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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073, Amendments 593 596 and 597
Sponsor	ModernaTX, Inc
Submission Date	December 2, 2022 (EUA request for 6 months through 5 years)
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Signatory Authority	Peter Marks, M.D., Ph.D., Director, CBER
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Review Completion Date	December 7, 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 0.2 mL suspension for intramuscular injection (for 6 months through 5 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 with the Moderna COVID-19 Vaccine
Intended Population	Individuals 6 months through 5 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 December 2, 2022, has led to over 640 million cases of coronavirus disease 2019 (COVID-19), including 6.6 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 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 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. On October 12, 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 6 through 17 years of age.

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) in individuals 18 years of age and older 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 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 Moderna COVID-19 Vaccine (previously reviewed by FDA),
- post-marketing safety surveillance data with primary series and booster doses of the 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).

Evidence considered by FDA to support the October 12, 2022, authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 through 17 years of age included:

- 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 Moderna COVID-19 Vaccine used as a primary series and booster dose in individuals 6 through 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.

FDA determined that for the 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 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 with Moderna COVID-19 Vaccine. Furthermore, this extensive experience with the 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 infer 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 Moderna COVID-19 Vaccine for use as a booster dose. This approach is additionally supported by data from a recently published observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, which demonstrated that bivalent booster doses provided additional protection against symptomatic SARS-CoV-2 infection.[2]

In the current EUA request submission, Moderna has provided safety and effectiveness data from evaluation of a booster dose of the Moderna COVID-19 Vaccine in individuals 17 months through 5 years of age. Clinical data on a booster dose of the Moderna COVID-19 Vaccine (mRNA-1273) in individuals 17 months through 5 years of age consist of safety and immunogenicity data from an ongoing Phase 2/3 study, in which 145 participants 17 months through 5 years of age received a 10 µg booster dose of mRNA-1273 administered at least 6 months after completion of a 2-dose primary series (25 µg) of mRNA-1273. Given the protocol-specified interval of at least 6 months between completion of the primary series and the booster dose, participants who were 6 months through 5 years of age at the time of enrollment into Part 1 of P204 (primary series) were 17 months through 5 years of age by the time of receipt of the booster dose. Data from these participants were considered supportive of effectiveness in individuals down to 6 months of age based on the analyses of immunogenicity from the primary series of the Moderna COVID-19 Vaccine (EUA Clinical Review Memorandum dated 16 June 2022), which demonstrated a higher immune response in the younger cohort of participants 6-23 months compared to the cohort of participants 2-5 years. 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 to the nAb responses generated after the 2-dose mRNA-1273 primary series in young adults 18-25 years of age from Study P301, the most clinically relevant population for whom vaccine efficacy was demonstrated in a clinical endpoint efficacy trial. 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 (a median duration of follow-up of 99 days post-booster dose through the data cutoff of August 18, 2022) revealed no new safety concerns. No new safety concerns were identified when also including an additional 113 participants who received a higher dose level of the booster and/or primary series dose in the study (a median duration of follow-up post-booster to the data cutoff of 105 days). Solicited local and systemic reactions among booster dose recipients were mostly mild to moderate in severity and generally of short duration. The most common solicited local adverse reactions after a booster dose in participants 17 months through 36 month and 37 months through 5 years were pain at the injection site (41.7% and 56.0%, respectively), erythema (10.8% and 4.0%, respectively), and swelling (10.8% and 12.0%, respectively). The most common solicited systemic adverse reactions after a booster dose for participants 17 months through 36 months of age were irritability/crying (52.5%), sleepiness (26.7%), and loss of appetite (23.3%). The most common solicited systemic adverse reactions after a booster dose for participants 37 months through 5 years of age were fatigue (32.0%), headache (20.0%), and myalgia (12.0%). 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 cutoff, there were no cases of myocarditis or pericarditis and no serious adverse events reported among 258 booster dose recipients. The extrapolation of safety data from booster recipients 17 months through 5 years of age down to the 6 month through 16 month age group is reasonable given the reassuring safety profile of the primary series in the youngest age cohort of participants 6-23 months who received the primary series in Study P204 Part 2, 21.3% of whom were between the ages of 6 months to 12 months (EUA review memorandum, dated June 16, 2022) and based on previous experience with booster doses of the Moderna COVID-19 Vaccine in other age groups demonstrating that adverse reactions after a booster dose generally occurred at similar to lower frequencies compared to those after the primary series.

Post-marketing safety data for the 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 November 30, 2022, more than 245 million doses of the Moderna COVID-19 Vaccine and over 14 million doses of Moderna COVID-19, Bivalent have been administered in the US. In recipients of any age and all doses, the most frequently reported non-medication error preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) for Moderna COVID-19 Vaccine, Bivalent were headache, pyrexia, fatigue, pain, chills, pain in extremity, dizziness, nausea, arthralgia, 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 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 months-5 years of age, when administered at least 2 months after the completion of a primary series with Moderna 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 months through 5 years of age as a single booster dose (10 µg) administered at least 2 months after completion of a primary series with Moderna 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,[3] 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.[4] 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.[5,6] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[5] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.[7,8] 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 December 2, 2022, has led to over 640 million cases of coronavirus disease 2019 (COVID-19), including 6.6 million deaths worldwide.[1] In the US, more than 98 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[9] Approximately 3.6% of cases occurred in children 0 months through 4 years of age.[10]

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, including, most recently, the Omicron sublineages. 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.5, BQ.1, BQ1.1, and BF.7 sublineages, which account for the majority of COVID-19 cases in the US currently.[11] 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.[12] Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available monovalent vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the recently 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, and potentially other circulating Omicron sublineages (e.g., BQ.1, BQ1.1, BF.7, and XBB), is an important public health need.

