivalent (Original and Omicron BA.4/BA.5) vaccine would potentially not be available prior to the optimal timeframe for deployment of the vaccine in a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered that it may be appropriate to issue an Emergency Use

Authorization of a bivalent (Original and Omicron BA.4/BA.5) vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine (Original and Omicron BA.1), plus supportive pre-clinical animal data for the recommended bivalent vaccine (Original and Omicron BA.4/BA.5), as well as data from use of already-authorized vaccines. Section 5.2 of this memo provides FDA considerations for this approach, which underlay EUA of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) on August 31, 2022, for use as a single booster dose in individuals 18 years of age and older.

4 Regulatory Considerations for an Omicron Booster EUA

4.1 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 United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met [section 564 of the FD&C Act (21 USC. 360bbb-3)].

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, 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 authorize 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 known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

4.2 FDA Guidance for Industry Related to COVID-19 Vaccines, Including Modified COVID-19 Vaccines

Appendix 2 of the FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (originally issued in October 2020 and last updated March 2022) discusses an approach to CMC, nonclinical and clinical data to support the safety and effectiveness of a modified vaccine to address emerging SARS-CoV-2 variants. Although the approach outlined in Appendix 2 does not specifically address considerations for multivalent modified vaccines, the approach and associated immunogenicity endpoints and analyses for supporting vaccine

effectiveness are relevant to bivalent modified vaccines. In discussions with COVID-19 vaccine manufacturers, FDA has advised that effectiveness of a bivalent (original and Omicron variant) vaccine should be supported by immunobridging analyses demonstrating: 1) statistically superior neutralizing geometric mean titers (GMTs) against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 2) statistically non-inferior neutralizing antibody seroresponse rates against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 3) statistically non-inferior neutralizing antibody GMTs against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine; and 4) statistically non-inferior neutralizing antibody seroresponse rates against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine. FDA also advised vaccine manufacturers that, as discussed in the guidance document for monovalent modified vaccines, safety data to support EUA of a modified bivalent vaccine should include analyses of adverse events collected during the immunogenicity evaluation period. While the guidance encouraged clinical evaluation of modified vaccines across different age groups, the guidance also indicates that extrapolation of data accrued in one age group to support EUA of a modified vaccine in other age groups could be considered.

5 EUA Amendment Request for the Bivalent Moderna COVID-19 Vaccine Booster Dose for Individuals 6-17 Years of Age

5.1 Summary of the EUA Request

On August 26, 2022 and September 1, 2022, Moderna submitted requests to amend the EUA to include use of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 12-17 years of age and 6-11 years of age, respectively, as a single booster dose after either completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. For individuals 12 years and older, each 50 µg dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is formulated to contain 25 µg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized spike (S) protein of the original SARS-CoV-2 strain and 25 µg of mRNA encoding the S protein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical. For individuals 6-11 years, each 25 µg dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains half of the mRNA components included in each 50 µg dose.

The EUA amendment request is based on:

- Extrapolation of clinical trial data that supported the previous authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA/5) for use in individuals 18 years of age and older,
- Clinical trial data with the original (monovalent) Moderna COVID-19 Vaccine used as a primary series and booster dose in individuals 6-17 years of age, and
- Product quality and manufacturing information for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA/5) presentation intended for use in individuals 6-years of age and older.

5.2 FDA Approach to Extrapolation from Available Clinical Data

Due to the rapid evolution of SARS-CoV-2 virus variants, including the currently predominant

circulating Omicron sublineages, improved protection for the upcoming winter season could be achieved with expeditious authorization and deployment of modified COVID-19 vaccines, for use as booster doses, that are more closely antigenically matched to currently circulating SARS- CoV-2 than the currently authorized COVID-19 vaccines. The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized under EUA for use as a booster dose in individuals 18 years of age and older based on the totality of evidence, as summarized below and reviewed in detail in the August 31, 2022 FDA Decision Memorandum, indicating that an improved booster dose antibody response to SARS-CoV-2 Omicron sublineages, and therefore the potential for improved vaccine effectiveness results from inclusion of an Omicron component in the vaccine, together with the original (ancestral/reference) component, as a bivalent formulation.

Authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was based on extrapolation of available immunogenicity and safety data from a clinical trial that evaluated the bivalent (Original and Omicron BA.1) vaccine formulation in individuals ≥18 years of age who received the bivalent vaccine (N=437) or original (monovalent) vaccine (N=377) as a second booster dose and who were followed for a median of 1.5 and 2.0 months, respectively. These data demonstrated that: 1) neutralizing antibody responses against Omicron BA.1 elicited by the bivalent (Original and Omicron BA.1) vaccine formulation were statistically superior compared to those elicited by the original (monovalent) mRNA-1273 vaccine; 2) neutralizing antibody responses against the reference strain (D614G) elicited by the bivalent (Original and Omicron BA.1) vaccine formulation were statistically non-inferior to those elicited by the original (monovalent) mRNA-1273 vaccine; and 3) the reactogenicity profile of the bivalent booster dose was similar to that of the original (monovalent) booster dose, and no new safety signals were identified in the clinical trial.

Extrapolation of these data to support authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was considered in the context of the totality of available evidence, which included:

- Extensive knowledge of the safety and efficacy of the mRNA COVID-19 vaccine platform;
- Safety, immunogenicity, efficacy, and observational effectiveness data from the original (monovalent) Moderna COVID-19 Vaccine (mRNA-1273); and
- Immunogenicity data from two other bivalent vaccine candidates manufactured using the same process as mRNA-1273 (containing Original and Beta mRNA components and Beta and Delta mRNA components, respectively), which are not reviewed in detail in the August 31, 2022 FDA Decision Memorandum but which, as reported by the Sponsor and as similar to the data for the bivalent (Original and Omicron BA.1) vaccine reviewed in the aforementioned memorandum, showed statistically significant increases in neutralizing antibody GMTs, as compared to the original mRNA-1273 vaccine, to the variant components included in the modified vaccines.

Together, these data informed FDA's assessment of the effectiveness and the known and potential benefits and risks of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Moderna COVID-19 Vaccine, FDA determined that it was reasonable to extrapolate the available safety, efficacy, immunogenicity, and real-world evidence supporting a favorable benefit-risk balance for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk

balance for use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a single booster dose (including for individuals who previously received primary vaccination and two booster doses) at least 2 months after either completion of primary vaccination or the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. While the available clinical safety and immunogenicity data with the bivalent (Original and Omicron BA.1) vaccine booster dose reflected a median interval of 4.9 months (range: 3.1-14.6 months) after the previous COVID-19 vaccine dose, authorization of a minimum interval of 2 months for booster vaccination with Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was also based on extrapolation of data from a published study with mRNA-1273 boosters evaluating shorter intervals between the primary series and booster doses, along with clinical experience in immunocompromised individuals who received third primary series doses within 1 to 2 months of the second primary series dose.[23]

As mentioned in Section 4.2 above, FDA considers that safety and effectiveness data for a bivalent COVID-19 vaccine accrued in a certain age group could be extrapolated to support emergency use authorization in other age groups. Accumulated experience with mRNA COVID-19 vaccines has demonstrated that while some differences in safety profile and magnitude of neutralizing antibody responses are apparent across various age groups, the relationship between safety profile of and neutralizing antibody response to primary series doses as compared to booster doses has been very similar across age groups. FDA therefore considers that it is reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine booster dose to any age group for which available evidence has supported (or would support) emergency use authorization of a booster dose of any COVID-19 vaccine manufactured by the same process as the bivalent vaccine. In the case of the Moderna COVID-19 Vaccine, the original (monovalent) vaccine has been authorized under EUA for use as a booster dose in individuals 18 years of age and older, and the data package submitted with the current EUA request would have supported the authorization of the original (monovalent) vaccine as a booster dose in individuals 6 through 17 years of age, if there was not a more favorable benefit/risk balance anticipated for the bivalent vaccine. Thus, FDA considers that it is reasonable to extrapolate safety and effectiveness data with bivalent (Original and Omicron BA.1) vaccine accrued in individuals ≥18 years of age to support EUA of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 years of age and older. Manufacturing and product quality information sufficient to support an EUA for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) presentation intended for use in individuals 6 years of age and older was previously reviewed in the August 31, 2022 FDA Decision Memorandum.

Finally, FDA considered that it was reasonable to extrapolate the totality of clinical experience with administration of heterologous booster doses to support authorization of a bivalent mRNA COVID-19 vaccine booster dose following primary vaccination with the Novavax COVID-19 Vaccine, Adjuvanted (authorized for use in individuals 12 years of age and older). Published literature and data submitted to the agency by the respective sponsors regarding the safety and immunogenicity of the heterologous boosting with various COVID-19 vaccines[23] indicate: 1) heterologous primary series or booster doses provide similar vaccine effectiveness to homologous regimens; 2) heterologous schedules with mRNA and vectored vaccines show similar or more robust immunogenicity compared with homologous schedules; and 3) limited safety data for heterologous schedules have generally shown similar to transiently increased reactogenicity compared with homologous regimens.[24]

6 FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Clinical Studies

Data to support the EUA amendment requests are from three ongoing clinical studies summarized below. 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 booster vaccine effectiveness in adolescents (12 through 17 years) and children (6 through 11 years) via immunobridging analyses which required demonstration of non-inferiority of neutralizing antibody GMCs and SRRs after booster vaccination in each pediatric age group compared to after the primary series in young adults.

Study mRNA-1273-P203 is an ongoing multi-center, multi-part study evaluating the safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents 12-17 years of age. Part 1A of P203 was a randomized, placebo-controlled, double-blinded study in which 3,732 participants 12-17 years were randomized 2:1 to receive 2 doses of either 100 µg of mRNA-1273 or placebo on Day 1 and Day 29. Data from this part of the study informed the EUA of mRNA-1273 primary series in individuals 12-17 years and are described in the EUA Clinical Review Memorandum dated 16 June 2022. Following the authorization of an alternate COVID-19 vaccine for use in this age group, the study transitioned to Part 1B, an open-label, cross-over phase to allow placebo recipients from Part 1A to receive active study vaccination. Part 1C-1 was an open-label phase to evaluate the safety and immunogenicity of a 50 µg booster dose of mRNA-1273 in participants from Part 1A and Part 1B who completed the 2-dose primary series (100 µg, 1 month apart) at least 5 months prior. Additional parts added to the P203 study protocol evaluated mRNA-1273 as a heterologous booster (Part 1C-2) and a 50 µg primary series (Part 2); however, data are not yet available from these parts of the study. In the context of this EUA submission, only Part 1C-1 of Study P203 will be presented.

Study P204 is an ongoing Phase 2/3 study to evaluate the safety, 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 was the open-label, dose-escalation, age de-escalation phase; Part 2 is the randomized, observer-blind, placebo-controlled expansion phase evaluating the selected dose for each age group (50 µg for 6-11 years and 25 µg for 6 months-5 years); and Part 3 is the open-label assessment of a lower dose (25 µg) primary series regimen in children 6 years through 11 years (including a pre-planned third dose). Following the emergence of the Omicron variant and suggested improved protection in adults following a mRNA-1273 booster dose (BD), protocol amendment 7 to Study P204 (dated 18 Feb 2022) introduced an optional mRNA-1273 booster dose 6 months following dose 2 of the primary series for all Part 1 participants and for Part 2 participants 6 through 11 years of age. This EUA submission pertains only to the safety and immunogenicity analyses of data collected from children 6 years through 11 years of age (6-11 years) enrolled in the optional 25 µg mRNA-1273 booster dose portion of P204 who had completed the 2-dose primary series (50 µg, 1 month apart) at least 6 months prior. The designs of the primary series portions of Part 1 and Part 2 of the study are described in the EUA Clinical Review Memorandum dated 16 June 2022.

Table 1. Ongoing Clinical Studies Used to Support Emergency Use Authorization Request of Moderna COVID-19 Vaccine, Bivalent in Individuals 6 Years Through 17 Years

Study Number	Description	mRNA-1273 Age Cohort 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 primary series** 18-25 years* 295
P203	Phase 2/3 randomized, placebo-controlled study to evaluate safety, reactogenicity, and effectiveness of mRNA-1273 in healthy adolescents ages 12-17 years	**50 µg booster dose** 12-17 years 1,364
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	**25 µg booster dose** 6-11 years 1,294

*Immunobridging comparator group

6.2 Study P301: Adults 18 Years of Age and Older

Study P301 is a 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 memorandum for Spikevax on the FDA website.

6.3 Study P203 Part 1C-1: Adolescents 12 Years through 17 Years of Age

6.3.1 Study Design

Part 1C-1 of Study P203 was an open-label phase to evaluate the safety and immunogenicity of a 50 µg booster dose of mRNA-1273 in participants 12-17 years (adolescents). Participants 12-17 years who completed a 2-dose primary series of mRNA-1273 (100 µg dose administered 28 days apart) in Part 1A or Part 1B of P203 were offered a 50 µg booster dose at least 5 months after completion of the primary series. Enrollment in Part 1C-1 began in November 2021.

Vaccine effectiveness was inferred from an immunobridging evaluation comparing 50 µg post-booster dose immune responses of adolescents in Study P203 to the immune response post-primary series of young adults 18-25 years of age from Study P301 (a clinically relevant subgroup of the study population in whom VE has been demonstrated). Immunobridging success required demonstration of non-inferiority (in adolescents after a booster dose compared to young adults after primary series doses) of two measures of immunogenicity as measured by pseudovirus neutralizing antibodies (nAb) against SARS-CoV-2: geometric mean concentration (GMC) and seroresponse rate (SRR).

6.3.1.1 Evaluation of immunogenicity for Part 1C-1

Immunogenicity analyses for the booster phase were based on neutralizing antibody (nAb) concentrations measured using a validated pseudovirus neutralization assay against the ancestral strain (D614G form of the USA-WA1/2020 Wuhan strain) conducted at (b) (4) (b) (4) Neutralizing antibody concentrations were measured in both the group of adolescent booster dose recipients in P203 Part 1C-1 and the P301 comparator group of young adults. Neutralizing antibody (nAb) levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses. This differed from the Duke pseudovirus neutralization assay used previously for other parts of P203 and Study P301 which reported results as 50% inhibitory dose (ID50) neutralization titers. Details regarding the assay are provided in Section 7.1. The co-primary immunogenicity objectives were to demonstrate the non-inferiority of nAb GMCs against the ancestral strain (D614G) in adolescent (12-17 years) mRNA-1273 50 µg booster dose recipients compared to young adult (18-25 years) mRNA-1273 100 µg 2-dose primary series recipients, at 28 days post-booster and 28 days post-Dose 2 of primary series, respectively. The protocol specified success criteria for the co-primary endpoints were:

Co-primary endpoint 1: GMC

The GMC ratio (adolescent booster/young adult primary series) is non-inferior if the lower bound (LB) of the 95% confidence interval (CI) ≥ 0.67 and the GMC ratio point estimate ≥0.8.

Co-primary endpoint 2: SRR

The difference in the SRRs (adolescent booster minus young adult primary series) is non-inferior if the LB of the 95% CI ≥-10%.

Seroresponse was defined in the protocol as a change from pre-Dose 1 for young adult 2-dose primary series recipients and adolescent booster dose recipients, and includes the following:

- Seroresponse for participants with pre-Dose 1 < LLOQ is defined as ≥ 4 x LLOQ,
- Seroresponse for participants with pre-Dose 1 ≥ LLOQ is defined as ≥ 4-fold increase in concentration compared to pre-Dose 1

The protocol specified analyses sets for immunogenicity are listed in Table 2 below. The Per Protocol Immunogenicity Subset- Pre-booster SARS-CoV-2 Negative (PPIS-Neg) was used for the analyses of the co-primary immunogenicity endpoints.

Table 2. Immunogenicity Analysis Populations, Study P203, Part 1C-1

Population	Description
Full Analysis Set (FAS)	All participants who received a booster dose in Part 1C-1.
Immunogenicity Subset	A subset of participants in the FAS selected for immunogenicity testing with: • baseline (pre-Dose 1 of Part 1A) SARS-CoV-2 status available • pre-booster SARS-CoV-2 status available • have baseline (pre-Dose 1 of Part 1A) and at least 1 post-booster antibody assessment for the analysis endpoint.
Per-protocol (PP) Immunogenicity Subset	All participants in the PP immunogenicity subset who: • received 2 doses of mRNA-1273 in Part 1A per schedule • received a booster dose in Part 1C-1 • had a negative RT-PCR 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 (pre-Dose 1 of Part 1A) • had booster dose Day 29 (occurring between 21 and 42 days after booster dose vaccination) antibody assessment for the analysis endpoint • had no major protocol deviations that impact key or critical data.

Population	Description
PP Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative (PPIS-Neg)	Participants who are in PP Immunogenicity Subset (Part 1C-1) and are pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster).

Source: Reviewer-generated table adapted from Study protocol P203 Amendment 4, Section 8.4, Table 6, and P203 Statistical Analysis Plan

6.3.1.2 Evaluation of efficacy

Study P203 Part 1C-1 did not include formal assessment of vaccine efficacy. However, participants were actively monitored for potential COVID-19 cases throughout the study. Any confirmed symptomatic SARS-CoV-2 infection in a participant is captured as a medically attended adverse events (MAAE) along with relevant concomitant medications and details about severity, seriousness, and outcome.

6.3.1.3 Evaluation of safety

The primary safety objective for Part 1C-1 was to describe the safety and reactogenicity of a 50 µg booster dose of mRNA-1273 when administered at least 5 months following completion of the primary series. All participants recorded solicited local and systemic reactions and antipyretic/pain medication usage from Day 1 through Day 7 after the booster dose in an e-diary. Unsolicited AEs were collected through 28 days after booster dose. MAAEs, serious adverse events (SAEs), and adverse events of special interest (AESIs), including any suspected cases of myocarditis and/or pericarditis, will be collected through the entire study period of up to 12 months after the booster dose. AEs leading to discontinuation from study participation post-booster will be recorded through the last day of study participation.

An independent Cardiac Event Adjudication Committee (CEAC), consisting of pediatric and adult cardiologists, evaluated suspected cases of myocarditis, pericarditis, or myopericarditis based on the CDC working case definition.

The protocol specified analyses sets for safety are listed in Table 3 below.

Table 3. Safety Analysis Populations, Study P203, Part 1C-1

Population	Description
Safety Set	All participants who received a booster dose in Part 1C-1. Used for analysis of safety except for solicited ARs.
Solicited Safety Set	All participants who received a booster dose in Part 1C-1 and had at least 1 post-booster solicited adverse reaction assessment. Used for the analyses of solicited ARs.

Source: Reviewer-generated table adapted from Study protocol P203 Amendment 4, Section 8.4, Table 6, and P203 Statistical Analysis Plan

6.3.2 Participant Disposition and Demographics and Other Baseline Characteristics

6.3.2.1 Inclusion in analysis populations

As of the data cutoff of May 16, 2022, a total of 1,364 participants received a booster dose in Part 1C-1, 1,346 of whom received their primary series in Part 1A and 18 of whom received their primary series during the Part 1B cross-over phase.

6.3.2.2 Participant disposition

Disposition of P203 Part 1C-1 participants who contributed to the immunogenicity and safety analyses are presented below in Table 4. Discontinuation was rare and occurred in 0.8% of participants in this phase of the study. 4 participants discontinued from the study due to being lost to follow up, 6 participants withdrew consent (mostly due to logistical challenges and compliance with protocol procedures), and 1 participant discontinued due to a personal conflict interfering with study visits.

From the Full Analysis Set of P203 Part 1C-1, 372 participants were included in the Immunogenicity Subset. There was a higher percentage of participants found to have positive pre-booster SARS-CoV-2 status (13.7%) compared to positive pre-primary series SARS-CoV-2 status (3.8%).

Table 4. Disposition of Participants 12-17 Years in Study P203, Part 1C-1, All Enrolled

Disposition	12-17 Years mRNA-1273 50 µg Booster Dose n (%)
Full Analysis Set[a]	**N=1364**
Discontinued from study[b]*	11 (0.8)
Reason for discontinuation of study[b]	--
Lost to follow up[b]	4 (0.3)
Withdrawal of consent by participant[b]	6 (0.4)
Other*	1 (<0.1)
Safety Set[b,c]	**N=1364**
Solicited Safety Set[b,d]	1312 (96.2)
Immunogenicity Subset[e]	**N=372**
PP Immunogenicity Subset[f,g]	327 (87.9)
Excluded from PP Immunogenicity Subset	45 (12.1)
Reason for exclusion from the PP Immunogenicity Subset	--
Positive baseline SARS-CoV-2 status in Part 1A	14 (3.8)
Had no Immunogenicity data at BD-Day 29	26 (7.0)
Had no Immunogenicity at BD-Day 1	5 (1.3)
PP Immunogenicity Subset-Pre-booster SARS-CoV-2 Negative (PPIS-Neg)[f,h]	257 (69.1)
Excluded from PPIS-Neg	70 (18.8)
Reason for exclusion from PPIS-Neg	
Positive pre-booster SARS-CoV-2 status	51 (13.7)
Missing pre-booster SARS-CoV-2 status	19 (5.1)

Source: EUA 27073. Amendment 496, P203, Part 1C-1, Tables 14.1.1.1.5, 14.1.2.1.5, and 14..1.2.7.1
Abbreviations: BD = booster dose; COVID-19=coronavirus disease 2019; mITT=modified intent-to-treat; PP=per-protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2.
a. The FAS consists of all participants who received at least 1 BD in Part 1C-1.
b. Percentages are based on the number of subjects in the Full analysis Set in Part 1C-1
c. The Safety Set consists of all participants who received a BD in Part 1C-1.
d. The Solicited Safety Set consists of all participants who received BD in Part 1C-1, and contributed any solicited AR data (i.e., had at least 1 post-booster solicited safety assessment in Part 1C-1). Percentages are based on the number of subjects in Safety Set
e. The Immunogenicity Subset consists of a subset of participants in the FAS for Part C who had baseline SARS-CoV-2 status available and had pre-booster SARS-CoV-2 status available, and had baseline (pre-Dose 1) and at least 1 post-booster ant body assessment for the analysis endpoint.
f. The PP Immunogenicity Subset consists of all participants in the Immunogenicity Subset for Part 1C-1 who met all of the following criteria: received 2 doses of mRNA-1273 in Part 1A per schedule; received BD in Part 1C-1; 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 (pre-dose 1 of Part 1A); had BD-Day 29 (occurring between 21 and 42 days after BD vaccination) antibody assessment for the analysis endpoint; and had no major protocol deviations that impacted key or critical data.
g. Percentages are based on the number of subjects in the Immunogenicity Subset in Part 1C-1
h. The PP Immunogenicity Pre-booster SARS-CoV-2 Negative Subset consists of participants who are in the PP Immunogenicity Subset (Part 1C-1, BD), and are pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster), ie, RT-PCR result was not positive if available at BD-Day 1 and a negative bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on or before BD-Day 1.

*This participant withdrew due to a personal conflict interfering with the study schedule

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

Participants 12-17 years of age who previously received the primary series of mRNA-1273 in Part 1A or Part 1B of the study began enrollment into Part 1C-1 of the study in November 2021. At the time of the data lock point (May 16, 2022), the median duration of follow up was 116 days post-booster dose. The duration of follow-up was ≥ 56 days post-booster dose for 94.6% of participants and ≥ 28 days post-booster dose for 97.4% of participants.

6.3.2.4 Demographics and other baseline characteristics

The PPIS-Neg, which contributed to the co-primary endpoints for the study, consisted of 257 adolescent participants who received mRNA-1273 primary series and booster in Study P203 and 295 young adult participants who received the primary series of mRNA-1273 in Study P301 (Table 5). In the adolescent population, 17.5% were 16-17 years of age and 82.5% were 12-15 years of age. Both sexes were equally represented among both age groups. Adolescent participants from P203 were less racially and ethnically diverse compared to the participants in the P301 study with less than 22.6% of participants from P203 belonging to communities of color (non-white and/or Hispanic) compared to 50.5% of participants from P301. There was a lower percentage of participants from P203 who were obese as compared to those from P301. In the PPIS-Neg for participants 12-17 years, the median duration between Dose 2 of primary series to receipt of the booster dose (BD) was 295 days.

Table 5. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age (Study P203 Part 1C-1; PPIS-Neg) and 18 Through 25 Years of Age (Study P301; Per-Protocol Immunogenicity Subset)

Characteristics	P203 12-17 years mRNA-1273 50 µg Booster Dose N=257	P301 18-25 years mRNA-1273 100 µg Primary Series N=295
Sex, n (%)	--	--
Female	126 (49.0)	152 (51.5)
Male	131 (51.0)	143 (48.5)
Age (Years)	--	--
Mean (SD)	13.9 (1.5)	22.4 (2.2)
Median	14.0	23.0
Age Group, n (%)	--	--
≥12 to <16 years	212 (82.5)	--
≥16 to <18 years	45 (17.5)	--
Race, n (%)	--	--
White	225 (87.5)	206 (69.8)
Black	4 (1.6)	29 (9.8)
Asian	9 (3.5)	30 (10.2)
American Indian or Alaska Native	0	3 (1.0)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
Multiracial	15 (5.8)	14 (4.7)
Other	3 (1.2)	8 (2.7)
Not reported	1 (0.4)	3 (1.0)
Ethnicity, n (%)	--	--
Hispanic or Latino	32 (12.5)	77 (26.1)
Not Hispanic or Latino	223 (86.8)	216 (73.2)
Not reported	2 (0.8)	0
Unknown	0	2 (0.7)

Characteristics	P203 12-17 years mRNA-1273 50 µg Booster Dose N=257	P301 18-25 years mRNA-1273 100 µg Primary Series N=295
Race and Ethnicity Group[a]	--	--
White non-Hispanic	199 (77.4)	146 (49.5)
Communities of Color	58 (22.6)	149 (50.5)
Obesity[b], n (%)	--	--
Obese	46 (17.9)	67 (22.7)
Non-Obese	211 (82.1)	227 (76.9)
Missing	0	1 (0.3)
Time Since Primary Series Dose 2 to Booster	--	--
Median (Days) (min, max)	295.0 (290.0, 307.0)	--

Source: EUA 27073. Amendment 496,, P203, Tables 14.1.3.14.3, and 14.1.6.5.2
Abbreviations: BD=booster dose; kg=kilograms; m^2=meters squared; min=minimum; max=maximum; N=total number of participants in the analysis set; n=number of participants fulfilling the item; PPIS-Neg= Per Protocol Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative; 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 P203 and BMI ≥30 kg/m2 for P301.
Notes: - Percentages are based on the number of subjects in the Per- Protocol Immunogenicity Subset for Part 1C-1.

The demographic characteristics of the Safety Set for booster recipients in P203 are shown in Table 6. Overall, baseline characteristics were similar between participants in the PPIS and Safety Set. In the Safety Set, 6.5% of participants had evidence of prior SARS-CoV-2 infection at baseline (pre-Dose 1 of primary series) and 40.1% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 6. Demographics and Other Baseline Characteristics, Participants 12 Through 17 Years of Age (Study P203), Safety Set

Characteristic	12-17 years mRNA-1273 50 µg BD N=1364
Sex, n (%)	--
Female	665 (48.8)
Male	699 (51.2)
Age (Years)	--
Mean (SD)	14.1 (1.5)
Median	14.0
Age Group, n (%)	--
≥12 to <16 years	1093 (80.1)
≥16 to <18 years	271 (19.9)
Race, n (%)	--
White	1158 (84.9)
Black	43 (3.2)
Asian	66 (4.8)
American Indian or Alaska Native	7 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	71 (5.2)
Other	10 (0.7)
Not reported	4 (0.3)
Unknown	4 (0.3)
Ethnicity, n(%)	--
Hispanic or Latino	179 (13.1)
Not Hispanic or Latino	1174 (86.1)
Not reported	11 (0.8)

Characteristic	12-17 years mRNA-1273 50 µg BD N=1364
Race and Ethnicity Group[a], n (%)	--
White non-Hispanic	1009 (74.0)
Communities of Color	354 (26.0)
Missing	1 (<0.1)
Obesity[c], n (%)	--
Obese	268 (19.6)
Non-Obese	1096 (80.4)
Baseline (pre-Dose 1) SARS-CoV-2 status[b], n (%)	--
Positive	89 (6.5)
Negative	1198 (87.8)
Missing	77 (5.6)
Pre-booster SARS-CoV-2 status, n (%)	--
Positive	547 (40.1)
Negative	709 (52.0)
Missing	108 (7.9)
Time Since Primary Series Dose 2 to Booster	--
Median (Days) (min, max)	315.0 (63, 422)

Source: EUA 27073. Amendment 496,, P203, Tables 14.1.3.14.1, and 14.1.6.5.1
Abbreviations: BD=booster dose; kg=kilograms; m^2=meters squared; min=minimum; max=maximum; N=total number of participants in the analysis set; n=number of participants fulfilling the item; 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. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 in Part A. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1 in Part A.
c. Obesity is defined as BMI ≥ 95th percentile of the WHO growth reference data for P203 and BMI ≥30 kg/m2 for P301.
Note: Percentages are based on the number of safety subjects for Part 1C-1.

6.3.3 Vaccine Effectiveness

6.3.3.1 Primary immunogenicity analyses

Vaccine effectiveness of the mRNA-1273 booster dose in the adolescent population was inferred based on the evaluation of nAb GMC and the SRR against the ancestral SARS-CoV-2 strain (D614G) elicited after a booster dose in P203 Part 1C-1 compared to those after the primary series in young adults from Study P301. Co-primary endpoints, described in Section 6.3.1, were in participants without evidence of prior SARS-CoV-2 infection pre-booster (PPIS-Neg) for the adolescent group and without evidence of prior SARS-CoV-2 infection pre-primary series (PPIS) for the young adult group.

Results for the co-primary endpoint of GMC ratio (adolescents/young adults) are displayed in Table 7, below. The GMC ratio was 5.1 (95% CI 4.5, 5.8) which met the pre-specified success criteria of a lower bound (LB) of the 95% CI ≥ 0.67 and a point estimate of ≥ 0.8.

Table 7. Geometric Mean Antibody Concentration (GMC) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose, Adolescent Participants 12-17 Years, Study P203 Part 1C-1, PPIS-Neg Compared to 28 Days Post-Primary Series, Young Adult Participants 18-25 Years, Study P301, PPIS

Adolescents 12-17 Years mRNA-1273 50 µg Booster Dose GMC [95% CI][a] N1 = 257	Young Adults 18-25 Years mRNA-1273 100 µg Primary Series GMC [95% CI][a] N1 = 294	GMC Ratio (Adolescent/Young Adults) [95% CI][a]	Met Success Criteria[b]
7172.0 [6610.4, 7781.4]	1400.4 [1272.7, 1541.0]	5.1 [4.5, 5.8]	Yes

Source: EUA 27073. Amendment 496,, P203, 14.2.1.1.3.5.1.1
LLOQ: 10, ULOQ: 281600
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.
Abbreviations: BD=booster dose; CI=confidence interval; GMC=geometric mean concentration; N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint; nAB=neutralizing antibody
a. The log-transformed antibody levels are analyzed using t-test method with the group variable (adolescents in P203 and young adults in P301) and 95% CI is calculated based on the t test method for the log-transformed values/difference in the log-transformed values for GM value. The resulted means and 95% CI are back transformed to the original scale for presentation.
b. Success criteria: the lower bound of the 95% CI of the GMC ratio is ≥ 0.67 and point estimate ≥0.8.

Among the adolescent booster dose recipients in study P203 who were included in the PPIS-Negative Subset, the GMC observed at 28 days post-booster dose was approximately 18-fold higher compared to the GMC observed immediately pre-booster, and approximately 4-fold higher compared to the GMC observed at 28 days post-primary series.

Results for the co-primary endpoint of difference in SRRs between adolescents and young adults are displayed in Table 8, below. The difference in SRRs was 0.7% (95% CI -0.8, 2.4) which met the pre-specified success criterion of a LB of the 95% CI ≥ -10%.

Table 8. Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose (from pre-Dose 1), Adolescent Participants 12-17 Years, Study P203 Part 1C-1, PPIS-Neg Compared to 28 Days Post-Primary Series, Young Adult Participants 18-25 Years, Study P301, PPIS

Adolescents 12 -17 Years 50 µg Booster Dose SRR[a] % (n/N1) [95% CI][b]	Young Adults 18-25 Years 100 µg Primary Series SRR[a] % (n/N1) [95% CI][b]	Difference in SRR (Adolescents minus Young Adults) [95% CI][c]	Met Success Criteria[d]
100% (257/257) [98.6, 100.0]	99.3% (292/294) [97.6, 99.9]	0.7% [-0.8, 2.4]	Yes

Source: EUA 27073 Amendment 496, P203, Tables 14.2.1.2.3.5.1.1
LLOQ: 10, ULOQ: 281600
Abbreviations: CI=confidence interval; n = Number of subjects with non-missing data at the corresponding timepoint; N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint; nAb=neutralizing antibody; SRR=seroresponse rate
a. Seroresponse from pre-Dose 1 baseline at a subject level is defined as a change from below the LLOQ to equal or above 4 x 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. Co-primary endpoint 2: The difference in the SRRs (adolescent booster minus young adult primary series). Success criteria: the lower bound of the 95% CI in SRR difference is ≥-10%.

To assess for the change in nAb concentration attributable solely to the booster dose, FDA requested a post hoc analysis using a revised seroresponse definition based on the proportion of adolescent participants achieving a ≥ 4-fold rise in nAb concentrations from the pre-booster time point, rather than pre-Dose 1 -. For this descriptive post hoc analysis, seroresponse following booster was defined as follows:

- Seroresponse for participants with pre-booster nAb concentrations < LLOQ, as a post-booster nAb concentration ≥ 4 x LLOQ,
- Seroresponse for participants with pre-booster nAb concentrations ≥ LLOQ, as ≥ 4-fold rise in those with pre-booster nAb concentration.

Results of this post hoc analysis are shown in Table 9. In this post hoc analysis, the difference in SRRs was -2.8% (95% CI -5.9, -0.6), which would also have met the protocol specified success criteria for the co-primary endpoint of SRR, of the lower bound of the 95% CI in SRR difference is ≥ -10%. The lower SRR observed among booster recipients 12-17 years using this revised seroresponse definition was likely due to the substantially higher pre-booster GMC in

participants 12-17 years (400.4 AU/mL) compared to the pre-Dose 1 GMC in participants 18-25 years (11.1 AU/mL), making it more difficult comparatively for participants 12-17 years to achieve the 4-fold rise required to demonstrate seroresponse.

Table 9. Post Hoc Analysis of Seroresponse Rate (SRR) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-BD (from pre-BD), Adolescent Participants 12-17 Years, Study P203 Part 1C-1, PPIS-Neg Compared to 28 Days Post-Primary Series, Young Adult Participants 18-25 Years, Study P301, PPIS

Adolescents 12 -17 Years mRNA-1273 50 µg BD SRR[a] % (n/N1) [95% CI][b]	Young Adults 18-25 Years mRNA-1273 100 µg Primary Series SRR[a] % (n/N1) [95% CI][b]	Difference in SRR (Adolescents minus Young Adults) [95% CI][c]
96.5% (248/257) [93.5, 98.4]	99.3% (292/294) [97.6, 99.9]	-2.8% [-5.9, -0.6]

Source: EUA 27073. Amendment 516, P203, Tables 14.2.3.1.5.1.2
LLOQ: 10, ULOQ: 281600
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.
Abbreviations: BD=booster dose; CI=confidence interval; n = seroresponders; N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint; nAb=neutralizing antibody; SRR=seroresponse rate
a. Seroresponse from pre-booster (for P203 participants) or pre-Dose 1 (for P301 participants) at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if pre-booster 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.