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 6 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) is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 through 11 years of age and 50 µg in 0.5 mL in individuals 12 years of age and older. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 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. 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 5 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 and a first booster dose for individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate or who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. The authorized dosing interval for a booster is at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine. 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 for young children include the following:

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.

Monoclonal antibodies have been deployed for prophylaxis and for treatment of COVID-19 in older children and adults. However, some variants have emerged that are relatively resistant to neutralization by the existing monoclonal antibodies. FDA recently announced that bebtelovimab is not currently authorized for use in the US because it is not expected to neutralize Omicron variants BQ.1 and BQ1.1.

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 monovalent 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 monovalent 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.[13,14,15,16,17,18,19,20,21,22,23]

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.[13,14,15] Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[13,14,15,16] 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[13,17,18,19] 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.[22,23]

In a recently published observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, the relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥2 monovalent vaccine doses among persons for whom 2–3 months and ≥8 months had elapsed since last monovalent dose was 30% and 56% among persons aged 18–49 years, 31% and 48% among persons aged 50–64 years, and 28% and 43% among persons aged ≥65 years, respectively, with relative benefits increasing with time since receipt of the most recent monovalent vaccine dose. Absolute vaccine effectiveness after ≥2 monovalent vaccine doses against symptomatic SARS-CoV-2 infection was 43% (95% CI: 39–46%) among persons aged 18–49 years, 28% (95% CI: 22–33%) among persons aged 50–64 years, and 22% (95% CI: 15-29%) among persons aged ≥65 years.[2]

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 ICMRA 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 on 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 and on October 12, 2022, for use as a single booster dose in individuals 6 through 17 years of age.

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 Months Through 5 Years of Age

5.1 Summary of the EUA Request

On December 2, 2022, Moderna submitted a request to amend the EUA to include use of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 months through 5 years of age, as a single booster dose after completion of primary vaccination with Moderna COVID-19 Vaccine. This EUA amendment included non-clinical, clinical, CMC and postmarketing data previously submitted and reviewed under various IND amendments.

For individuals 6 months through 5 years of age, each 10 µg dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is formulated to contain 5 µg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized spike (S) protein of the original SARS-CoV-2 strain and 5 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.

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 months through 5 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 months through 5 years of age.

5.2 FDA Approach to Extrapolation from Available Clinical Data

Due to the rapid evolution of SARS-CoV-2 virus variants, including the currently 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 6 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 and October 12, 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) in individuals 6 through 17 years of age and individuals 18 years of age and older 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 profile for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk profile for use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a single booster dose in individuals 6 years of age and older 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 and the clinical data for the monovalent booster described in Section 6 below reflected a minimum interval of 6 months between Dose 2 and the booster 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.[24]

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 EUA 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) EUA 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 bivalent vaccine has been authorized under EUA for use as a booster dose in individuals 6 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 months through 5 years of age, if there was not a more favorable benefit/risk profile 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 months of age and older.

The drug substance manufacturing process and quality control are the same for all Moderna COVID-19 Vaccine presentations, except for changes related to the quality release tests specific to each SARS-CoV-2 variant lineage. The drug substance manufacturing and quality control information to support an EUA for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) presentation for use in individuals 6 months through 5 years of age was previously reviewed in the August 31, 2022 FDA Decision Memorandum. The drug product manufacturing and quality control information was submitted as amendments to the EUA and was reviewed and found acceptable.

6. FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Clinical Studies

Data to support the EUA amendment request are from two 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 children (6 months through 5 years of age) via immunobridging analyses which required demonstration of non-inferiority of neutralizing antibody responses and seroresponse rates after booster vaccination in children compared to after the primary series in young adults.

Study mRNA-1273-P204 is an ongoing, multi-part 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 the primary series 2-dose regimen 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 3-dose primary series).

Following the emergence of the Omicron variant and suggested improved protection in adults following an mRNA-1273 booster dose, protocol amendment 7 to Study P204 (dated 18

February 2022) introduced an optional mRNA-1273 booster dose at least 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 amendment pertains only to the safety and immunogenicity analyses of data collected from children 17 months through 7 years of age (from Part 1) enrolled in the optional booster dose portion of P204 who had completed the 2-dose primary series at least 6 months prior to the booster dose. The designs of the primary series portions of Part 1 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 Months Through 5 Years of Age

Study Number	Description	mRNA-1273 Age Cohort
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[a] N=295
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 primary series** **10 µg booster dose** 17 months - 5 years[b] N=145 **All Safety Participants[c]** 17 months – 7 years[b] N=258

a. Immunobridging comparator group
b. Imputed age at time of booster dose
c. Includes participants who received 50 µg primary series doses and/or a 25µg booster dose