Subgroup analyses of primary immunogenicity endpoints

Most of the study participants in Study P203 Part 1C-1 were White and Non-Hispanic; therefore, subgroup analyses by race and ethnicity were not conducted, as the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results. The GMC ranges post-booster were similar among adolescents 12-15 years and 16-17 years. When these two age cohorts were analyzed separately against young adults from P301, the GMC ratios, SRR, and associated 95% confidence intervals would have met study success criteria for both age cohorts. Subgroup analyses by sex were comparable between males and females.

Subgroup analyses of co-primary endpoints based on baseline SARS-CoV-2 status are shown in Table 10. Neutralizing antibody GMCs were notably higher after booster vaccination in participants 12-17 years with evidence of prior SARS-CoV-2 infection pre-booster compared to those with negative SARS-CoV-2 status pre-booster.

Table 10. Subgroup Analyses of Co-Primary Immunogenicity Endpoints of GMCs and SRR as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose, Adolescent Participants 12-17 Years, Study P203 Part 1C-1, PPIS, Compared to at 28 Days Post-Primary Series, Young Adult Participants 18-25 Years, Study P301, PPIS

Pre-Booster SARS-CoV-2 Status	Adolescents 12-17 Years mRNA-1273 50 µg BD GMC [95% CI][a]	Young Adults 18-25 Years* mRNA-1273 100 µg Primary Series GMC [95% CI][a]	GMC Ratio (Adolescents/ Young adults) [95% CI][a]	Adolescents 12 -17 Years mRNA-1273 50 µg BD SRR[b] % (n/N1) [95% CI][c]	Young Adults 18-25 Years* mRNA-1273 100 µg Primary Series SRR[b] % (n/N1) [95% CI][c]	Difference in SRR (Adolescents minus Young Adults) [95% CI][d]
Any	(n=327) 7760.9 [7180.3, 8388.4]	(n=294) 1400.4 [1272.7, 1541.0]	**5.5 [4.9, 6.3]**	100 (327/327) [98.9, 100.0]	99.3 (292/294) [97.6, 99.9]	**0.7 [-0.5, 2.4]**
Positive	(n=51) 13456.8 [11061.8, 16370.5]	(n=294) 1400.4 [1272.7, 1541.0]	**9.6 [7.5, 12.3]**	100 (51/51) [93.0, 100.0]	99.3 (292/294) [97.6, 99.9]	**0.7 [-6.4, 2.4]**
Negative	(n=257) 7172.0 [6610.4, 7781.4]	(n=294) 1400.4 [1272.7, 1541.0]	**5.1 [4.5, 5.8]**	100 (257/257) [98.6, 100.0]	99.3 (292/294) [97.6, 99.9]	**0.7 [-0.8, 2.4]**

Source: EUA 27073. Amendment 496, P203, Tables 14.2.1.2.3.5.1.3 and 14.2.1.1.3.5.1.3
LLOQ: 10, ULOQ: 281600
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.
Abbreviations: BD=booster dose; CI=confidence interval; GMC=geometric mean concentration; n = Number of subjects with non-missing data at the corresponding timepoint. N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint; nAB=neutralizing antibody; SRR=seroresponse rate
a. The log-transformed antibody levels are analyzed using t-test method with the group variable (adolescents in P203 and young adults in P301) and 95% CI is calculated based on the t test method for the log-transformed values/difference in the log-transformed values for GM value. The resulted means and 95% CI are back transformed to the original scale for presentation.
b. Seroresponse from pre-dose 1 baseline at a subject level is defined as a change from below the LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on N1
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
*For 18-25 years comparator group, data from the PPIS are presented for all 3 analyses, which consists of all participants in the immunogenicity subset with negative SARS-CoV-2 status at baseline (pre-Dose 1 of primary series).

6.3.3.2 Clinical efficacy

Due to the open-label study design of Part 1C-1 and the lack of a comparator group, vaccine efficacy was not assessed. In the ongoing study, participants are actively monitored for potential cases of COVID-19. As of the data cutoff, there were no reports of severe COVID-19 cases among booster recipients 12-17 years of age in the study.

6.3.4 Safety

6.3.4.1 Overview of adverse events

Safety analyses included data available through the cutoff date of May 16, 2022, with a median duration of follow up of 116 days from booster dose. Table 11 below summarizes AEs among booster recipients in the study. Solicited local and systemic ARs within 7 days post-booster dose were reported by 95.1% and 76.6% of study participants, respectively.

Among booster recipients, 14.2% (n=194) reported unsolicited AEs occurring within 28 days after booster vaccination, with 269 reported events. Severe unsolicited AEs were rare, reported

in 0.3% (n=4) of participants (events of vomiting, fatigue [n=2], and hypersensitivity [further discussed in Section 6.4.4.5]).

Through the data cutoff, 165 (12.1%) of participants reported unsolicited AEs that were medically-attended. Among these, only two were assessed by the investigator as related to study vaccine (events of vomiting and fatigue). As of May 16, 2022 (116 days of median follow-up duration), there were no SAEs, AESIs, AEs leading to study discontinuation, or deaths reported after the booster dose in the study.

Table 11. Number and Percentage of Participants Reporting at Least One Safety Event, Participants 12-17 Years, Study P203 Part 1C-1, Safety Set and Solicited Safety Set

Event Type	12-17 Years mRNA-1273 50 µg Booster Dose
Solicited adverse reactions within 7 days[a]	**n/N1 (%)**
Any solicited reaction	1248/1312 (95.1)
Solicited local adverse reaction	1208/1312 (92.1)
Grade 3 solicited local adverse reaction	57/1312 (4.3)
Solicited systemic adverse reaction	1004/1311 (76.6)
Grade 3 solicited systemic adverse reaction	108/1311 (8.2)
Unsolicited adverse events[b]	**n/N (%)**
Unsolicited adverse event up to 28 days after booster injection	194/1364 (14.2)
Non-serious unsolicited adverse event	194/1364 (14.2)
Related non-serious unsolicited AE	57/1364 (4.2)
Severe non-serious unsolicited AE	4/1364 (0.3)
Related severe non-serious unsolicited AE	3/1364 (0.2)
Medically attended adverse events[b,c]	165/1364 (12.1)
Related MAAE[c]	2/1364 (0.1)
SAE[c]	0
AESI[c]	0
Deaths[c]	0
AE leading to study discontinuation[c]	0

Source: EUA 27073. Amendment 496, P203, Tables 14.3.1.1.1.5.1, 14.3.1.7.5.1.1, 14.3.1.7.5.2.1
Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BD=booster dose; MAAE=medically attended adverse event; SAE=serious adverse event; N=number of participants who received a booster dose in Part 1C-1; N1 = Number of exposed participants who submitted any data for the event;
a. Percentages are based on the number of exposed participants who submitted any data for the event (N1)
b. Percentages are based on the number of safety participants in Part 1C-1.
c. All numbers reflect AEs reported through the data cut-off of May 16, 2022.
Note: The Safety Set (N) consists of all participants who received a booster dose in Part 1C-1. The Solicited Safety Set (N1) consists of all participants who received booster dose in Part 1C-1, and contributed any solicited AR data, ie, had at least one post-booster solicited safety assessment in Part 1C-1. There were no reported Grade 4 adverse reactions or events.

6.3.4.2 Solicited adverse reactions

The frequency and severity of solicited local and systemic adverse reactions within 7 days following the booster dose are shown below in Table 12 and Table 13, respectively. Assessment of booster dose reactogenicity is limited by the open-label study design for this part of P203. To provide a frame of reference to assess the rates of solicited adverse reactions following a booster dose, the rates of solicited adverse reactions following Dose 1 and Dose 2 of the primary series (double-blinded Study P203 Part 1A, reviewed in FDA EUA memorandum) are included in these tables.

By order of frequency, adverse reactions in participants 12 through 17 years of age following administration of the booster dose of mRNA-1273 were pain at the injection site (91.1%), fatigue (58.7%), headache (57.2%), myalgia (40.4%), chills (30.6%), axillary swelling/tenderness

(28.1%), arthralgia (21.1%), nausea/vomiting (17.9%), swelling at the injection site (13.5%), erythema at the injection site (9.2%), and fever (6.1%).

6.3.4.2.1 Solicited local adverse reactions

Overall, solicited local ARs following a booster dose appeared to be less frequent compared to after the primary series doses, except for axillary swelling or tenderness which was reported at a slightly higher rate after the booster dose compared to after the primary series doses. Injection site pain was the most frequently reported solicited local adverse reaction among adolescent booster dose recipients. Solicited local ARs following booster dose were mostly Grade 1 or Grade 2. Grade 3 local adverse reactions were reported by 4.3% of booster dose recipients, the majority of which was Grade 3 injection site pain. There were no solicited local ARs with Grade 4 severity after any dose of mRNA-1273.

Most solicited local reactions reported within 7 days of booster dose occurred within 1 to 2 days post-vaccination with a median onset of 1-day post-vaccination and resolved after a median of 3 days (range 1 to 27 days). Solicited local adverse reactions persisting beyond 7 days post-booster were reported by 1.4% of participants.

Delayed solicited local reactions (defined as beginning after Day 7) were reported by one (<0.1%) booster dose recipient in the Safety Set (N=1364). The one participant reported ARs of pain and swelling with onset occurring 11 days post-vaccination and had a duration of 1 day.

Table 12. Frequency of Solicited Local Adverse Reactions in Adolescent Participants 12-17 Years Within 7 Days of Primary Series Dose 1 & Dose 2 (Study P203, Part 1A) and 7 Days of Booster Dose (Study P203 Part 1C-1), Solicited Safety Set

Event	Primary Series Dose 1 mRNA-1273 100 µg N=2482 n (%)	Primary Series Dose 2 mRNA-1273 100 µg N=2478 n (%)	Booster Dose mRNA-1273 50 µg N=1312 n (%)
Local adverse reaction	N1=2482	N1=2478	N1=1312
Any	2339 (94.2)	2314 (93.4)	1208 (92.1)
Grade 3	170 (6.8)	220 (8.9)	57 (4.3)
Pain[a]	N1=2482	N1=2478	N1=1312
Any	2310 (93.1)	2290 (92.4)	1196 (91.2)
Grade 3	133 (5.4)	126 (5.1)	39 (3.0)
Erythema (redness)[b]	N1=2482	N1=2478	N1=1311
Any ≥25 mm	334 (13.5)	484 (19.5)	120 (9.2)
Grade 3	21 (0.8)	72 (2.9)	9 (0.7)
Swelling (hardness)[b]	N1=2482	N1=2478	N1=1311
Any ≥25 mm	403 (16.2)	509 (20.5)	176 (13.4)
Grade 3	27 (1.1)	56 (2.3)	9 (0.7)
Axillary swelling or tenderness[c]	N1=2481	N1=2477	N1=1311
Any	578 (23.3)	519 (21.0)	367 (28.0)
Grade 3	10 (0.4)	7 (0.3)	4 (0.3)

Source: EUA 27073. Amendment 496, P203, Tables 14.3.1.1.1.5.1
a. Pain Grade 3: any use of prescription pain reliever/prevents daily activity
b. Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm
c. Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity
Note: The primary series phase of Study P203 (Part 1A) was not conducted contemporaneously with the booster phase (Part 1C-1).
Any=Grade 1 or higher.
N=The Solicited Safety Set for each dose consists of all participants who were received any study injection and contr buted any solicited AR data (i.e., had at least 1 post-baseline, 1 post dose-2, or 1 post-booster solicited safety assessment through 6 days post-vaccination).
N1 = Number of exposed participants who submitted any data for the event
No grade 4 solicited local adverse reactions were reported.

6.3.4.2.2 Solicited systemic adverse reactions

In general, within 7 days after a booster dose, solicited systemic adverse reactions occurred at a higher frequency compared to after Dose 1 of the primary series, but at a lower frequency when compared to after Dose 2 of the primary series. Fatigue and headache were the most frequently reported solicited systemic ARs, reported in 58.7% and 57.1% of booster recipients, respectively. Systemic ARs following booster dose were mostly Grade 1 or Grade 2. Grade 3 systemic ARs were reported by 8.2% of booster dose recipients, and there were no Grade 4 systemic ARs reported after the booster dose. Fever was reported by 6.1% of booster recipients compared with 2.5% and 12.2% of mRNA-1273 recipients after Dose 1 and Dose 2 of the primary series, respectively. Fever ≥39°C post-booster was rare and was reported by 0.6% of booster recipients.

Most solicited systemic adverse reactions reported within 7 days of booster dose occurred within 1 to 2 days post-vaccination with a median onset of 1-day post-vaccination and resolved after a median of 2 days (range 1 to 27 days). Solicited systemic adverse reactions persisting beyond 7 days post-booster vaccination were reported by 3.7% of booster recipients, of which the majority were fatigue and headache.

Among booster recipients in the solicited safety set, 39.3% reported use of medication for pain or fever.

Table 13. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Participants 12-17 Years, Study P203, Solicited Safety Set

Event	Primary Series Dose 1 mRNA-1273 100 µg N=2482 n (%)	Primary Series Dose 2 mRNA-1273 100 µg N=2478 n (%)	Booster Dose mRNA-1273 50 µg N=1312 n (%)
Any systemic adverse reaction	N1=2482	N1=2478	N1=1311
Any	1701 (68.5)	2134 (86.1)	1004 (76.6)
Grade 3	108 (4.4)	340 (13.7)	108 (8.2)
Grade 4	0	3 (0.1)	0
Fever[a]	N1=2480	N1=2477	N1=1297
Any: ≥38.0°C	63 (2.5)	302 (12.2)	79 (6.1)
Grade 3: 39°C to 40.0°C	9 (0.4)	46 (1.9)	8 (0.6)
Grade 4: >40.0°C	0	1 (<0.1)	0
Headache[b]	N1=2480	N1=2478	N1=1311
Any	1106 (44.6)	1739 (70.2)	748 (57.1)
Grade 3	56 (2.3)	112 (4.5)	28 (2.1)
Grade 4	0	1 (<0.1)	0
Fatigue[c]	N1=2481	N1=2478	N1=1311
Any	1188 (47.9)	1679 (67.8)	769 (58.7)
Grade 3	33 (1.3)	188 (7.6)	53 (4.0)
Grade 4	0	0	0
Myalgia[c]	N1=2480	N1=2477	N1=1311
Any	668 (26.9)	1154 (46.6)	529 (40.4)
Grade 3	24 (1.0)	129 (5.2)	47 (3.6)
Grade 4	0	0	0
Arthralgia[c]	N1=2480	N1=2477	N1=1311
Any	371 (15.0)	716 (28.9)	316 (24.1)
Grade 3	15 (0.6)	57 (2.3)	17 (1.3)
Grade 4	0	0	0

Event	Primary Series Dose 1 mRNA-1273 100 µg N=2482 n (%)	Primary Series Dose 2 mRNA-1273 100 µg N=2478 n (%)	Booster Dose mRNA-1273 50 µg N=1312 n (%)
Nausea/vomiting[d]	N1=2480	N1=2477	N1=1311
Any	281 (11.3)	591 (23.9)	234 (17.8)
Grade 3	2 (<0.1)	2 (<0.1)	2 (0.2)
Grade 4	0	1 (<0.1)	0
Chills[e]	N1=2480	N1=2477	N1=1311
Any	456 (18.4)	1066 (43.0)	399 (30.4)
Grade 3	4 (0.2)	11 (0.4)	7 (0.5)
Grade 4	0	0	0
Use of antipyretic or pain medication	N1=2482	N1=2478	N1=1312
Any	748 (30.1)	1242 (50.1)	515 (39.3)

Source: EUA 27073. Amendment 496, P203, Tables; 14.3.1.1.1.5.1; 14.1.5.3.5
a. Fever: 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.
Note: The primary series phase of Study P203 (Part 1A) was not conducted contemporaneously with the booster phase (Part 1C-1).
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 for each dose consists of all participants who were received any study injection and contributed any solicited AR data (i.e., had at least 1 post-baseline, 1 post dose-2, or 1 post-booster solicited safety assessment through 6 days post-vaccination).
Medications were collected on the eDiary.

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions to evaluate the reactions post-booster dose by sex, race, and ethnicity. No notable differences were observed among the demographic subgroups, although some race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Subgroup analysis was also performed for solicited local and systemic reactions based on pre-booster SARS-CoV-2 status. SARS-CoV-2 positive (pre-booster) participants reported slightly lower rates of local ARs compared to SARS-CoV-2 negative (pre-booster) participants. Similarly, systemic reactions were reported at a numerically lower rate overall in SARS-CoV-2 positive (pre-booster) participants (69.7%) compared to SARS-CoV-2 negative (pre-booster) participants (80.7%). Notably, fever was reported by 2.7% of SARS-CoV-2 positive (pre-booster) participants compared to 8.5% of SARS-CoV-2 negative (pre-booster) participants.