6.2 Study P301

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 (nAb) 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 P204

6.3.1 Study Design

In the open-label booster phase of Study P204, participants who completed the primary series of mRNA-1273 (two doses of either 25 µg or 50 µg administered 28 days apart) in the dose-finding Part 1 portion of P204 were offered a booster dose of mRNA-1273 at least 6 months after completion of the 2-dose primary series. Participants were 6 months through 5 years of age at the time of the primary series and 17 months through 7 years of age at the time of the booster dose. The vaccine dose was based on the age of the participants at the time of the boosting (i.e., participants <6 years of age received a 10 µg dose and participants ≥6 years of age received a 25 µg dose). 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 of mRNA1273 as compared to young adults in Study P301 following a 2-dose primary series of mRNA-1273) of the neutralizing antibody responses against the ancestral strain of SARS-CoV-2 as measured by both the geometric mean concentration (GMC) and seroresponse rate (SRR). Participants will be followed for 12 months after receipt of the booster dose.

6.3.1.1 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 booster dose recipients in P204 (children 17 months through 5 years) 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 primary immunogenicity objective was to demonstrate the non-inferiority of the nAb response against the ancestral strain (D614G) in children who received an mRNA-1273 10 µg booster dose following a 25 µg primary series 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) was non-inferior if the lower bound (LB) of the 95% confidence interval (CI) ≥0.667.

Co-primary endpoint 2: Seroresponse rate (SRR)

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

Seroresponse was defined in the protocol as a change from pre-Dose 1 for both young adult primary series recipients and child 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 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. Only participants who received the 25 µg primary series followed by the 10 µg booster dose were included in the immunogenicity subsets and contributed to the analyses of the immunogenicity endpoints.

Table 2. Immunogenicity Analysis Populations, Participants 17 Months Through 5 Years of Age*, 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. • received a 25 µg primary series and a 10 µg booster dose
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 per schedule • Received a booster dose per schedule in the 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.

BD= booster dose
* Imputed age at booster dose in study P204
Source: Reviewer-generated table adapted from P204 Statistical Analysis Plan

6.3.1.2 Evaluation of efficacy

The booster phase of P204 did not include a formal assessment of vaccine efficacy. However, participants were 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.

6.3.1.3 Evaluation of safety

The primary safety objective of the booster phase of Study P204 is to describe the safety and reactogenicity of mRNA-1273 administered as a booster dose at least 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 3 below. For the analyses of solicited safety, only participants who received the 25 µg primary series followed by the 10 µg booster dose were included. For all other safety analyses, all participants were included, regardless of dose level of primary series or booster dose received.

Table 3. Safety Analysis Populations, Participants 17 Months Through 7 Years of Age, Study P204, Booster Phase

Population	Description
Safety Set	All participants who received a booster dose in booster phase. Used for safety analyses (except for solicited ARs).
Solicited Safety Set	All participants in the safety set who received a 25 µg primary series and a 10 µg booster dose and also 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 the booster phase

AR= adverse reaction
Source: Reviewer-generated table adapted from P204 Statistical Analysis Plan

6.3.2 Participant Disposition and Demographics and Other Baseline Characteristics

6.3.2.1 Inclusion in analysis populations

This EUA amendment includes data from the start of the booster phase of Study P204 through the data cutoff date of August 18, 2022, in participants ages 17 months through 7 years who received a 2-dose primary series of mRNA-1273 in Part 1 (25 µg or 50 µg) and a booster dose of mRNA-1273 (10 µg or 25 µg) at least 6 months after Dose 2 of the primary series.

As of the data cutoff, among participants who received the 25 µg primary series followed by the 10 µg booster dose, the median duration of follow-up after the booster dose was 99 days. When including all booster recipients in the study, regardless of the dose level of primary series or booster dose received, the median duration of follow-up after the booster dose was 105 days.

Age at time of booster dose was not systemically collected, but only reviewed by the investigator to determine the dose of the booster (10 µg for those <6 years of age and 25 µg for those ≥6 years). Imputed ages of participants at time of booster dose are presented in Table 6 and used for the analyses included in this review.

6.3.2.2 Participant disposition

The dispositions of participants who contributed safety data in the booster phase of P204 are shown in Table 4. Overall, 258 participants received a booster dose in the booster phase of the study and are included in the Safety Set. Of the 258 participants in the Safety Set, 145 received a 25 µg primary series followed by a 10 µg booster dose and 113 received a higher dose level of the primary series and/or booster dose vaccine. Six participants discontinued from the study, none of which were due to AEs.