6.3.4.3 Unsolicited adverse events

Through the May 16, 2022, data cutoff for Part 1C-1 of Study P203, 1329 (97.4%)study participants had been followed for at least 28 days. Unsolicited AEs which occurred within 28 days of booster vaccination and at rates of ≥ 1% are shown in Table 14. Unsolicited AEs were most frequently reported under the System Organ Class (SOC) *Infections and Infestations* (7.5% of participants), of which COVID-19 and asymptomatic COVID-19 were the most frequently reported Preferred Terms (PTs), in 3.0% and 1.2% of participants, respectively. In subgroup analyses of unsolicited AEs based on pre-booster SARS-CoV-2 status, participants

with positive SARS-CoV-2 status pre-booster reported COVID-19 at a lower frequency (1.8%) and asymptomatic COVID-19 at a higher frequency (2.4%) compared to participants with negative SARS-CoV-2 status pre-booster (4.2% and 0.4%, respectively). Headache and fatigue were the next most commonly reported unsolicited AEs by PT in the overall booster population, in 2.0% and 1.8% of participants, respectively.

Overall, aside from the PTs of COVID-19 and asymptomatic COVID-19 discussed above, unsolicited AEs occurred at similar rates among participants with negative and positive SARS-CoV-2 status pre-booster. Rates of unsolicited AEs were also generally similar across subgroups based on sex, race and ethnicity, though the low number of participants in several subgroups limited determination of any particular patterns.

Table 14. Participant Incidence of Unsolicited Adverse Events Occurring in ≥ 1% of Participants Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Participants 12-17 Years, Study P203, Part 1C-1, Safety Set

Adverse Event	mRNA-1273 50 µg Booster Dose N=1364 n (%)
Any unsolicited adverse event	194 (14.2)
System Organ Class Preferred Term	--
Infections and infestations	102 (7.5)
COVID-19	41 (3.0)
Asymptomatic COVID-19	17 (1.2)
Upper respiratory tract infection	16 (1.2)
Nervous system disorders	27 (2.0)
Headache	27 (2.0)
Musculoskeletal and connective tissue disorders	13 (1.0)
General disorders and administration site conditions	45 (3.3)
Fatigue	24 (1.8)
Injury, poisoning, and procedural complications	14 (1.0)

Source: EUA 27073. Amendment 496, P203, Table 14.3.1.8.5.1.1
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities;
Note: Percentages are based on the number of participants in the Safety Set (N). The Safety Set consists of all participants who received booster dose.

6.3.4.4 Adverse events of special 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). As of the data cutoff, there were no protocol-defined AESIs reported after booster dose in P203 Part 1C-1.

6.3.4.5 FDA Standard MedDRA Queries

FDA Standard MedDRA Queries (SMQs) were conducted to evaluate for constellations of unsolicited AEs with onset following study vaccination through the data cutoff. SMQs are pre-determined sets of MedDRA preferred terms (PTs) grouped together to represent medical concepts, , including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which captured AEs considered clinically relevant by the FDA will be discussed.

SMQ *Hypersensitivity*

Through the data cutoff, events under the SMQ *Hypersensitivity* were reported by 10 participants (0.7%). Within 28 days of vaccination, hypersensitivity events were reported by 9 (0.7%) participants (events of asthma, dermatitis, hypersensitivity, rash, allergic rhinitis, and urticaria [4 participants]). All events were assessed as mild to moderate, except for one event under the PT hypersensitivity which was considered severe: a 12-year-old male who reported allergic reaction (thought to be likely to something outdoors) with swelling, itching, and hives occurring 15 days post-booster dose. FDA agrees with the investigator's assessment that this event was unlikely to be related to study vaccine. None of the identified events under the SMQ *Hypersensitivity* were clinically consistent with anaphylaxis.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (including *Cardiomyopathy*, *Cardiac arrhythmia, Cardiac failure, Ischemic heart disease, and Noninfectious myocarditis and pericarditis*). The search also included additional terms based on the CDC working case definition of myocarditis and pericarditis (Appendix B). Analysis of the data through the data cutoff identified 4 events, described below. None of these events were considered by the FDA to be consistent with vaccine-associated myocarditis or pericarditis.

- A 14-year-old female experienced cardiac arrythmia 101 days post-booster dose. The participant reported experiencing intermittent palpitations following an episode of symptomatic COVID-19, but the participant did not seek medical attention. Approximately 1 month after the event, a physical examination by the investigator noted irregular heartbeat. The participant was otherwise asymptomatic and no work-up was conducted. At a subsequent follow-up visit, the rhythm was noted by the investigator to be regular, and the AE was considered resolved. The investigator considered the event not related to mRNA-1273-booster. FDA agrees with the investigator's assessment that this event was unlikely to be related to study vaccine.

- A 15-year-old male experienced dyspnea on the day of the booster dose administration. Potentially relevant medical history include depression, anxiety, post-traumatic stress disorder and attention deficient and hyperactivity disorder. The site reported that the participant experienced mild shortness of breath on the day of the booster dose and the day after which resolved without medical intervention or medication. There was no associated chest pain and no other concurrent AEs reported. The investigator considered the event related to mRNA-1273-booster. FDA agrees with the investigator's assessment that this event was likely to be related to study vaccination, possibly as an immunization anxiety-related reaction, commonly reported in the adolescent age cohort following other routinely administered vaccinations.

- A 13-year-old male experienced dyspnea 26 days after receiving booster dose, associated with concurrent AE of symptomatic COVID-19. The investigator considered the event not related to mRNA-1273-booster. FDA agrees with the investigator's assessment that this event was unlikely to be related to study vaccine.

- A 13-year-old male with history of anxiety experienced dyspnea 101 days after receiving booster dose. No other AEs were reported concurrently, and no further details are available on the event. The event was reported as resolved 28 days after onset. The

investigator considered the event not related to mRNA-1273-booster. FDA agrees with the investigator's assessment that the event was not related to study vaccine.

6.3.4.6 Serious adverse events

There were no reported serious adverse events after booster dose.

6.3.4.7 Deaths

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

6.3.4.8 AEs leading to study withdrawal

There were no reported AEs leading to study withdrawal after booster dose.

6.3.4.9 Pregnancies

No pregnancies were reported through the data cutoff.

6.3.5 Summary for Participants 12 through 17 Years of Age

The primary evidence to support effectiveness of a booster dose in adolescents 12-17 years of age was a comparison of the immune responses generated following a single mRNA-1273 booster dose vaccination in adolescents in Study P203 to the immune responses after a 2-dose mRNA-1273 primary series to a clinically relevant young adult subgroup (18-25 years) from Study P301 study population for whom VE has been demonstrated. The adolescent participants in Study P203 Part 1C-1 had received a single mRNA-1273 booster dose at least 5 months after completion of the mRNA-1273 primary series. The study met the pre-specified success criteria for the two co-primary endpoints of GMC ratio and difference in SRRs. The GMC ratio (adolescents post-booster/young adults post-primary series) was 5.1 (95% CI 4.5, 5.8), which met the pre-specified success criteria of a LB of the 95% CI ≥ 0.67 and a point estimate of ≥ 0.8. Based on the protocol definition for seroresponse, defined as pre-primary series to post-booster, the difference in SRRs (adolescents post-booster minus young adults post-primary series) was 0.7% (95% CI -0.8, 2.4), which met the pre-specified success criteria of demonstration of a LB of the 95% CI ≥ -10%. In a post-hoc analysis using a more clinically meaningful seroresponse definition comparing neutralizing antibody concentrations pre-booster to post-booster, the difference in SRRs was -2.8% (-5.9, -0.6), which would have met the protocol pre-specified criterion for non-inferiority.

Although interpretation of the data across demographic subgroups was limited due to small samples sizes in certain populations, the results within each subgroup were generally consistent with those in the overall study population. The primary immunogenicity endpoints were based on a population of participants without evidence of SARS-CoV-2 infection pre-booster. Subgroup analyses of the primary endpoints based on a population of participants with evidence of prior SARS-CoV-2 infection pre-booster and in all participants, regardless of pre-booster SARS-CoV-2 status, resulted in GMC ratios and SRR differences that also would have met the study criteria for non-inferiority. Pre-booster SARS-CoV-2 status positive participants had numerically higher GMCs (with non-overlapping CIs) post-booster compared to those who were SARS-CoV-2 status negative pre-booster.

Due to the open-label study design and the lack of a contemporaneous comparator arm, Part 1C-1 of Study P203 did not include an evaluation of vaccine efficacy. Study participants were

monitored for COVID-19 cases throughout the study. As of the data cutoff, there were no reported severe cases of COVID-19 among booster recipients.

Solicited local and systemic reactions among adolescent booster dose recipients were mostly mild to moderate in severity and of short duration. Similar to post-primary series findings, the most common solicited adverse reactions post-booster dose were pain at the injection site (91.2%), fatigue (58.7%), and headache (57.1%). Grade 3 reactions were reported at rates of 4.3% and 8.2% for solicited local and systemic reactions, respectively. Most solicited local and systemic ARs were reported somewhat less frequently in participants with evidence of prior SARS-CoV-2 infection pre-booster compared to participants without evidence of prior SARS-CoV-2 infection pre-booster.

An analysis of the safety data through the data cutoff of May 16, 2022, with a median duration of follow-up of 116 days post-booster dose, revealed no new safety concerns. As of the data cutoff, there were no cases of myocarditis or pericarditis and no SAEs reported among booster recipients.

6.4 Study P204: Children 6 Years through 11 Years of Age

6.4.1 Study Design

In the booster phase of Study P204 (Part 1 and 2), participants 6-11 years (children) who completed a 2-dose primary series of mRNA-1273 (50 µg dose administered 28 days apart) were offered a 25 µg booster dose at least 6 months after completion of the 2-dose primary series. This includes participants who were randomized initially to receive the mRNA-1273 primary series, and those who were randomized to receive placebo, but then were crossed-over during the study to receive the mRNA-1273 primary series. The primary objectives of the booster phase of Study P204 were to evaluate the safety and reactogenicity and to infer vaccine effectiveness of a booster dose of mRNA-1273 based on immunobridging to participants 18-25 years (young adults) in Study P301 for whom clinical efficacy has been demonstrated. Immunobridging required demonstration of non-inferiority (children in Study P204 following a booster dose compared to young adults in study P301 following a 2-dose primary series) of immune response by both GMC and SRR as measured by neutralizing antibodies against SARS-CoV-2. Participants will be followed up for 12 months after receipt of the booster dose.

6.4.1.1 Evaluation of immunogenicity for booster phase

Immunogenicity analyses for the booster phase were based on nAb concentrations measured using a validated pseudovirus neutralization assay against the ancestral strain (D614G form of the USA-WA1/2020 Wuhan strain) conducted at (b) (4). Neutralizing antibody concentrations were measured in both the 6-11 years booster dose recipients in P204 and the P301 comparator group of young adults. Neutralizing antibody levels are reported as nAb concentration (arbitrary unit [AU]/mL) in the analyses. This differed from the Duke pseudovirus neutralization assay used previously for Study P301 which reported results as 50% inhibitory dose (ID50) neutralization titers. Details regarding the assay are provided in Section 7.1.

The co-primary immunogenicity objectives were to demonstrate the non-inferiority of nAb GMCs against the ancestral strain (D614G) in children (6-11 years) who received a mRNA-1273 25 µg booster dose compared to young adult (18-25 years) mRNA-1273 100 µg 2-dose primary series recipients, at 28 days post-booster and 28 days post-Dose 2 of primary series, respectively. The protocol specified success criteria for the co-primary endpoints were:

Co-primary endpoint 1: GMC

The GMC ratio (children booster/young adults primary series) is non-inferior if the LB of the 95% CI ≥ 0.667.

Co-primary endpoint 2: SRR

The difference in the SRRs (children booster minus young adults primary series) is non-inferior if the LB of the 95% CI ≥ −10%.

Seroresponse was defined in the protocol as a change from pre-Dose 1 for young adult 2-dose primary series recipients and 6-11 year old booster dose recipients, and includes the following:

- Seroresponse for participants with pre-Dose 1 < LLOQ is defined as ≥ 4 x LLOQ,
- Seroresponse for participants with pre-Dose 1 ≥ LLOQ is defined as ≥ 4-fold increase in concentration compared to pre-Dose 1

The protocol specified analysis sets for immunogenicity are listed in Table 15 below. The Per Protocol Immunogenicity Subset- Pre-booster SARS-CoV-2 Negative (PPIS-Neg) was used for the analyses of the co-primary immunogenicity endpoints.

Table 15. Immunogenicity Analysis Populations, Study P204, Booster Phase

Population	Description
Full Analysis Set (FAS)	All participants who received at least one booster dose.
Immunogenicity Subset	A subset of participants in the FAS (Booster Dose Analysis) with: • available baseline (pre-dose 1 of mRNA-1273) SARS-CoV-2 status • available baseline (pre-dose 1 of mRNA-1273) and at least one post-booster antibody assessment for the analysis endpoint.
Per-protocol Immunogenicity Subset (PPIS)	All participants in Immunogenicity Subset for Booster Dose Analysis who meet all the following criteria: • Received 2 doses of mRNA-1273 vaccination in Part 1 open-label phase or Part 2 blinded phase per schedule • Received booster dose in booster phase • Had a negative SARS-CoV-2 status at baseline (pre-dose 1 of mRNA-1273) • Had BD-Day 1 and BD-Day 29 Ab assessment for the analysis endpoint • Had no major protocol deviations that impacted key or critical data
Per Protocol (PP) Immunogenicity Subset-Pre-booster SARS-CoV-2 Negative (PPIS-Neg)	All participants in PPIS (Booster Dose Analysis) who are pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster), i.e., RT-PCR result is not positive if available at BD-Day 1 and a negative bAb specific to SARS-CoV-2 nucleocapsid on or before BD-Day 1.

Source: Reviewer-generated table adapted from P204 Statistical Analysis Plan

6.4.1.2 Evaluation of efficacy

The booster phase of P204 did not include a formal assessment of vaccine efficacy. However, participants were actively monitored for potential cases of COVID-19 throughout the study. Any confirmed symptomatic SARS-CoV-2 infection in a participant is captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome.

6.4.1.3 Evaluation of safety

The primary safety objective of the Part 2 booster phase of Study P204 is to describe the safety and reactogenicity of mRNA-1273 administered as a booster dose 6 months following completion of the primary series. 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 the booster. Unsolicited AEs were collected through 28 days after booster, while MAAEs, SAEs, and AESIs, including MIS-C and myocarditis and/or pericarditis, will be collected through the entire study period, up to 12 months after booster. AEs leading to discontinuation from study participation post-booster will be recorded through the last day of study participation.

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.

The protocol specified analysis sets for safety are listed in Table 16 below.

Table 16. Safety Analysis Populations, Study P204, Booster Phase

Population	Description
Safety Set	All participants who received a booster dose in booster phase. Used for analysis of safety except for solicited ARs.
Solicited Safety Set	All participants who received booster dose and contributed any solicited AR data, i.e., have at least one post-booster solicited safety assessment in booster phase. Used for the analyses of solicited ARs in Booster Dose analysis.

6.4.2 Participant Disposition and Demographics and Other Baseline Characteristics

6.4.2.1 Inclusion in analysis populations

This EUA amendment includes data from the start of the booster phase of Study P204 through the data cutoff of May 23, 2022 in participants 6-11 years who received a 2-dose primary series of mRNA-1273 (in Part 1 or Part 2) and a booster dose of 25 µg mRNA-1273 at least 6 months after Dose 2. A total of 1,294 participants received a booster dose in the booster phase of P204, 1,115 of whom received the primary series during the original double-blinded Part 2 phase of the study, 3 of whom initially received placebo in Part 2 of the study, crossed over to receive mRNA-1273, and then received a booster dose, and 176 of whom received the primary series (50 µg dose) during the Part 1 phase of the study. Post-booster data from Part 1 participants (N=184) who received a higher dose level of mRNA-1273 primary series (100 µg) compared to the dose level currently authorized for use (50 µg) and then received a booster dose are not included in study analyses. No SAEs or AESIs were reported among these 184 study participants as of the data cutoff.

6.4.2.2 Participant disposition

The disposition of P204 participants who contributed to the immunogenicity and safety analyses of the booster phase is presented below in Table 17. Overall, 1,294 participants received a 25 µg booster dose in the booster phase of P204 at least 6 months after receipt of a 50 µg dose level of the 2-dose primary series in Part 1 (n=176) or Part 2 (n=1118) of the study. Only 1 participant discontinued from the study, due to withdrawal of consent.

The P204 Per-Protocol Immunogenicity Subset- pre-booster SARS-CoV-2 negative (PPIS-Neg), used for the primary immunogenicity analyses, consisted of a similar number of participants from Part 1 (n=40) and Part 2 (n=55). Among all participants in the Immunogenicity Subset, there was a higher percentage of participants found to have positive pre-booster SARS-CoV-2 status (17.5%) compared to positive baseline (pre-primary series) SARS-CoV-2 status (7.1%),

which may be reflective of the changing SARS-CoV-2 epidemiology in the US between the time of study of the primary series (March to November 2021) and the booster dose (February to May 2022).

Table 17. Disposition of Participants 6 Through 11 Years of Age in Study P204 Booster Phase, All Enrolled

Disposition	Parts 1 & 2[a] mRNA-1273 25 µg BD n(%)
Full Analysis Set (FAS)	1294
Discontinued from Study[b]	1 (<0.1)
Immunogenicity Subset[c]	154
PP Immunogenicity Subset (PPIS)[d,e]	129 (83.8)
Excluded from PP Immunogenicity Subset	25 (16.2)
Reason for exclusion	--
Positive baseline SARS-CoV-2 status	11 (7.1)
Received Incorrect Vaccination in Booster Dose	4 (2.6)
Had no immunogenicity data at BD-Day 29	10 (6.5)
PP Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative (PPIS-Neg)[e]	95 (61.7)
Excluded from PPIS-Neg	34 (22.1)
Reason for exclusion	--
Positive pre-booster SARS-CoV-2 status	27 (17.5)
Missing pre-booster SARS-CoV-2 status	7 (4.5)
Safety Set	1294
Solicited Safety Set[f]	1280 (98.9)

Source: Study P204 (6-11 years) Tables 14.1.1.2.1, 14.1.1.2.2, 14.1.1.3.3, 14.1.1.3.4, and 14.1.2.3.4 (Amendment 503)
Ab=ant body; BD=booster dose; PP=per protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2
a. FAS and Safety Set numbers include Part 1 mRNA-1273 selected primary series dose participants (n=176), Part 2 mRNA-1273 participants (n=1115), and Part 2 Placebo-mRNA-1273 participants (n=3) who received booster dose. Cross-over vaccination began November 1, 2021, following authorization of an alternative COVID-19 vaccine for this age group in October 2021. These participants were not included in the Immunogenicity Subset, PPIS, and PPIS-Neg for booster dose analysis.
b. Participant discontinued due to withdrawal of consent by participant.
c. The Immunogenicity Subset consists of participants in the Full Analysis Set (FAS) who had baseline SARS-CoV-2 status available and had baseline (pre-dose 1) and at least 1 post-booster antibody assessment for the analysis endpoint.
d. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset for Booster Dose Analysis who meet all of the following criteria: received 2 planned doses of study vaccination per schedule; received booster dose in Booster Dose Analysis; had a negative SARS-CoV-2 status at baseline (pre-dose 1); had BD-Day 1 and BD-Day 29 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.
e. Percentages are based on the number of participants in the Immunogenicity Subset in booster dose analysis.
f. Percentages are based on the number of participants in the Safety Set in booster dose analysis.

6.4.2.3 Follow-up duration for participants 6 through 11 years of age

The overall median duration of follow-up after booster dose was 29 days, with a slightly longer median follow-up of 32 days for Part 1 participants.

6.4.2.4 Demographic and baseline characteristics

The PPIS-Neg, the population used to assess primary immunogenicity endpoints, consisted of 95 participants 6-11 years from Study P204 who received mRNA-1273 primary series and booster. The comparator group was composed of 295 young adult participants who received the primary series of mRNA-1273 in Study P301. Compared to the young adults, the children included a greater proportion of White (76.8% vs 69.8%) and multiracial (7.4% vs 4.7%) participants and a smaller proportion of Black (5.3% vs 9.8%) and Asian (5.3% vs 10.2%) participants. Fewer P204 participants self-identified as Hispanic or Latino (15.8%) compared to young adult participants (26.1%). A smaller proportion of participants were classified as obese in the 6-11 years age group (12.6%) compared to the young adult group (22.7%). In the PPIS-

Neg for participants 6-11 years, the median duration between Dose 2 of primary series to receipt of the booster dose (BD) was 222 days. Participants who received the primary series in Part 1 of Study P204 had a longer interval between Dose 2 to BD (305 days) compared to those who received the primary series in Part 2 (217 days).

Overall, the demographic characteristics for the PPIS-Neg were similar to those for the PPIS in Study P204.

Table 18. Demographics and Other Baseline Characteristics, Participants 6 Through 11 Years, Study P204 Booster Phase (Part 1 and 2), PPIS-Neg, and Participants 18 Through 25 Years, Study P301, Per-Protocol Immunogenicity Subset (PPIS)

Characteristic	P204 Parts 1 & 2 6-11 Years mRNA-1273 25 µg BD N=95	P301 18-25 Years mRNA-1273 100 µg PS N=295
Sex, n (%)	--	--
Female	49 (51.6)	152 (51.5)
Male	46 (48.4)	143 (48.5)
Age	--	--
6-8 years, n (%)	53 (55.8)	--
9-11 years, n (%)	42 (44.2)	--
Mean (SD)	8.3 (1.5)	22.4 (2.2)
Median age, years	8.0	23.0
Race, n (%)	--	--
White	73 (76.8)	206 (69.8)
Black or African American	5 (5.3)	29 (9.8)
Asian	5 (5.3)	30 (10.2)
American Indian or Alaska Native	1 (1.1)	3 (1.0)
Native Hawaiian or other Pacific Islander	1 (1.1)	2 (0.7)
Multiracial	7 (7.4)	14 (4.7)
Other	0	8 (2.7)
Not reported	2 (2.1)	3 (1.0)
Unknown	1 (1.1)	0
Ethnicity, n (%)	--	--
Hispanic or Latino	15 (15.8)	77 (26.1)
Not Hispanic or Latino	78 (82.1)	216 (73.2)
Not reported	1 (1.1)	0
Unknown	1 (1.1)	2 (0.7)
Race and ethnicity group[a], n (%)	--	--
White non-Hispanic	59 (62.1)	146 (49.5)
Communities of Color	35 (36.8)	149 (50.5)
Missing	1 (1.1)	0

Characteristic	P204 Parts 1 & 2 6-11 Years mRNA-1273 25 µg BD N=95	P301 18-25 Years mRNA-1273 100 µg PS N=295
Obesity status[b], n (%)	--	--
Obese	12 (12.6)	67 (22.7)
Non-obese	83 (87.4)	227 (76.9)
Missing	0	1 (0.3)
Median time from Dose 2 to Booster, days (min, max)[c]	222 (202, 367)	N/A

Source: P204 (6-11 years) Table 14.1.3.15.2 (Amendment 503)
BD = booster dose ; PS = primary series ; PPIS-Neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status; PPIS = Per-Protocol Immunogenicity Subset
Note : Percentages are based on the number of Per-Protocol Immunogenicity Subset participants in booster dose analysis for P204 and Per-Protocol Immunogenicity Subset participants for P301.
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. Time from Dose 2 is calculated as: Date of Booster minus Date of Dose 2 of mRNA-1273 plus 1. Median time from Dose 2 of primary series to booster was 305 days for participants from Part 1 and 217 days for participants from Part 2.

The demographic and baseline characteristics for the Safety Set for booster dose recipients 6-11 years of age are presented in Table 19. In the Booster Dose Analysis Safety Set, approximately 8% of participants had evidence of prior SARS-CoV-2 infection at baseline (pre-Dose 1 of primary series) and 33% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Participants who received 100 µg dose mRNA-1273 primary series followed by 25 µg booster in dose-finding Part 1 of the study (N=184) are not included in Table 19. The demographic and baseline characteristics of these participants were generally similar compared with Part 1 and 2 participants who received the authorized 50 µg dose primary series and 25 µg booster dose.

Table 19. Demographic and Baseline Characteristics, Participants 6 Through 11 Years of Age, Study P204 Booster Phase (Part 1 and 2), Safety Set

Characteristic	P204 Parts 1 & 2 mRNA-1273 25 µg BD N=1294
Sex, n (%)	--
Female	622 (48.1)
Male	672 (51.9)
Age	--
Mean (SD)	8.5 (1.6)
Median	8.0
Race, n (%)	--
White	850 (65.7)
Black	142 (11.0)
Asian	101 (7.8)
American Indian or Alaska Native	6 (0.5)
Native Hawaiian or other Pacific Islander	1 (<0.1)
Multiracial	153 (11.8)
Other	24 (1.9)
Not reported	14 (1.1)
Unknown	3 (0.2)
Ethnicity, n (%)	--

Characteristic	P204 Parts 1 & 2 mRNA-1273 25 µg BD N=1294
Hispanic or Latino	202 (15.6)
Not Hispanic or Latino	1079 (83.4)
Not reported	10 (0.8)
Unknown	3 (0.2)
Race and ethnicity group[a], n (%)	--
White non-Hispanic	699 (54.0)
Communities of color	593 (45.8)
Missing	2 (0.2)
Obesity status[b], n (%)	--
Obese	283 (21.9)
Non-obese	1011 (78.1)
Baseline SARS-CoV-2 status[c], n (%)	--
Negative	1173 (90.6)
Positive	102 (7.9)
Missing	19 (1.5)
Pre-booster SARS-CoV-2 status[d], n (%)	--
Negative	763 (59.0)
Positive	432 (33.4)
Missing	99 (7.7)
Median time from Dose 2 to Booster, days (min, max)[e]	225 (124, 378)

Source: P204 (6-11 years) Tables 14.1.3.13.2, Table 14.1.6.2, and 14.1.4.1.3.2 (Amendment 503)
Note: Part 1 & Part 2 mRNA-1273 primary series – booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Percentages are based on the number of safety participants (N). The Safety Set of Part 1 consists of all enrolled participants and Part 2 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.
c. Baseline SARS-CoV-2 Status: Negative is defined as a negative RT-PCR test for SARS-CoV-2, and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1. Positive is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid on or before Day 1.
d. Pre-booster SARS-CoV-2 Status: Negative is defined as negative RT-PCR test and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at the date of booster dose. Positive is defined as immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test at the date of booster dose and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid at the date of booster dose.
e. Time from Dose 2 is calculated as: Date of Booster minus Date of Dose 2 of mRNA-1273 plus 1. Median time from Dose 2 of primary series to booster was 221 days for participants from Part 2 and 315 days for participants from Part 1.

6.4.3 Vaccine Effectiveness

6.4.3.1 Primary immunogenicity endpoints

Vaccine effectiveness of the mRNA-1273 booster dose in children was inferred based on the evaluation of the nAb GMC and SRR against the ancestral SARS-CoV-2 strain (D614G) elicited after the booster dose in Study P204 as compared to those following the primary series of mRNA-1273 in young adults from Study P301. The co-primary endpoints, described in Section 6.4.1, were evaluated in participants without evidence of prior SARS-CoV-2 infection pre-booster (PPIS-Neg) for the 6-11 years age group and without evidence of prior SARS-CoV-2 infection pre-primary series (PPIS) for the young adult group.

Results for the co-primary endpoint of GMC ratio (children to young adults) are displayed in Table 20 below. The GMC ratio was 4.2 (95% CI 3.5, 5.0) which met the pre-specified success criterion of a lower bound (LB) of 95% CI ≥ 0.667.

Table 20. Geometric Mean Antibody Concentrations (GMC) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose, Participants 6-11 Years, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18-25 Years, Study P301, PPIS

Children 6-11 Years mRNA-1273 25 µg BD GMC [95% CI][a] N1=95	Young Adults18-25 Years mRNA-1273 100 µg PS GMC [95% CI][a] N1=294	GMC Ratio [Children/Young Adults] [95% CI][a]	Met Success Criterion[b]
5847.5 [4999.6, 6839.1]	1400.4 [1281.1, 1530.8]	4.2 [3.5, 5.0]	Yes

Source: EUA 27073 Amendment 503, P204 (6-11 years), Table 14.2.1.1.4.1.1.2
LLOQ: 10, ULOQ: 281600
BD = booster dose; CI = confidence interval; GMC = geometric mean concentration; PPIS-Neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status; PPIS = Per-Protocol Immunogenicity Subset; PS = primary series
N1 = Number of participants who have nAb data available at the time point for specific analysis.
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.
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 GMC Ratio is ≥0.667 based on the noninferiority margin of 1.5.

Among booster recipients 6-11 years who were included in the PPIS-Neg Subset, the GMC observed at 28 days post-booster dose was approximately 12-fold higher compared to GMC observed immediately pre-booster, and approximately 4-fold higher compared to GMC observed at 28 days post-primary series.

Results for the co-primary endpoint of difference in SRR between children and young adults are displayed in Table 21 below. The difference in SRR was 0.7% (95% CI -3.5, 2.4) which met the pre-specified success criterion of a LB of the 95% CI ≥ −10%.

Table 21. Seroresponse Rates (SRR) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose (from pre-Dose 1), Participants 6-11 Years, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18-25 Years, Study P301, PPIS

Children 6-11 Years mRNA-1273 25 µg BD SRR[a] % (n/N1) [95% CI][b]	Young Adults 18-25 mRNA-1273 100 µg PS SRR[a] % (n/N1) [95% CI][b]	Difference in Seroresponse Rate (Children minus Young Adults) [95% CI][c]	Met Success Criterion[d]
100.0% (88/88) [95.9, 100.0]	99.3% (292/294) [97.6, 99.9]	0.7% [-3.5, 2.4]	Yes

Source: EUA 27073 Amendment 503, Study P204 (6-11 years) Table 14.2.1.2.5.1.1.2
LLOQ: 10, ULOQ: 281600
BD = booster dose; CI = confidence interval, PPIS-Neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status; PPIS = Per-Protocol Immunogenicity Subset; PS = primary series
n = number of seroresponders; N1 = Number of participants who have nAb data available at the time point(s) for specific analysis.
a. Seroresponse from pre-Dose 1 baseline at a participant level is defined as a change from below the LLOQ to equal or above 4 x 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%.

To assess for the change in nAb concentration attributable solely to the booster dose, FDA requested a post hoc analysis using a revised seroresponse definition based on the proportion

of participants 6-11 years achieving a ≥ 4-fold rise in nAb concentrations from the pre-booster time point, rather than pre-Dose 1. For this descriptive post hoc analysis, seroresponse following booster was defined as follows:

- Seroresponse for participants with pre-booster nAb concentrations < LLOQ, as a post-booster nAb concentration ≥ 4 x LLOQ,
- Seroresponse for participants with pre-booster nAb concentrations ≥ LLOQ, as ≥ 4-fold rise in those with pre-booster nAb concentration.

Results of this post hoc analysis are shown in Table 22 below. In this analysis, the difference in SRR was -6.7% (95% CI -13.8, -2.7). The lower SRR observed among booster recipients 6-11 years using this revised seroresponse definition was likely due to the substantially higher pre-booster GMC in children (485.6 AU/mL) compared to the pre-Dose 1 GMC in young adult participants (11.1 AU/mL), making it more difficult comparatively for participants 6-11 years to achieve the 4-fold rise required to demonstrate seroresponse.

Table 22. Post Hoc Analyses of Seroresponse Rates (SRR) as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D615G) at 28 Days Post-Booster Dose (from pre-BD), Participants 6-11 Years, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18-25 Years, Study P301, PPIS

Children 6-11 Years mRNA-1273 25 µg BD SRR[a] % (n/N1) [95% CI][b]	Young Adults 18-25 Years mRNA-1273 100 µg PS SRR[a] % (n/N1) [95% CI][b]	Difference in SRR % (Children minus Young Adults) [95% CI][c]
92.6% (88/95) [85.4, 97.0]	99.3% (292/294) [97.6, 99.9]	- 6.7% [-13.8, -2.7]

Source: EUA 27073 Amendment 503; Study P204 (6-11 years) Table 14.2.3.1.3.1.2, Response to IR dated September 9, 2022 (Am 515)
N1: number of participants with nAb values available at baseline (pre-booster for P204 and pre-dose 1 for P301) and specified post-baseline time point; n=number of seroresponders
BD=booster dose; CI = confidence interval; PPIS-Neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status; PPIS = Per-Protocol Immunogenicity Subset; PS = primary series
a. Seroresponse from pre-booster (for P204 participants) or pre-Dose 1 (for P301 participants) at a participant level is defined as a change from below the LLOQ to equal or above 4 x 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.

Subgroup analyses of primary immunogenicity endpoint

Most of the study participants in Study P204 were White, Non-Hispanic, and non-obese; therefore, subgroup analyses of co-primary endpoints by race, ethnicity, and obesity status were not conducted, as the number of participants in most subgroups would be too small to allow for meaningful interpretation of the results. Subgroup analyses by sex were comparable between males and females.

Subgroup analyses of co-primary endpoints based on pre-booster SARS-CoV-2 status are shown in Table 23. Neutralizing antibody GMCs were notably higher after booster vaccination in participants 6-11 years with evidence of SARS-CoV-2 infection pre-booster compared to those with negative SARS-CoV-2 status pre-booster.

Table 23. Subgroup Analyses of Co-Primary Immunogenicity Endpoints of GMCs and SRRs as Measured by Pseudovirus nAb Assay against the Ancestral Strain (D614G) at 28 Days Post-Booster, Participants 6-11 Years, Study P204, PPIS, Compared to at 28 Days Post-Primary Series, Participants 18-25 Years, Study P301, PPIS

Pre-booster SARS-CoV-2 Status	6-11 Years mRNA-1273 25 µg BD GMC [95% CI][a]	18-25 Years* mRNA-1273 100 µg PS GMC [95% CI][a]	GMCR (6-11y/ 18-25y) [95% CI][a]	6-11 Years mRNA-1273 25 µg BD SRR[b], % (n/N1) [95% CI][c]	18-25 Years* mRNA-1273 100 µg PS SRR[b], % (n/N1) [95% CI][c]	Difference in SRR % (6-11y minus 18-25y) [95% CI][d]
Any	N1=129 6586.1 [5758.5, 7532.6]	N1=294 1400.4 [1281.2, 1530.7]	**4.7 [4.0, 5.5]**	100% (120/120) [97.0, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7 [-2.4, 2.4])**
Positive[e]	N1=27 8903.7 [6518.6, 12161.6]	N1=294 1400.4 [1274.1, 1539.2]	**6.4 [4.6, 8.8]**	100% (25/25) [86.3, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7 [-12.7, 2.5]**
Negative[f]	N1=95 5847.5 [4999.6, 6839.1]	N1=294 1400.4 [1281.1, 1530.8]	**4.2 [3.5, 5.0]**	100% (88/88) [95.9, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7 [-3.5, 2.4]**

Source: EUA 27073 Amendment 503, Study P204 (6-11 years) Table 14.2.1.1.4.1.2.2 and Table 14.2.1.2.5.1.2.2
LLOQ: 10, ULOQ: 281600
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.
BD = booster dose; CI = confidence interval; GMC = geometric mean concentration; GMCR= GMC Ratio; nAb = neutralizing antibody; PPIS=per-protocol immunogenicity subset; PS= Primary Series; SRR=seroresponse rate
N1 = number of participants who have nAb data available at the time point for specific analysis; n=number of seroresponders
* The 18-25 years comparator group, for whom data are presented for all 3 analyses, consists of all participants in the per-protocol immunogenicity subset with negative SARS-CoV-2 status at baseline (pre-Dose 1 of primary series).
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 of GMC and GMC Ratio with 95% CIs.
b. SRR = Seroresponse rate at BD-Day 29 from baseline (pre-dose 1 of the primary series) is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
e. Positive is defined as immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test at the date of booster dose and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid at the date of booster dose.
f. Negative is defined as negative RT-PCR test and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid at the date of booster dose.