Table 4. Disposition of Participants 17 Months Through 7 Years of Age*, Study P204 Booster Phase, All Enrolled

Disposition	17m -5y* mRNA-1273 25 µg PS/ 10 µg BD n (%)	17m – 7y* mRNA-1273 All Boosted [a] n (%)
Full Analysis Set (FAS)[b]	145	258
Safety Set[b]	145	258
Discontinued from Study	6 (4.1)	6 (2.3)
Reason for discontinuation	--	--
Withdrawal of consent	5 (3.4)	5 (1.9)
Other[c]	1 (0.7)	1 (0.4)

Disposition	17m -5y* mRNA-1273 25 µg PS/ 10 µg BD n (%)	17m – 7y* mRNA-1273 All Boosted [a] n (%)
Solicited Safety[d]	145 (100)	--

Source: IND 19745 Amendment 395, Study P204 (Booster 6 months to <6 years) Tables 14.1.1.2.1.1, 14.1.1.3.3.1
BD=booster dose; PS=Primary Series (2 doses administered 4 weeks apart).
Percentages are based on the number of participants in the Safety Set
*Age at booster dose was not systematically collected. These were imputed based on a birthday of the 15th day of participant birth month and year because the participant's day of birth was not collected,
a. All Boosted=all booster recipients, regardless of dose level of primary series or booster dose received
b. FAS and Safety Set numbers include Part 1 mRNA-1273 primary series dose participants who received a booster dose
c. Other was reported as due to personal reason
d. Solicited Safety=all individuals who had available solicited safety data. Those individuals who received a 25 µg primary series and a 10 µg booster dose contributed the primary solicited safety data.

The disposition of participants who contributed to immunogenicity analyses are shown in Table 5. Only participants who received the 25 µg primary series followed at least 6 months later by the 10 µg booster dose are included in the immunogenicity subsets. A total of 56 participants were included in the Per-Protocol Immunogenicity Subset- pre-booster SARS-CoV-2 negative (PPIS-Neg), used for the primary immunogenicity analyses.

Table 5. Disposition of Participants 17 Months Through 5 Years of Age*, Study P204 Booster Phase, Immunogenicity Subsets

Disposition	mRNA-1273 25 µg PS 10 µg BD n (%)
Immunogenicity Subset[a]	N=101
Per-Protocol Immunogenicity Subset (PPIS)[b]	74 (73.3)
Reason for exclusion from PPIS[c]	--
Positive baseline SARS-CoV-2 status	4 (4.0)
Received incorrect PS vaccination	2 (2.0)
Received incorrect BD vaccination	4 (4.0)
Had no immunogenicity data at BD-Day 29	4 (4.0)
Had no immunogenicity data at BD-Day 1	13 (12.9)
PP Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative[d] (PPIS-Neg)	56 (55.4)
Reason for exclusion from PPIS-Neg[c]	--
Positive pre-booster SARS-CoV-2 status	14 (13.9)
Missing pre-booster SARS-CoV-2 status	4 (4.0)

Source: IND 19745 Amendment 395, Study P204 (Booster 6 months to <6 years) Tables 14.1.1.3.3.1, 14.1.1.2.3.3
Percentages are based on the number of participants in the Immunogenicity Subset
BD=booster dose; PP=per protocol; PS=Primary Series (2 doses administered 4 weeks apart) , SARS-CoV-2=severe acute respiratory syndrome coronavirus-2
* Imputed age at time of booster dose
a. 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.
b. The Per-protocol (PP) Immunogenicity Subset consists of all participants in the Immunogenicity Subset for Booster Dose Analysis who met 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.
c. A subject who has multiple reasons for exclusion is listed under the reason appearing earliest
d. SARS-CoV-2 Negative defined by RT-PCR if available at BD-Day 1 and a negative bAb specific to SARS-CoV-2 nucleocapsid on or before BD-Day 1.

6.3.2.3 Demographic and baseline characteristics

The PPIS-Neg was the population used to assess primary immunogenicity endpoints, and included 56 children who received the 25 µg mRNA-1273 primary series followed by the 10 µg mRNA-1273 booster in Study P204. 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 (78.6% vs 69.8%) and multiracial (8.9% vs 4.7%) participants and a smaller proportion of Black (1.8% vs 9.8%) participants. Fewer P204 participants self-identified as Hispanic or Latino (7.1%) compared to young adult participants in P301 (26.1%). In the PPIS-Neg, the median duration between Dose 2 of primary series to receipt of the booster dose (BD) was 302.5 days.

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

Table 6. Demographics and Other Baseline Characteristics, Participants 17 Months Through 5 Years of Age*, Study P204 Booster Phase, PPIS-Neg, and Participants 18 Through 25 Years of Age, Study P301, Per-Protocol Immunogenicity Subset (PPIS)**

Characteristic	P204 17m – 5y* mRNA-1273 25 µg PS 10 µg BD N=56	P301 18-25 Years** mRNA-1273 100 µg PS N=295
Sex, n (%)	--	--
Female	28 (50.0)	152 (51.5)
Male	28 (50.0)	143 (48.5)
Age at Dose 1 of primary series	--	--
Median, years (minimum, maximum)	1 (0.5, 4)	23 (18, 25)
Age at booster dose[a]	--	--
Median, years (minimum, maximum)	2.3 (1.4, 5.6)	--
Race, n (%)	--	--
White	44 (78.6)	206 (69.8)
Black or African American	1 (1.8)	29 (9.8)
Asian	4 (7.1)	30 (10.2)
American Indian or Alaska Native	0 (0.0)	3 (1.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	2 (0.7)
Multiracial	5 (8.9)	14 (4.7)
Other	2 (3.6)	8 (2.7)
Not reported	0 (0.0)	3 (1.0)
Ethnicity, n (%)	--	--
Hispanic or Latino	4 (7.1)	77 (26.1)
Not Hispanic or Latino	52 (92.9)	216 (73.2)
Unknown	0 (0.0)	2 (0.7)
Race and ethnicity group[b], n (%)	--	--
White non-Hispanic	41 (73.2)	146 (49.5)
Communities of Color	15 (26.8)	149 (50.5)
Obesity status[c], n (%)	--	--
Obese	13 (23.2)	67 (22.7)
Non-obese	43 (76.8)	227 (76.9)
Missing	0	1 (0.3)
Median time from Dose 2 to Booster, days (min, max)[d]	302.5 (251, 377)	N/A