6.4.3.2 Clinical efficacy

Due to the open-label study design of the booster phase of the study and the lack of a comparator group, as well as the limited median duration of follow-up (29 days post-booster), vaccine efficacy was not assessed. In the ongoing study, participants are actively monitored for potential cases of COVID-19. As of the data cutoff, there were no reports of severe COVID-19 cases among booster recipients 6-11 years of age in the study.

6.4.4 Safety

6.4.4.1 Overview of adverse events

Safety analyses included data from participants 6-11 years of age in the booster phase of Study P204 through the cutoff date of May 23, 2022, with a median duration of follow-up of 29 days post-booster. A total of 1,294 participants contributed to the P204 booster phase Safety Set, with a total of 1,280 participants contributing to the booster phase Solicited Safety Set.

Table 24 below summarizes adverse events among booster recipients in the study. Overall, 91.1% of participants (n=1,165) experienced any solicited local AR within 7 days after booster, and 64.3% (n=823 participants) experienced any solicited systemic AR within 7 days after booster. Unsolicited adverse reactions within 28 days after booster were reported by 13.1% of participants (n=169), with all assessed as nonserious except for 1 participant (<0.1%) who experienced an SAE. Severe unsolicited AEs within 28 days were reported by 0.5% of booster recipients (n=6) and consisted of events that were generally consistent with solicited reactogenicity events.

Through the data cutoff, 116 (9.0%) participants reported unsolicited AEs that were medically-attended adverse events. There was 1 investigator assessed AESI reported, which will be discussed further in Section 6.4.4.4 below. There were no reported events of MIS-C, myocarditis, or pericarditis and no reported deaths or AEs leading to discontinuation.

Table 24. Safety Overview, Participants 6 Through 11 Years of Age, Study P204 Booster Phase, Safety Set, Solicited Safety Set

Participants Reporting at Least One Safety Event	6-11 Years mRNA-1273 25 µg BD
Solicited Ars	**n/N1 (%)**
Solicited local AR within 7 days	1165/1279 (91.1)
Grade 3 or 4 solicited local AR	33/1279 (2.6)
Solicited systemic AR within 7 days	823/1280 (64.3)
Grade 3 or 4 systemic AR	78/1280 (6.1)
Unsolicited AEs	**n/N (%)**
Unsolicited AE to 28 days after booster injection	169/1294 (13.1)
Nonserious unsolicited AE	168/1294 (13.0)
Related nonserious unsolicited AE	52/1294 (4.0)
Severe nonserious unsolicited AE	6/1294 (0.5)
Related severe nonserious unsolicited AE	6/1294 (0.5)
MAAE[a]	116/1294 (9.0)
Related MAAE	10/1294 (0.8)
SAE[a]	1/1294 (<0.1)
Related SAE	0
AESI[a,b]	1/1294 (<0.1)
Deaths[a]	0
AE leading to study discontinuation[a]	0

Sources: P204 Table (6-11 years) 14.3.1.3.7.1.2, 14.3.1.7.4.1.2, 14.3.1.7.4.6.2. (Amendment 503)
AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BD = booster dose; MAAE=medically attended adverse event; N = number of safety participants in the booster dose analysis; N1=number of exposed participants who submitted any data for the event; SAE=serious 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) in booster dose analysis. The Safety Set consists of all participants who received a booster dose in booster phase. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (i.e., had at least 1 postbaseline solicited safety assessment).
a. Numbers reflect AEs reported through the data cutoff
b. This event did not meet the protocol definition of an AESI but was categorized as an AESI by the investigator. See details in Section 6.4.4.4 below.

6.4.4.2 Solicited adverse reactions

The frequency and severity of solicited local and systemic ARs within 7 days following the booster dose are shown below in Table 25 and Table 26, respectively. Assessment of booster dose reactogenicity is limited by the open-label study design for this part of the study. To provide a frame of reference to assess the rates of solicited adverse reactions following a

booster dose, the rates of solicited ARs following Dose 1 and Dose 2 of the primary series from the double-blinded Part 2 portion of this study (reviewed in FDA EUA memorandum) are included in the same table.

By order of frequency, solicited ARs after a booster dose were pain at the injection site (90.1%), fatigue (48.9%), headache (38.2%), axillary swelling/tenderness (27.8%), myalgia (21.0%), chills (14.0%), nausea/vomiting (13.1%), arthralgia (12.5%), swelling at the injection site (10.9%), erythema at the injection site (10.7%), and fever (8.5%).

6.4.4.2.1 Solicited local reactions

Overall, solicited local ARs following booster dose appeared to be less frequent compared to after the primary series doses, except for axillary swelling or tenderness which occurred more frequently after booster vaccination (27.8%) than after primary series doses (15.5% post-Dose 1 and 18.0% post-Dose 2). Pain at the injection site was the most frequently reported solicited local AR following the booster dose (90.1%). Grade 3 local ARs were reported by 2.6% of booster recipients, the majority of which were Grade 3 injection site pain.

Solicited local ARs reported within 7 days of booster dose had a median onset of 1-day post-vaccination and resolved after a median of 3 days (range 1 to 27 days). Delayed solicited injection site reaction (defined as beginning after 7 days post-booster) was reported by 1 (<0.1%) booster recipient who experienced injection site swelling on Day 9 that lasted 1 day.

Table 25. Frequency of Solicited Local Adverse Reactions in Participants 6 Through 11 Years Within 7 Days of Primary Series Dose 1 and Dose 2 (Study P204 Part 2) and 7 Days of Booster Dose (Study P204 Booster Phase), Solicited Safety Set*

Event	Primary Series Dose 1 P204 Part 2 mRNA-1273 50 µg N=3004 n(%)	Primary Series Dose 2 P204 Part 2 mRNA-1273 50 µg N=2988 n(%)	Booster Dose P204 Booster Phase mRNA-1273 25 µg N=1280 n(%)
Any local adverse reaction	N1=3004	N1=2988	N1=1279
Any	2814 (93.7)	2849 (95.3)	1165/1279 (91.1)
Grade 3	54 (1.8)	122 (4.1)	33/1279 (2.6)
Pain at injection site	N1=3004	N1=2988	N1=1279
Any	2796 (93.1)	2832 (94.8)	1152/1279 (90.1)
Grade 3	28 (0.9)	81 (2.7)	24/1279 (1.9)
Erythema (redness)	N1=3004	N1=2988	N1= 1279
Any ≥25 mm	349 (11.6)	559 (18.7)	137/1279 (10.7)
Grade 3	16 (0.5)	33 (1.1)	4/1279 (0.3)
Swelling (hardness)	N1=3004	N1=2988	N1= 1279
Any ≥25 mm	354 (11.8)	507 (17.0)	139/1279 (10.9)
Grade 3	19 (0.6)	20 (0.7)	4/1279 (0.3)
Axillary swelling or tenderness	N1=3004	N1=2988	N1= 1279
Any	465 (15.5)	537 (18.0)	355/1279 (27.8)
Grade 3	3 (<0.1)	3 (0.1)	4/1279 (0.3)

Source: P204 (6-11 years) Table 14.3.1.1.1.2.1, Table 14.3.1.1.2.2.1. (Amendment 364) and Table 14.3.1.3.7.1.2 (Amendment 503)
* Solicited Safety Set for Primary Dose 1 and 2 includes all randomized 6-11 years old participants in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose.
Note: The primary series phase of Study P204 was not conducted contemporaneously with the booster phase.
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).
Grade 3 grade for injection site erythema (redness) or swelling (hardness) is defined as: ≥100 mm.
Grade 3 for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: prevents daily activity.

6.4.4.2.2 Solicited systemic reactions

In general, within 7 days after booster dose, solicited systemic ARs were reported more frequently compared to after Dose 1 of the primary series but less frequently when compared to after Dose 2 of the primary series. Fatigue was the most frequently reported solicited systemic AR, reported in 48.9% of participants post-booster dose. Grade 3 or higher systemic ARs were reported by 6.1% of booster recipients. Fatigue was the most common Grade 3 solicited AR post-booster and was reported by 3.7% of booster recipients. Fever was reported by 8.5% of booster recipients compared with 3.3% and 23.9% of participants after Dose 1 and Dose 2, respectively. One participant (<0.1%) with concurrent COVID-19 reported Grade 4 fever (temperature >40.0°C/104.0°F) of 104.5°F 4 days following booster dose.

Solicited systemic ARs reported within 7 days of booster dose had a median onset of 1-day post-vaccination and resolved after a median of 2 days (range 1 to 14 days). Among booster recipients in the solicited safety set, 36.1% reported use of medication for pain or fever.

Table 26. Frequency of Solicited Systemic Adverse Reactions in Participants 6 Through 11 Years Within 7 Days of Primary Series Dose 1 and Dose 2 (Study P204 Part 2) and 7 Days of Booster Dose (Study P204 Booster Phase), Solicited Safety Set*

Event	Primary Series Dose 1 P204 Part 2 mRNA-1273 50 µg N=3004 n(%)	Primary Series Dose 2 P204 Part 2 mRNA-1273 50 µg N=2988 n(%)	Booster Dose P204 Booster Phase mRNA-1273 25 µg N=1280 n(%)
Any systemic adverse reaction	N1=3004	N1=2988	N1=1280
Any	1740 (57.9)	2335 (78.1)	823 (64.3)
Grade 3	53 (1.8)	364 (12.2)	77 (6.0)
Grade 4	0	0	1 (<0.1)
Fever	N1=3003	N1=2988	N1=1276
Any: ≥38.0° C	99 (3.3)	714 (23.9)	108 (8.5)
Grade 3: 39°C to 40.0°C	17 (0.6)	115 (3.8)	16 (1.3)
Grade 4: >40.0°C	0	0	1 (<0.1)
Headache	N1=3002	N1=2986	N1=1280
Any	938 (31.2)	1622 (54.3)	489 (38.2)
Grade 3	18 (0.6)	119 (4.0)	22 (1.7)
Grade 4	0	0	0
Fatigue	N1=3002	N1=2986	N1=1279
Any	1298 (43.2)	1925 (64.5)	625 (48.9)
Grade 3	31 (1.0)	191 (6.4)	47 (3.7)
Grade 4	0	0	0
Myalgia	N1=3002	N1=2986	N1=1280
Any	438 (14.6)	843 (28.2)	269 (21.0)
Grade 3	11 (0.4)	71 (2.4)	19 (1.5)
Grade 4	0	0	0
Arthralgia	N1=3002	N1=2986	N1=1279
Any	260 (8.7)	482 (16.1)	160 (12.5)
Grade 3	3 (<0.1)	25 (0.8)	12 (0.9)
Grade 4	0	0	0
Nausea/vomiting	N1=3002	N1=2986	N1=1279
Any	325 (10.8)	716 (24.0)	168 (13.1)
Grade 3	5 (0.2)	19 (0.6)	6 (0.5)

Event	Primary Series Dose 1 P204 Part 2 mRNA-1273 50 µg N=3004 n(%)	Primary Series Dose 2 P204 Part 2 mRNA-1273 50 µg N=2988 n(%)	Booster Dose P204 Booster Phase mRNA-1273 25 µg N=1280 n(%)
Grade 4	0	0	0
Chills	N1=3002	N1=2986	N1=1279
Any	309 (10.3)	904 (30.3)	179 (14.0)
Grade 3	3 (<0.1)	19 (0.6)	4 (0.3)
Grade 4	0	0	0
Use of antipyretic or pain medication	N=3004	N=2988	N=1280
Any	730 (24.3)	1423 (47.6)	462 (36.1)

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 (Amendment 364) and Table 14.3.1.3.7.1.2 and 14.1.8.3.2 (Amendment 503)
* Solicited Safety Set for Primary Dose 1 and 2 includes all randomized 6-11 years old participants in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose.
Note: The primary series phase of Study P204 was not conducted contemporaneously with the booster phase.
Any=Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity for headache, fatigue, myalgia, arthralgia: Grade 3: prevents daily activity; Grade 4: requires emergency room visit or hospitalization
Toxicity for nausea/vomiting: Grade 3: prevents daily activity;.Grade 4: requires emergency room visit or hospitalization for hypotensive shock
Toxicity for chills: Grade 3: prevents daily activity and requires medical intervention; Grade 4: requires emergency room visit or hospitalization
Toxicity for fever: Grade 3: 39 - 40 C; Grade 4: >40 C.

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited ARs by sex, race, and ethnicity. Overall, no notable differences were observed among the demographic subgroups, although some race subgroups had too few participants to draw meaningful conclusions.

Subgroup analysis was also performed for solicited local and systemic reactions by pre-booster SARS-CoV-2 status. Local ARs were generally reported by a numerically lower proportion of participants with a positive pre-booster SARS-CoV-2 status (86.2%) compared to those with a negative pre-booster SARS-CoV-2 status (94.2%). Rates of systemic ARs were also numerically lower for pre-booster SARS-CoV-2 positive participants (58.6%) compared to pre-booster SARS-CoV-2 negative participants (67.0%). Notably, fever was reported by 4.4% of pre-booster SARS-CoV-2 positive participants compared to 10.6% of pre-booster SARS-CoV-2 negative participants.

6.4.4.3 Unsolicited adverse events

Through the May 23, 2022 data cutoff, 717 participants (55.4%) had at least 28 days of follow-up after BD. The median follow-up time after BD for all participants was 29 days.

Table 27 below shows rates of unsolicited AEs which occurred within 28 days of booster vaccination and at rates ≥ 1%. Overall, 169 participants (13.1%) reported 238 unsolicited AEs. Unsolicited AEs were most commonly reported under System Organ Class (SOC) *Infections and infestations* (6.2%) and *General disorders and administration site conditions* (2.6%). The most commonly reported AE by Preferred Term was COVID-19, reported by 25 participants (1.9%).

In general, unsolicited AEs were reported at similar rates among participants with negative and positive pre-booster SARS-CoV-2 status, except for cases of COVID-19 which occurred at a higher rate among participants without evidence of prior SARS-CoV-2 infection pre-booster (2.6%) compared to those with evidence of prior SARS-CoV-2 infection pre-booster (0.9%). No cases of COVID-19 were severe.

Table 27. Participant Incidence of Unsolicited Adverse Events Occurring in ≥ 1% of Participants Within 28 Days Following Booster Dose, by MedDRA Primary System Organ Class and Preferred Term, Participants 6 Through 11 Years of Age, Study P204, Safety Set

Unsolicited Adverse Event	mRNA-1273 25 µg BD N=1294 n (%)
Any unsolicited adverse event	169 (13.1)
System Organ Class Preferred Term	--
Infections and infestations	80 (6.2)
COVID-19	25 (1.9)
Upper respiratory tract infection	17 (1.3)
Nervous system disorders	15 (1.2)
Headache	15 (1.2)
Respiratory, thoracic and mediastinal disorders	23 (1.8)
Skin and subcutaneous tissue disorders	13 (1.0)
General disorders and administration site conditions	34 (2.6)
Fatigue	13 (1.0)

Source: P204 (6-11 years) Table 14.3.1.10.3.2 (Amendment 503)
Abbreviations: BD=booster dose; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities
Note: Percentages are based on the number of safety participants (N).

6.4.4.4 Adverse events of special 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). Through the data cutoff, there was one AESI as assessed by the investigator, which did not meet the protocol definition of an AESI. This was an event of mild chest pain in a 12-year-old male participant (11 years at enrollment) with onset 3 days post-booster dose. Relevant medical history included bronchial hyperactivity, seasonal allergy, food allergy, and eczema. Other AEs reported by the participant near the time of chest pain onset included fatigue, sore throat, abdominal pain upper, and respiratory tract infection viral, and the participant reported taking concomitant inhaled bronchodilator and seasonal allergy medication at the time of the event. A cardiac workup including electrocardiogram, high sensitivity troponin 1, erythrocyte sedimentation rate, and C-reactive protein were all reported to be normal. The event resolved the same day. The investigator considered the event to be non-cardiac chest pain of unknown etiology and assessed it as related to study vaccination due to the temporal association. In FDA's assessment, the participant's concurrent symptoms (fatigue, sore throat) and medical history (bronchial hyperactivity/seasonal allergies) support an alternative viral etiology, though relatedness of the AE of chest pain to study vaccination cannot be ruled out due to its onset 3 days following vaccination.

6.4.4.5 FDA Standard MedDRA Queries

FDA Standard MedDRA Queries (SMQs) were conducted to evaluate for constellations of unsolicited AEs with onset following BD through the data cutoff date. SMQs are pre-determined sets of MedDRA preferred terms (PTs) grouped together to represent medical concepts,

including but not limited to allergic, neurologic, inflammatory, cardiac, and autoimmune disorders. Only the SMQs which captured events considered clinically relevant by the FDA will be discussed.

SMQ *Hypersensitivity*

Through the data cutoff, events under the SMQ *Hypersensitivity* were reported by 24 participants (1.9%). Within 28 days of booster dose vaccination, hypersensitivity events were reported by 22 participants (1.7%). The most common event was urticaria, which occurred in 8 participants (0.6%).

There was one event of serum sickness-like reaction considered mild in severity reported in a 8 year old male 10 days post-booster dose. Concurrent symptoms included generalized pruritis, arthralgia, myalgia, chills, and nausea with joint and extremity swelling. No fever or upper respiratory symptoms were reported, and there were no known new exposures or sick contacts. Treatment with antihistamines and steroids was initiated 2 days after onset of symptoms. Extremity swelling resolved 16 days after symptom onset. The participant's symptoms resolved within one month except for continued intermittent urticaria for which he is being treated with antihistamines. The event is considered to be resolving. FDA agrees with the investigator assessment that the event is related to study vaccine.

None of the events yielded by the SMQ *Hypersensitivity* were clinically consistent with anaphylaxis.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, the safety data was queried using several cardiac-related SMQs (including *Cardiomyopathy*, *Cardiac arrhythmia, Cardiac failure, Ischemic heart disease, and Noninfectious myocarditis and pericarditis*). The search also included additional terms based on the CDC working case definition of myocarditis and pericarditis (Appendix B). Analysis of the data through the data cutoff identified 2 events in 2 participants (0.2%). One was the AESI of chest pain described in Section 6.4.4.4 above. The other was an event of dyspnea in a 10-year-old female which occurred 27 days after booster dose vaccination. The event resolved the same day and was assessed by the investigator as related to study vaccine. In FDA assessment, given the latency of onset, this event was unlikely to be related to vaccine. Neither of these events was considered by the FDA to be consistent with vaccine-associated myocarditis or pericarditis.

SMQ *Arthritis*

A total of 5 events under the SMQ *Arthritis* were reported in 5 participants (0.4%) within 28 days of booster dose vaccination, including 4 events of arthralgia which were graded mild to moderate in severity. As described in Section 6.4.4.2.2, arthralgia was included as a solicited adverse reaction for the 7 days following booster vaccination and was reported by 12.5% of participants, the majority of which were also graded as mild to moderate in severity.

There was 1 event of juvenile idiopathic arthritis (JIA) reported within 28 days of booster dose vaccination. The nonserious moderate event of JIA occurred 8 days post-booster dose in a 9-year-old male. This participant had a history of a prior SAE of post-viral transient synovitis of bilateral hips (approximately 4 months post-Dose 2 of his primary series) diagnosed following magnetic resonance imaging that showed fluid around both hip joints with negative laboratory

study results and negative COVID-19 test. At that time, a family history of autoimmune disorders was reported. At a follow up visit 3 months after the diagnosis of synovitis, the participant was referred to a rheumatology specialist due to physical exam findings of swollen fingers and decreased grip strength bilaterally and associated elevated autoimmune laboratory results. He was diagnosed with JIA and started on immunosuppressive medication, the timing of which coincided with the safety follow-up reporting period after the administration of the booster dose, but was not associated with worsening of synovitis symptoms during the 8 days after vaccination. The investigator assessed the event as not related to study vaccine. FDA agrees with the investigator assessment.

6.4.4.6 Serious adverse events

A 7-year-old male participant with a past medical history significant for eczema and seasonal allergies reported one SAE of severe abdominal pain 16 days post-booster dose that required hospitalization and had previously reported a nonserious mild AE of abdominal pain 5 days post-booster dose that resolved after 2 days. On the same day as SAE onset, the participant also reported nonserious AEs of food allergy (peanut allergy) and vomiting. While hospitalized, the participant had laboratory and radiologic testing done including magnetic resonance imaging (MRI), abdominal ultrasound, and a COVID-19 test, all of which were negative. The participant improved with intravenous fluid and anti-emetic treatment and was discharged the next day with a diagnosis of “stomach inflamed”. The investigator considered the event not related to study vaccination. In FDA’s assessment, symptoms of food allergy and vomiting offer a plausible alternative etiology for severe abdominal pain onset. However, given the previously reported imbalance in the rates of abdominal pain following mRNA-1273 primary series compared to placebo for this age group (EUA Review Memorandum) and the limited information available for this case, the potential for relatedness to study vaccine cannot be ruled out.

6.4.4.7 Deaths

There were no reported deaths in the booster phase of Study P204 through the data cutoff.

6.4.4.8 AEs leading to discontinuation from study participation

There were no reported AEs leading to study discontinuation in the booster phase of Study P204 through the data cutoff.

6.4.5 Summary for Participants 6 through 11 Years of Age

The primary evidence to support effectiveness of a booster dose in children 6-11 years is a comparison of the immune responses generated following a single mRNA-1273 booster dose vaccination in children 6-11 years of age in Study P204 to the immune responses after a 2-dose mRNA-1273 primary series in a clinically relevant young adult subgroup (18-25 years) from the Study P301 study population for whom VE has been demonstrated. The study met the pre-specified success criteria for the two co-primary endpoints of GMC ratio and difference in SRR. The GMC ratio (children to young adults) was 4.2 (95% CI 3.5, 5.0), which met the pre-specified success criterion of a LB of the 95% CI ≥ 0.667. Based on the protocol definition of seroresponse, defined from pre-Dose 1 of the primary series to 28 days post-booster dose, the difference in SRR (children minus young adults) was 0.7% (95% CI −3.5, 2.4), which met the pre-specified success criterion of a LB of the 95% CI ≥ -10%. In a descriptive post hoc analysis using a more clinically meaningful seroresponse definition comparing neutralizing antibody concentrations from pre-booster dose to 28 days post-booster dose, the difference in SRR was -6.7% (95% CI -13.8, -2.7).

The immunogenicity data across demographic subgroups were generally consistent with those observed in the overall study population, although interpretation of the results was limited by the small number of participants in most subgroups. The primary immunogenicity endpoints were based on a population of participants without evidence of SARS-CoV-2 infection pre-booster. Analyses of the primary endpoints based on a population of all participants, regardless of pre-booster SARS-CoV-2 status, resulted in GMC ratios and SRR differences that also would have met the study criteria for non-inferiority. Participants with evidence of SARS-CoV-2 infection pre-booster had numerically higher nAb GMCs compared to those with negative SARS-CoV-2 pre-booster status.

Due to the open-label study design, lack of a comparator group, and short median duration of follow-up after booster dose (29 days), an assessment of vaccine efficacy was not conducted. As of the data cutoff, there were no reports of severe COVID-19 cases among booster recipients.

Solicited local and systemic adverse reactions among booster recipients were mostly mild to moderate in severity and generally of short duration. The most frequently reported solicited adverse reactions after booster dose were injection site pain (90.1%), fatigue (48.9%), and headache (38.2%). Grade 3 reactions were reported at rates of 2.6% and 6.0% for solicited local and systemic reactions, respectively. Fever was reported by 8.5% of booster recipients, with Grade 3 fever reported by 1.3% of booster recipients and Grade 4 fever reported by 1 booster recipient (<0.1%). Most solicited local and systemic adverse reactions were reported by a numerically lower proportion of participants with evidence of prior SARS-CoV-2 infection pre-booster compared to participants without evidence of prior SARS-CoV-2 infection pre-booster.

An analysis of the safety data through the data cutoff of May 23, 2022, with a median duration of follow-up of 29 days post-booster dose, revealed no new safety concerns. As of the data cutoff, there were no cases of myocarditis, pericarditis, or MIS-C among booster recipients. There was one SAE of abdominal pain in a 7-year-old that occurred 16 days post-booster dose that is considered by FDA to be potentially related to study vaccination, though a plausible alternative etiology exists.

6.5 FDA Review of Post-authorization Safety Data

As of September 14, 2022, more than 230 million doses of the Moderna COVID-19 vaccine (including both the original and bivalent formulations) have been administered to individuals of all ages in the US (CDC COVID Data Tracker, accessed on September 21, 2022). It is not known what proportions of these numbers represent unauthorized use of the vaccines. The Moderna COVID-19 Vaccine, Bivalent is currently authorized (as of August 31, 2022) for use as a single booster dose at least two months following primary or booster vaccination among individuals at least 18 years of age. In addition, extensive post-authorization safety data for the original Moderna COVID-19 Vaccine (monovalent) are relevant for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain the original SARS-CoV-2 strain.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the original Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent, and the results are briefly summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding the number of doses administered, and lack of direct and unbiased comparison groups. Reports in

VAERS may not be medically confirmed and are not verified by the FDA. Also, there is no certainty that the reported event was actually due to the vaccine. A 3rd, 4th, or 5th COVID-19 vaccine dose as recorded in VAERS may not represent a dose given as an authorized booster dose.

Among individuals vaccinated with the Moderna COVID-19 Vaccine, Bivalent from September 1, 2022 through September 27, 2022, there were 757 VAERS reports (755 US reports) among all ages, with 24 (3.2%) reported as serious.

> The most frequent PTs (Bivalent Vaccine): no adverse event, pyrexia, headache, incorrect dose administered, fatigue, chills, pain, underdose, nausea, and pain in extremity.

As of September 21, 2022, there were 480,312 VAERS reports (396,894 US reports) following vaccination with the original Moderna COVID-19 vaccine among all ages, with 124,916 (26%) reported as serious. There were 69,116 reports (48,777 US) following a 3rd, 4th, or 5th dose (i.e., booster dose).

> The most frequent PTs among all ages, and all doses were: headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, injection site pain
>
> The most frequent PTs among all ages, ≥ 3 doses of vaccine were: headache, pyrexia, fatigue, SARS-COV-2 test, expired product administered, chills, COVID-19, pain, nausea, pain in extremity.

The Moderna COVID-19 Vaccine, Bivalent is not currently authorized for use among individuals less than 18 years of age, however, post-authorization safety data for the original Moderna COVID-19 Vaccine (monovalent) are relevant for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain the original SARS-CoV-2 strain.

As of September 22, 2022, there were 9,043 VAERS reports (8,298 [91.8%] US reports) following vaccination with the original Moderna COVID-19 vaccine among children 12 through 17 years of age, of which 766 (8.5%) were serious reports. There were 817 reports (806 US) after a 3rd, 4th, or 5th dose. Although 804 reports (793 US) were for dose 3, these reports may represent a 3rd dose in the primary series, rather than a booster dose.

> The most frequent PTs among individuals 12 through 17 years of age, all doses, were: product administered to patient of inappropriate age, no adverse event, pyrexia, interchange of vaccine products, pain in extremity, product storage error, headache, myocarditis, fatigue, and chest pain.

As of September 22, 2022, there were 368 VAERS reports (289 [78.5%] US reports) following vaccination with the original Moderna COVID-19 vaccine among individuals 6 through 11 years of age, of which 80 (21.7%) were serious reports. There were 44 reports (43 US) after a 3rd, 4th, or 5th dose. Note that 43 reports (42 US) were for dose 3 and possibly represent a 3rd dose in the primary series, rather than a booster.

> The most frequent PTs among individuals 6 through 11 years of age, all doses, were: product administered to patient of inappropriate age, no adverse event, incorrect dose

administered, pyrexia, wrong product administered, interchange of vaccine products, expired product administered, vomiting, chest pain, and product storage error.

Safety concerns previously identified from post-authorization safety surveillance data in VAERS for the original Moderna COVID-19 Vaccine are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets.

Anaphylaxis

Post-authorization surveillance for the original Moderna COVID-19 Vaccine 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. Anaphylaxis is an important identified risk in the pharmacovigilance plan (PVP), and it is included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information.

As of September 8, 2022, there have been a total of 1,049 US VAERS reports of anaphylactic/anaphylactoid reaction following the original Moderna COVID-19 Vaccine among individuals of all ages (based on an automated search). Of these, 1 case was reported among individuals 12 through 17 years of age, and there were 0 reports among children 6 through 11 years of age. PTs included in the automated VAERS query were as follows: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. The estimated crude reporting rate for anaphylaxis following the original Moderna COVID-19 Vaccine for all ages in the US is 4.6 cases per million doses administered which is similar to estimated rates for other vaccines.

Myocarditis and Pericarditis

Post-marketing safety data with Moderna COVID-19 Vaccine are relevant to Moderna COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process and both vaccines contain the original SARS-CoV-2 strain.

As of September 8, 2022, there have been a total of 1,720 US VAERS reports of myocarditis/pericarditis following the original Moderna COVID-19 Vaccine among individuals of all ages (based on an automated search). Of these, 8 reports were in adolescents 12 through 17 years of age, all of which occurred in individuals 15-17 years of age, and there were 0 reports in children 6 through 11 years of age. The original Moderna COVID-19 Vaccine was authorized for use in ages 6 years through 17 years on June 17, 2022; authorized use of Moderna COVID-19 Vaccine in children has only occurred over the past 3 months. PTs included in the automated VAERS query were as follows: autoimmune myocarditis, autoimmune pericarditis, eosinophilic myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, pleuropericarditis.

Post-marketing data with authorized or approved monovalent mRNA COVID-19 Vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following receipt of the second primary series dose or first booster dose, with most booster doses likely administered at least 5 months after completing primary vaccination. For the Moderna COVID-19 Vaccine (Original), the observed risk is highest in males 18 through 24 years of age.

Although some cases of vaccine-associated myocarditis/pericarditis following the original Moderna Vaccine have required intensive care support, available data from short-term follow-up suggests that most individuals have had resolution of symptoms with conservative management. CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. Among individuals aged 12-29 years, available data from follow-up with cardiologists/healthcare providers at least 90 days after onset of myocarditis symptoms suggests most individuals fully recover from myocarditis following mRNA vaccination.[25] Information is not yet available about potential longer-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.

Some, but not all, observational analyses of post-marketing data suggest that there may be an increased risk of myocarditis and pericarditis in males under 40 years of age following the second dose of Moderna COVID-19 Vaccine (monovalent) primary series relative to other authorized or approved mRNA COVID-19 vaccines.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the vaccine Fact Sheets and Prescribing Information (Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience) for the original Moderna COVID-19 Vaccine. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis for the Moderna COVID-19 Vaccine. To help ensure appropriate monitoring of such risks and protect public health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration are conservatively managed and may not meet the definition of serious adverse events, this will help ensure that all cases are reported by the Sponsor and vaccination providers.

Review of the above VAERS data, as well as ongoing review of VAERS data and the Sponsor's periodic safety reports, did not identify new safety concerns for the original Moderna COVID-19 vaccine or bivalent Moderna COVID-19 vaccine. The extensive post-authorization safety data for the monovalent original Moderna COVID-19 Vaccine are relevant for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain an original SARS-CoV-2 strain. Most reported AEs are labeled events, including anaphylaxis, myocarditis and pericarditis, and consistent with the known safety profile for the original vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the Moderna COVID-19, Bivalent vaccine.

7 FDA Review of Other Information Submitted in Support of the EUA Amendment

7.1 Clinical Assay Information

Reporter Virus-Based Microneutralization Assay from (b) (4), (b) (4)

Immunogenicity analysis from two clinical studies P203 and P204 were used in support of the authorization of Moderna's bivalent booster (Wuhan-Hu-1+Omicron BA.4/BA.5) vaccine. In study P203, children from 12 through 17 years of age were administered the bivalent booster vaccine and in Study P204 children from 6 through 11 years of age were administered the bivalent booster vaccine. Post-booster dose vaccination serology samples from both clinical studies and a comparator group (from study P301, in participants 18-25 year of age in whom efficacy was demonstrated) were tested using a Reporter Virus Microneutralization assay validated at (b) (4). Similar to the pseudotyped virus neutralization assay developed at Duke University, the Reporter Virus Microneutralization assay from the (b) (4) (b) (4) is also a cell-based assay but one that uses an infectious, replication-competent SARS-CoV-2 that expresses the (b) (4). The assay measures the ability of SARS-CoV-2 neutralizing antibodies to inhibit the infection of 293T-ACE2 cells by the SARS-CoV-2-GFP Reporter Virus Particles (RVP). (b) (4) test serum samples, reference standard, and controls are (b) (4) with a known quantity of SARS-CoV-2-(b) (4) for (b) (4) prior to infection of 293T-ACE2 cells. Post infection, the cells are (b) (4)

The serum antibody concentration per test sample is determined by interpolating the mean of the replicate Foci Forming Unit (FFU) values from 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 reported titer is the antibody concentration associated with the lowest dilution with an antibody concentration within the quantifiable range of the assay. The antibody results are reported as the Geometric Mean Concentration (GMC) in AU/mL. The assay-validation study evaluated Precision and Ruggedness, Relative Accuracy, Selectivity, Dilutional Linearity, LLOQ, ULOQ, and Specificity. From the data, we conclude that the assay is validated and is appropriate for its intended purpose.

7.2 Chemistry, Manufacturing, and Control (CMC) Information

The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Drug Product (DP) is supplied in multi-dose vials containing a target volume of 3.2 mL (2.5 mL nominal) for extraction of five 0.5 mL doses or ten 0.25 mL doses. Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains mRNA encoding the Spike protein (S protein) from the SARS-CoV-2 Wuhan-Hu-1 strain (Original) and mRNA encoding the S protein from the SARS-CoV-2 Omicron sublineages BA.4 and BA.5 (Omicron BA.4/BA.5). A single 0.5 mL dose contains a total of 50 µg (25 µg each of Original and BA.4/BA.5) mRNA, total lipids of 1.01 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.25 mg tromethamine, 1.2 mg tromethamine hydrochloride, 0.021 mg acetic acid, 0.10 mg sodium acetate trihydrate, and 43.5 mg sucrose. Each 0.25 mL dose of Moderna COVID-19 Vaccine, Bivalent contains half of these ingredients.

Manufacturing and product quality information to support an EUA for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) presentation intended for use in individuals 6 years of age and older was previously reviewed in the August 31, 2022 FDA Decision Memorandum. The manufacture of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is performed at existing facilities that were previously included in the EUA for the manufacture of the original Moderna COVID-19 Vaccine. One manufacturing facility has not been included in the EUA for the manufacture of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), because we were not able to assess the facility's adequacy due to ongoing FDA inspection review. FDA may further consider the inclusion of that manufacturing facility following its review of the inspectional information and any other pertinent information.

7.3 Inspection of Clinical Study Sites

Bioresearch Monitoring inspections were conducted at 4 domestic clinical investigator sites participating in the conduct of study mRNA-1273-P203 in participants 12 through 17 years of age and at 6 domestic clinical investigator sites participating in the conduct of study mRNA-1273-P204 in participants 6 through 11 years of age. The inspections did not reveal problems impacting the data submitted in support of this EUA amendment.