Source: IND 19745 Amendment 395, P204 (6 months -<6 years) Table 14.1.3.15.1
BD=booster dose ; PS=Primary series (2 doses administered 4 weeks apart) ; 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 PPIS-Neg participants in BD analysis for P204 and PPIS participants for P301.
* Imputed age at time of booster dose in study P204
** Age at primary series in study P301
a. Age at time of BD was not systematically collected. The median age and range at time of booster dose were imputed using the 15th day of participant birth month and year as day of birth was not collected. Median age and range were imputed in months and then converted to years for display in this table.
b. White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
c. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data for P204 and BMI ≥30 kg/m2 for P301
d. Time from Dose 2 is calculated as: Date of Booster minus Date of Dose 2 of mRNA-1273 plus 1.

The demographic and baseline characteristics for the booster dose (BD) analysis Safety Set are presented in Table 7. The Safety Set includes all booster recipients, regardless of the dose level of the primary series or BD received. In the Safety Set, approximately 4.3% of participants had evidence of prior SARS-CoV-2 infection at baseline (pre-Dose 1 of primary series) and 28.3% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 7. Demographic and Baseline Characteristics, Participants 17 Months Through 7 Years* of Age, Study P204 Booster Phase, Safety Set

Characteristic	17 months – 5 years* mRNA-1273 25 µg PS 10 µg BD N=145	17 months – 7 years* mRNA-1273 All PS[a] All BD[a] N=258
Sex, n (%)	--	--
Female	65 (44.8)	119 (46.1)
Male	80 (55.2)	139 (53.9)
Age at Dose 1 of Primary Series	--	--
Median, years (min, max)	1 (0.5, 5)	2 (0.5, 5)
Age at Booster Dose[b]		
Median, years	2.3 (1.4, 5.9)	3.3 (1.4, 7)
Race, n (%)	--	--
White	116 (80.0)	216 (83.7)
Black	4 (2.8)	9 (3.5)
Asian	9 (6.2)	12 (4.7)
American Indian or Alaska Native	1 (0.7)	1 (0.4)
Multiracial	11 (7.6)	16 (6.2)
Other	4 (2.8)	4 (1.6)
Ethnicity, n (%)	--	--
Hispanic or Latino	15 (10.3)	24 (9.3)
Not Hispanic or Latino	129 (89.0)	232 (89.9)
Not reported	1 (0.7)	2 (0.8)
Race and ethnicity group[c], n (%)	--	--
White non-Hispanic	104 (71.7)	195 (75.6)
Communities of color	41 (28.3)	63 (24.4)
Obesity status[d], n (%)	--	--
Obese	31 (21.4)	44 (17.1)
Non-obese	114 (78.6)	214 (82.9)
Baseline SARS-CoV-2 status[e], n (%)	--	--
Negative	137 (94.5)	245 (95.0)
Positive	7 (4.8)	11 (4.3)
Missing	1 (0.7)	2 (0.8)
Pre-booster SARS-CoV-2 status[f], n (%)	--	--
Negative	92 (63.4)	159 (61.6)
Positive	33 (22.8)	73 (28.3)

Characteristic	17 months – 5 years* mRNA-1273 25 µg PS 10 µg BD N=145	17 months – 7 years* mRNA-1273 All PS[a] All BD[a] N=258
Missing	20 (13.8)	26 (10.1)
Dosing regimen, n (%)	--	--
25 µg PS, 10 µg BD	145 (100)	145 (56.2)
50 µg PS, 10 µg BD	0	59 (22.9)
25 µg PS, 25 µg BD	0	16 (6.2)
50 µg PS, 25 µg BD	0	38 (14.7)
Median time from Dose 2 to BD, days (min, max)[g]	307 (237, 392)	310 (237, 403)
Median duration of follow-up post BD, days (min, max)	99 (11, 144)	105 (11, 144)

Source: IND 19745 Amendment 395, P204 (6m - 5 years) Tables 14.1.3.13.1 and 14.1.6.1
PS=Primary Series (2 doses administered 4 weeks apart), BD=Booster Dose
* Imputed age at time of booster dose.
a. Includes all booster recipients, regardless of dose level of PS or BD received.
b. Age at time of BD was not systematically collected. The median age and range at time of booster dose were imputed using the 15th day of participant birth month and year as day of birth was not collected. Median ages were imputed in months and then converted to years for display in this table.,
c. 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.
d. Obesity is defined as BMI ≥95th percentile of the WHO growth reference data.
e. Baseline (pre-Dose 1 of primary series) 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.
f. 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.
g. Time from Dose 2 is calculated as: Date of Booster minus Date of Dose 2 of mRNA-1273 plus 1.

6.3.3 Vaccine Effectiveness

Primary immunogenicity endpoints

Vaccine effectiveness of the mRNA-1273 booster dose in children was inferred based on the nAb GMC and SRR against the ancestral SARS-CoV-2 strain (D614G) elicited after the booster dose in Study P204 as compared to nAb responses following the primary series of mRNA-1273 in young adults in Study P301. The co-primary endpoints, described in Section 6.3.1, were evaluated in participants without evidence of prior SARS-CoV-2 infection pre-booster (PPIS-Neg) for the P204 participants and without evidence of prior SARS-CoV-2 infection pre-primary series (PPIS) for the young adult group. Given the protocol-specified interval of at least 6 months between completion of the primary series and the booster dose, participants who were 6 months through 5 years of age at the time of enrollment into Part 1 of P204 (primary series) were 17 months through 5 years of age by the time of receipt of the 10 µg booster dose. Based on the analyses of immunogenicity from the primary series of the Moderna COVID-19 Vaccine (EUA Clinical Review Memorandum dated 16 June 2022), which demonstrated a higher immune response in the younger cohort of participants 6-23 months compared to the cohort of participants 2-5 years, it is reasonable to extrapolate the post-booster immune response in participants 17 months through 5 years of age down to a younger population to support effectiveness of a booster dose in individuals down to 6 months of age.

For participants 17 months through 5 years, only those who previously received the 25 µg two-dose primary series (dose level currently authorized for use in this age group) were included in

the primary immunogenicity analyses. Results for the evaluation of the co-primary endpoint of the GMC ratio (children to young adults) are displayed in Table 8 below. The GMC ratio was 4.1 (95% CI 3.2, 5.2) which met the pre-specified success criterion of a lower bound (LB) of 95% CI ≥0.667.

Table 8. Geometric Mean Concentrations (GMC) as Measured by Pseudovirus nAb Assay Against the Ancestral Strain (D614G) at 28 Days Post-Booster Dose, Participants 17 Months Through 5 years of Age*, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18 Through 25 Years of Age, Study P301, PPIS**

Children 17m-5y* mRNA-1273 10 µg BD GMC [95% CI][a] N1=56	Young Adults 18y-25y mRNA-1273 100 µg PS GMC [95% CI][a] N1=294	GMC Ratio [Children/Young Adults] [95% CI][a]	Met Success Criterion[b]
5713.2 [4604.2, 7089.3]	1400.4 [1274.5, 1538.7]	4.1 [3.2, 5.2]	Yes

Source: IND 19745 Amendment 395, P204 (6 months - 5 years), Table 14.2.1.1.4.1.1.1
LLOQ: 10, ULOQ: 4505600
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; nAb=neutralizing antibody
* Imputed age at booster dose
** Age at primary series in study P301
N1=Number of participants with available nAb data 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 least square (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 who were included in the PPIS-Neg Subset, the GMC observed at 28 days post-booster dose was approximately 16-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 9 below. The difference in SRR was 0.7% (95% CI - 6.1, 2.4) which met the pre-specified success criterion of a LB of the 95% CI ≥−10%.

Table 9. 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 17 Months Through 5 Years of Age*, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18 Through 25 Years of Age, Study P301, PPIS**

Children 17m-5y* mRNA-1273 10 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 SRR % (Children minus Young Adults) [95% CI][c]	Met Success Criterion[d]
100.0% (53/53) [93.3, 100.0]	99.3% (292/294) [97.6, 99.9]	0.7% [-6.1, 2.4]	Yes

Source: IND19745 Amendment 395, Study P204 (6 months - 5 years) Table 14.2.1.2.5.1.1.1
LLOQ: 10, ULOQ: 4505600
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; nAb=neutralizing antibody
* Imputed age at booster dose
** Age at primary series in study P301
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 primarily to the booster dose, a post hoc analysis was conducted using a revised seroresponse definition based on the proportion of booster recipients achieving a ≥4-fold rise in nAb concentrations from the pre-booster time point, rather than pre-Dose 1. For this post hoc analysis, seroresponse following booster was defined as follows:

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

Results of this post hoc analysis are shown in Table 10 below. In this analysis, the difference in SRR, as compared to the P301 group for whom the SRR definition was unchanged, was -4.7% (95% CI: -14.0, -0.9). The lower SRR observed among booster recipients using the alternate seroresponse definitions was likely due to the substantially higher pre-booster nAb GMC in children (354.4 AU/mL) as compared to the pre-Dose 1 GMC in young adult participants (11.1 AU/mL), making it more difficult for participants to demonstrate a 4-fold rise in nAb concentrations following the booster dose.