7.4 Pharmacovigilance Activities

Moderna is conducting safety-related post-authorization/post-marketing studies for the monovalent vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Moderna submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

Sponsor pharmacovigilance activities

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); myocarditis; pericarditis; multisystem inflammatory syndrome (MIS) in children and adolescents; COVID-19 resulting in hospitalization or death
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine, Bivalent and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The studies below are being conducted for Moderna Covid-19 Vaccine, Original monovalent in large scale databases with an active comparator and will include a

sub-analysis for Moderna COVID-19 Vaccine, Bivalent. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Moderna COVID-19 Vaccine, Bivalent in all age groups in the following studies:

- **Study mRNA-1273-P903.** Post-Authorization 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
  Objective: To assess the potential increased risk of prespecified AESIs, including myocarditis/pericarditis, after being vaccinated with Moderna COVID-19 vaccine, including the Bivalent Omicron modified vaccine, if feasible.

- **Study mRNA-1273-P911.** Long-term outcomes of myocarditis following administration of Spikevax (COVID-19 vaccine mRNA)
  Objective: To characterize long-term outcomes of myocarditis temporally associated with administration of Moderna COVID-19 vaccine, including the Bivalent Omicron modified vaccine, if feasible.

In addition, the Sponsor will conduct a new stand-alone post-authorization observational study to evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in all age groups of the general US population for individuals who receive a bivalent booster dose in the US. The protocol synopsis for this study will be submitted by 11/1/2022.

Other pharmacovigilance activities

Mandatory reporting by vaccination providers to VAERS, and to the extent feasible, to the Sponsor, for the following events:

- Vaccine administration errors whether or not associated with an AE
- Serious AEs (irrespective of attribution to vaccination)
- Myocarditis
- Pericarditis
- Cases of multisystem inflammatory syndrome in children
- Cases of COVID-19 that result in hospitalization or death

Active surveillance of vaccine recipients via the v-safe program: v-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine parents/guardians (or the recipient) for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant AE.

7.5 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.

8 Benefit/Risk in the Context of the Proposed EUA For Moderna COVID-19 Vaccine, Bivalent (Original And Omicron BA.4/BA.5) Booster Dose in Individuals 6 Years of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for nearly 96 million cases of COVID-19 and over 1 million deaths in the US. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5. Current treatment options for COVID-19 in individuals 6-17 years of age include antiviral medications, convalescent plasma, and monoclonal antibodies approved or authorized for the management of individuals with COVID-19. These interventions are generally most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2 they are usually not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19 including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA approved and authorized vaccines provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. Currently authorized COVID-19 vaccines for disease prevention in individuals 6-17 years of age include the two mRNA-based vaccines from Moderna and Pfizer-BioNTech and an adjuvanted, protein subunit vaccine from Novavax (in individuals 12-17 years of age only). These monovalent vaccines are based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. In the setting of the viral variants that have emerged, boosting with available vaccines (based on the ancestral strain) has been able to restore some degree of protection against serious and symptomatic disease, but it appears that effectiveness against transmission and symptomatic disease declines more rapidly than that against serious disease, as has been illustrated by studies conducted in the United States,[26,27] Israel,[21] Qatar,[18] Portugal,[28] and England.[13]

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have previously been evaluated by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the United States due to the rapid evolution of the SARS-CoV-2 variants. In addition to those clinical data, nonclinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response to current predominantly circulating BA.4 and BA.5 variants which is several-fold higher than the response provoked by the original (monovalent) vaccine.

Based on previous experience and available evidence, vaccination with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster dose is expected to provoke a stronger immune response to the currently circulating BA.4 and BA.5 variants. That noted, it is uncertain exactly how the magnitude of the increase in antibody response to the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster dose will translate into effectiveness against specific COVID-19 outcomes in humans, including symptomatic and serious disease with currently circulating variants, and this uncertainty is even greater for potential variants that may emerge in the future.

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the data from FDA Biologics Effectiveness and Safety (BEST) System, within a week after second dose of mRNA-based COVID-19 vaccine primary series, the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events was 2.1 per 100,000 doses for individuals aged 18–64 years (unpublished data), and 12.5 per 100,000 doses for males aged 18–25 years.[29] Within a week after a second dose of vaccine, the adjusted observed rate of myocarditis or pericarditis for individuals aged 18–64 years who received mRNA-based COVID-19 vaccines was 1.8 per 100,000 doses (unpublished data), and 13.0 per 100,000 doses for males aged 18–25 years.[29] The meta-analysis of BEST data for the Pfizer COVID-19 Vaccine reports excess cases per one million second doses for 12–15-year-old males as 132.2 (95%CI: 92.0-189.6), for 16-17-year-old males as 159.9 (95%CI: 59.9-414.3), and for 18-25- year-old males as 95.6 (95%CI: 61.0-147.4). Based on the data from BEST, within a week after the second dose of the Pfizer COVID-19 Vaccine primary series, the crude observed ratio (with adjustment for claims processing delay) of myocarditis or pericarditis was 0.73 cases per 100,000 vaccine doses among individuals aged 5-11 years, and 0.95 cases per 100,000 vaccine doses among male individuals aged 5-11 years (unpublished data, based on fewer than 10 cases). The Moderna COVID-19 Vaccine was authorized in June 2022 for use as a primary series in individuals 6-17 years of age and an equivalent measure for the Moderna COVID-19 Vaccine cannot be estimated at this time due to the insufficient data accumulated with the vaccine in this age group. The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns in addition to those previously characterized. In addition, passive and active surveillance systems will be utilized to continuously monitor adverse reactions and any emerging safety concerns post EUA.

The totality of the available evidence indicates that Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster doses will likely increase the immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant. Administration of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster is appropriate for all individuals 6-17 years of age at least two months after previous primary or booster vaccination but is particularly important in those individuals who have never been previously boosted since protection against symptomatic and serious COVID-19 may have waned over time since administration of the primary series.

Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns additional to the extensively characterized safety profile of originally authorized and approved mRNA COVID-19 vaccines, and post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge. Table 28 provides a summary of the benefit risk considerations in a standard FDA format.

Table 28. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for nearly 96 million cases and 1 million deaths in the US • There has been a succession of variants (Delta, Omicron BA.1 and most recently BA.5) that have led to a reduction in vaccine effectiveness • Although the available COVID-19 vaccines based on the original (ancestral) strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased	• COVID-19 is a serious disease associated with significant morbidity and mortality from initial infection and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals • Certain available COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals, but decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups.
Current Treatment Options	• Antiviral medications, convalescent plasma, and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity • There are two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6-17 years of age and an adjuvanted, protein subunit COVID-19 vaccine for use as a primary series in individuals 12-17 years of age; the mRNA vaccine from Pfizer-BioNTech is also authorized for use as a booster dose.	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • Vaccines play an important role in pandemic control and provide important protection.
Benefit	• The immunogenicity and safety of booster vaccines against Beta, Delta, and Omicron BA.1 variants were previously evaluated by both current mRNA vaccine manufacturers; however, these vaccines were not deployed in the US because of SARS-CoV-2 variant evolution • Non-clinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster • Uncertain how the magnitude of the increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease	• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses will likely increase the broad immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant • Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses is appropriate for all previously vaccinated individuals 6-17 years of age regardless of the number of prior COVID-19 vaccinations, but especially those who have never been previously boosted since protection against serious disease may have waned over time since administration of the primary series

8.2 Conclusions Regarding Benefit-Risk

For individuals 6-17 years of age, the known and potential benefits of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose outweigh the known and potential risks of the bivalent booster considering the totality of available evidence and the outstanding uncertainties. The benefit-risk profile of available mRNA COVID-19 vaccines is well understood following the administration of over one billion doses. FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. During the current wave of COVID-19 caused in large part by the BA.5 sublineage, administration of a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose is expected to have a favorable benefit-risk profile, potentially not only restoring protection against serious outcomes from COVID-19, but also by reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome. Broader protection against COVID-19 variants potentially elicited by the bivalent vaccine may also help protect against future emerging variants.

9 Overall Summary and Recommendations

Following review of information submitted in support of the EUA request, and VRBPAC recommendations from the June 28, 2022, meeting, the review team considered the following in its assessment of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5):

- As summarized in Section 2 of this review, the 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.

- The scientific evidence available to support this EUA request was as follows:
    - clinical safety and immunogenicity data from a study which evaluated a second booster dose with the bivalent (Original and Omicron BA.1) vaccine following a primary series and first booster with the original Moderna COVID-19 Vaccine,
    - clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Moderna COVID-19 Vaccine,
    - post-marketing safety surveillance data with primary series and booster doses of the original Moderna COVID-19 Vaccine, and
    - non-clinical immunogenicity data from a study of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

- Based on the totality of available scientific evidence, it is reasonable to conclude that the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), when administered as a single booster dose to individuals 6-17 years of age who have completed primary vaccination or a booster dose of an authorized or approved COVID-19 vaccine at least 2 months prior, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5. As summarized in Section 6, effectiveness of the original Moderna COVID-19 Vaccine as a booster dose in individuals 6-17 years was inferred by immunobridging based on a comparison of SARS-CoV-2 neutralizing antibody (nAb) responses against the original (ancestral) strain at 1 month post-booster dose in each pediatric age cohort (6-11 years, 12-17 years) to the nAb responses generated after the 2-dose primary series of Moderna COVID-19 Vaccine by young adults 18-25 years of age, in whom vaccine efficacy was demonstrated in a clinical endpoint efficacy trial. Immunobridging success criteria for the co-

primary endpoints of GMC ratio and difference in seroresponse rates were met for both pediatric age cohorts. As summarized in Section 5, FDA considers it reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine booster dose to any age group for which available evidence would support emergency use authorization of a booster dose of any COVID-19 vaccine manufactured by the same process as the bivalent vaccine. Thus, vaccine effectiveness of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA. 4/BA.5) in individuals 6-17 years can be inferred based on extrapolation of clinical immunogenicity data from evaluation of a related bivalent COVID-19 vaccine (manufactured using the same process as the original Moderna COVID-19 vaccine and containing original and Omicron BA.1 components) in adults ≥ 18 years of age. These data demonstrated statistically superior neutralizing antibody responses against Omicron BA.1, and statistically non-inferior neutralizing antibody responses against the original strain, for the bivalent vaccine compared to the original vaccine.

- Based on FDA's review of the available scientific evidence, including the data summarized in Section 6 and assessment of benefits and risks in Section 8 of this review, the known and potential benefits of a booster dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks when used as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6-17 years of age. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variant sublineages BA.4 and BA.5. Uncertainties related to benefits include that effectiveness of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to prevent COVID-19 is inferred and extrapolated from immunogenicity data with a different Omicron-containing bivalent vaccine (Original and Omicron BA.1) manufactured by the same process. It is also uncertain how any given magnitude of the increase in antibody response to a bivalent (Original and BA.4/BA.5) booster vaccine, relative to the original (monovalent) vaccine, will translate into effectiveness against COVID-19 outcomes, including symptomatic disease. However, this uncertainty is considered against available evidence demonstrating waning protection from COVID-19 vaccine primary series and booster doses, decreased effectiveness of currently available COVID-19 vaccines against Omicron BA.5 (the predominant SARS-CoV-2 sublineage in the US) compared to previous strains, and the time that would be needed to accrue clinical trial data with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to more directly assess effectiveness. Additional uncertainties include effectiveness against future SARS-CoV-2 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 and potential risks include generally self-limited common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, and axillary swelling/tenderness) and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Moderna COVID-19 Vaccine recipients 6-17 years of age. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

- The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is currently authorized under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination or the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine in individuals 12 years of age and older. The original (monovalent) Pfizer-BioNTech COVID-19 Vaccine, based on the

ancestral SARS-CoV-2 strain, is currently authorized for use under EUA as a first booster dose in individuals 5-11 years of age. COVID-19 vaccines based on currently circulating variants of concern are not currently approved or available for use in individuals 6-11 years of age.

Based on the considerations outlined above, the review team recommends authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination or the most recent booster dose with any FDA authorized or approved monovalent COVID-19 Vaccine in individuals 6-17 years of age.

10 Appendix A. Adverse Events of Special Interest

Table 29. Adverse Events of Special Interest

Medical Concept	Medical Concept Descriptions/Guidance
Anosmia, Ageusia	New onset of anosmia or ageusia associated with COVID-19 or idiopathic etiology DOES NOT INCLUDE anosmia or ageusia associated with sinus/nasal congestion, congenital, or traumatic etiologies
Subacute thyroiditis	Acute inflammatory disease of the thyroid (immune-mediated or idiopathic) DOES NOT INCLUDE new onset of chronic thyroiditis
Acute pancreatitis	New onset of pancreatitis in the absence of a clear, alternate etiology, such as alcohol, gallstones, trauma, recent invasive procedure, etc.
Appendicitis	Any event of appendicitis
Rhabdomyolysis	New onset of rhabdomyolysis in the absence of a clear, alternate etiology, such as drug/alcohol abuse, excessive exercise, trauma, etc.
Acute respiratory distress syndrome (ARDS)	New onset of ARDS/respiratory failure due to acute inflammatory lung injury DOES NOT INCLUDE non-specific symptoms of shortness of breath or dyspnea, nor events with underlying etiologies of heart failure or fluid overload
Coagulation disorders	New onset of thrombosis, thromboembolic event, or non-traumatic hemorrhage/bleeding disorder (e.g., stroke, DVT, pulmonary embolism, disseminated intravascular coagulation (DIC), etc.)
Acute cardiovascular injury	New onset of clinically confirmed, acute cardiovascular injury, such as myocarditis, pericarditis, arrhythmia, confirmed by ECG (e.g., atrial fibrillation, atrial flutter, supraventricular tachycardia), stress cardiomyopathy, heart failure, acute coronary syndrome, myocardial infarction, etc. DOES NOT INCLUDE transient sinus tachycardia/bradycardia, non-specific symptoms such as palpitations, racing heart, heart fluttering or pounding, irregular heartbeats, shortness of breath, chest pain/discomfort, etc.
Acute kidney injury	New onset of acute kidney injury or acute renal failure in the absence of a clear, alternate etiology, such as urinary tract infection/urosepsis, trauma, tumor, nephrotoxic medications/substances, etc. Increase in serum creatinine by ≥ 0.3 mg/dl (or ≥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

Medical Concept	Medical Concept Descriptions/Guidance
Acute liver injury	New onset in the absence of a clear, alternate etiology, such as trauma, tumor, hepatotoxic medications/substances, etc: >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 rash Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruptions, and necrotic or exfoliative reactions
Systemic inflammatory syndromes	Multisystem inflammatory syndrome in adults (MIS-A) or children (MIS-C) Kawasaki's disease Hemophagocytic lymphohistiocytosis (HLH)
Thrombocytopenia	Platelet count <150 x 10^9/L (thrombocytopenia) New clinical diagnosis, or worsening, of thrombocytopenic condition, such as immune thrombocytopenia, thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	Clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation without recent trauma for a period of no longer than 6 weeks, synovial increased leukocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. DOES NOT INCLUDE new onset of chronic arthritic conditions
New onset or worsening of neurological disease	Immune-mediated neurological disorders Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Peripheral facial nerve palsy (Bell's palsy) Transverse myelitis Encephalitis/Encephalomyelitis Aseptic meningitis Seizures/convulsions/epilepsy Narcolepsy/hypersomnia
Anaphylaxis	Anaphylaxis associated with study drug administration
Other syndromes	Fibromyalgia Postural Orthostatic Tachycardia Syndrome Chronic Fatigue Syndrome Myalgic encephalomyelitis Post viral fatigue syndrome Myasthenia gravis

Source: Sponsor's Clinical Study Protocol, mRNA-1273-P203, Appendix 4

11 Appendix B. List of Preferred Terms Used in the Enhanced Analysis for Potential Cases of Myocarditis or Pericarditis, Based on CDC Case Definition

The following PTs were used in the enhanced analysis to identify potential cases of myocarditis or pericarditis based on the CDC case definition (for adults).

- acute chest syndrome
- angina pectoris
- autoimmune myocarditis
- autoimmune pericarditis
- cardiac dysfunction
- cardiac function test abnormal
- cardiomyopathy
- cardiovascular function test abnormal
- chest discomfort
- chest pain
- conduction disorder
- defect conduction intraventricular
- dyspnoea
- dyspnoea at rest
- dyspnoea exertional
- ECG electrically inactive area
- ECG P wave inverted
- ECG signs of myocardial infarction
- ECG signs of myocardial ischemia
- ECG signs of ventricular hypertrophy
- electrocardiogram abnormal
- electrocardiogram ST segment
- electrocardiogram ST segment abnormal
- electrocardiogram ST segment depression
- electrocardiogram ST segment elevation
- electrocardiogram ST-T segment depression
- electrocardiogram ST-T segment abnormal
- electrocardiogram ST-T segment elevation
- eosinophilic myocarditis
- giant cell myocarditis
- hypersensitivity myocarditis
- immune-mediated myocarditis
- magnetic resonance imaging heart
- musculoskeletal chest pain
- myocardial edema
- myocarditis
- painful respiration
- palpitations
- pericardial effusion
- pericardial effusion malignant
- pericardial rub
- pericarditis
- pericarditis constructive
- pleuropericarditis
- syncope
- troponin
- troponin C
- troponin I
- troponin I increased
- troponin I normal
- troponin T increased

Table 30. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

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

Source: Sponsor's Clinical Overview, mRNA-1273-P203, Section 7.5.5.
Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
b Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

c To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d Adler et al 2015.
e Typically descr bed as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

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