Table 10. 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 17 Months Through 5 Years of Age*, Study P204, PPIS-Neg, Compared to 28 Days Post-Primary Series, Participants 18 Through 25 Years of Age, Study P301, PPIS**

Children 17m-5y* mRNA-1273 10 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]
94.6% (53/56) [85.1, 98.9]	99.3% (292/294) [97.6, 99.9]	- 4.7% [-14.0, -0.9]

Source: IND 19745 Amendment 395, Study P204Table 14.2.1.2.5.1.1.1.1
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; nAb=neutralizing antibody
* Imputed age at booster dose
** Age at primary series in study P301
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 the co-primary immunogenicity endpoints based on the imputed age at booster dose (17-23 months or 2-5 years of age) showed similar results between the 2 age cohorts, as shown in Table 11. The GMC ratios in both age cohorts and the SRR difference in the 2-5 years age cohort would have met the immunobridging success criteria (LB of the 95% CI ≥0.667 and -10%, respectively). Although all participants in the 17-23 months cohort met the seroresponse definition, the LB for the 95% CI for the SRR difference for this subgroup (LB=-18.7) was below the success criterion of LB ≥-10%, likely due to the small sample size included in this subgroup analysis (N=16).

Table 11. Subgroup Analyses Based on Age, 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 17 Months Through 5 Years of Age*, Study P204, PPIS-Neg, Compared to at 28 Days Post-Primary Series, Participants 18 Through 25 Years of Age, Study P301, PPIS**

Age* Cohort	mRNA-1273 10 µg BD GMC [95% CI][a]	Young adults 18-25 Years** mRNA-1273 100 µg PS GMC [95% CI][a]	GMC Ratio (children/ young adults) [95% CI][a]	mRNA-1273 10 µg BD SRR[b], % (n/N1) [95% CI][c]	Young adults 18-25 Years** mRNA-1273 100 µg PS SRR[b], % (n/N1) [95% CI][c]	Difference in SRR % (children minus young adults) [95% CI][d]
17-23 months	N1=16 5490.1 [3642.0, 8275.8]	N1=294 1400.4 [1272.6, 1541.1]	3.9 [2.6, 6.0]	100% (16/16) [79.4, 100]	99.3% (292/294) [97.6, 99.9]	0.7 [-18.7, 2.5]
2-5 years	N1=40 5805.0 [4497.1, 7493.2]	N1=294 1400.4 [1274.6, 1538.7]	4.2 [3.2, 5.4]	100% (37/37) [90.5, 100]	99.3% (292/294) [97.6, 99.9]	0.7 [-8.8, 2.5]

Source: IND 19745 Amendment 395, P204 (6 months - 5 years), FDA IR Response received 12/6/2022
Study P204 LLOQ: 10, ULOQ: 4505600
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; nAb=neutralizing antibody
N1=Number of participants with available nAb data 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.
* Imputed age at booster dose in study P204
** Age at primary series in study P301
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 least square (LS) means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b. 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.
c. 95% CI is calculated using the Clopper-Pearson method.
d. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

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

Table 12. Subgroup Analyses Based on Pre-Booster SARS-CoV-2 Status, 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 17 Months Through 5 Years of Age*, Study P204, PPIS, Compared to at 28 Days Post-Primary Series, Participants 18 Through 25 Years of Age, Study P301, PPIS**

Pre-booster SARS-CoV-2 Status	17m – 5y mRNA-1273 10 µg BD GMC [95% CI][a]	18-25 Years** mRNA-1273 100 µg PS GMC [95% CI][a]	GMC Ratio (6m-5y/ 18-25y) [95% CI][a]	17m – 5y mRNA-1273 10 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 % (6m-5y minus 18-25y) [95% CI][d]
Any[e]	N1=74 6425.8 [5329.4, 7747.7]	N1=294 1400.4 [1275.0, 1538.2]	**4.6** **[3.7, 5.7]**	100% (69/69) [94.8, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7%** **[-4.6, 2.4])**
Positive[f]	N1=14 10808.9 [7005.4, 16677.4]	N1=294 1400.4 [1274.0, 1539.4]	**7.7** **[5.0, 12.0]**	100% (13/13) [75.3, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7%** **[-22.2, 2.5]**
Negative[g]	N1=56 5713.2 [4604.2, 7089.3]	N1=294 1400.4 [1274.5, 1538.7]	**4.1** **[3.2, 5.2]**	100% (53/53) [93.3, 100.0]	99.3% (292/294) [97.6, 99.9]	**0.7%** **[-6.1, 2.4]**

Source: IND19745 Amendment 395, Study P204 (6 months - 5 years) Table 14.2.1.2.5.1.2.1
LLOQ: 10, ULOQ: 4505600
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; =nAb=neutralizing ant body; PPIS=per-protocol immunogenicity subset; PS=Primary Series; SRR=seroresponse rate
N1=number of participants who have data available at the time point for specific analysis; n=number of seroresponders
* Imputed age at booster dose
** 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 least square (LS) means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b. SRR=Seroresponse rate at BD-Day 29 (P204 group) or PS-Day 29 (P301) 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. Includes participants (N=4) whose pre-booster SARS-CoV-2 status was reported as missing
f. 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.
g. 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.

6.3.3.1 Clinical efficacy

Due to the open-label study design of the booster phase of the study, the lack of a comparator group, and the limited sample size, 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 17 months through 7 years of age in the study.

6.3.4 Safety

6.3.4.1 Overview of adverse events

Safety analyses included data from participants 17 months through 7 years of age in the booster phase of Study P204 through the cutoff date of August 18, 2022. Given the protocol-specified interval of at least 6 months between completion of the primary series and the booster dose, participants who were 6 months through 5 years of age at the time of enrollment into Part 1 of P204 (primary series) were 17 months through 7 years of age by the time of receipt of the booster dose. Thus, safety of a booster dose in younger individuals down to 6 months of age is

extrapolated based on the safety data from booster recipients 17 months through 7 years. This extrapolation is justified given the reassuring safety profile of the primary series in the youngest age cohort of participants 6-23 months from Study P204 Part 2, 21.3% of whom were between the ages of 6 months to 12 months (EUA review memorandum, dated June 16, 2022) and based on previous experience with booster doses of the Moderna COVID-19 Vaccine in other age groups demonstrating that adverse reactions after a booster dose generally occurred at similar to lower frequencies compared to those after the primary series.

A total of 258 participants (median age 39 months, range 17 months to 84 months) contributed to the overall P204 booster phase Safety Set. Among these 258 booster recipients, 145 received a 10 µg booster dose following the 25 µg primary series (dose level currently authorized for use in this age group). An additional 113 participants received a higher dose level (50 µg) of the primary series vaccine and/or a higher dose level (25 µg) of the booster vaccine. These additional participants are included in the safety analyses discussed below, with the exception of the solicited safety analyses, as they contribute to the overall safety database of a booster dose in this age group. Among all booster dose recipients, there was a median interval of 310 days between dose 2 of the primary series and the booster dose and a median safety follow-up post-booster dose of 105 days.

A total of 145 participants (i.e., only those who received a 25 µg primary series and a 10 µg booster dose, median age of 28 months with a range of 17 months to 71 months) contributed to the Solicited Safety set. This group received their booster dose a median of 307 days after the primary series and had a median safety follow-up post-booster dose of 99 days.

Table 13 below summarizes adverse events among booster recipients in the study. Among those participants (N=145) who received the primary series at the dose level currently authorized for this age group (25 µg) followed by a 10 µg booster dose, 75.2% of participants (n=109) experienced any solicited local AR within 7 days after booster, and 49.7% (n=72) experienced any solicited systemic AR within 7 days after booster.

Rates of unsolicited AEs were similar for participants who only received the 10 µg booster dose following the 25 µg primary series compared to all booster recipients, irrespective of the primary series dose and the booster dose administered. Among all booster recipients (N=258), unsolicited adverse reactions within 28 days after BD were reported by 21.7% of participants (n=56), all of which were assessed as non-serious and non-severe. Through the data cutoff, 77 (29.8%) participants reported medically attended adverse events and all were assessed by the investigator as unrelated to the booster dose. There were 2 investigator-assessed adverse events of special interest (an event of febrile seizure and an event of erythema multiforme), which will be discussed further in Section 6.3.4.4 below. Both events were assessed as unrelated to the study vaccine. There were no reported events of MIS-C, myocarditis, or pericarditis and no reported deaths or AEs leading to discontinuation.

Table 13. Safety Overview, Participants 17 Months Through 7 Years of Age*, Study P204 Booster Phase, Safety Set

Participants Reporting at Least One Safety Event	17m – 5y* mRNA-1273 25 µg PS 10 µg BD n (%)	17m – 7y* mRNA-1273 All BD Recipients** N (%)
Solicited Ars	**N1=145**	**N1=256**
Solicited local AR within 7 days	72 (49.7)	160 (62.5)
Grade 3 solicited local AR	1 (0.7)	2 (0.8)
Solicited systemic AR within 7 days	89 (61.4)	140 (54.7)
Grade 3 or 4 systemic AR	4 (2.8)	7 (2.7)
Unsolicited AEs	**N=145**	**N=258**
Unsolicited AE to 28 days after booster injection	35 (24.1)	56 (21.7)
Nonserious unsolicited AE	35 (24.1)	56 (21.7)
Related nonserious unsolicited AE	4 (6.8)	9 (3.5)
Severe nonserious unsolicited AE	0	0
MAAE[a]	48 (33.1)	77 (29.8)
Related MAAE	0	0
SAE[a]	0	0
AESI[a]	2 (1.4)	2 (0.8)
Deaths[a]	0	0
AE leading to study discontinuation[a]	0	0

Sources: IND 19745 Amendment 395, Study P204 (6months - 5 years), Tables 14.3.1.3.7.1.1, 14.3.1.7.4.1.1, 14.3.1.7.4.6.1.
AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction;=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; PS=primary series; BD=booster dose
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).
* Imputed age at booster dose
**Include all participants, regardless of dose level of primary series or booster dose received.
a. Numbers reflect AEs reported through the data cutoff of August 18, 2022

6.3.4.2 Solicited adverse reactions

The frequency and severity of solicited local and systemic ARs within 7 days following a 10 µg booster dose in participants who had received a 25 µg primary series are shown below in Table 14, Table 15, Table 16, and Table 17. Assessment of booster dose reactogenicity is limited by the open-label study design for this part of the study. To provide reference for the observed rates of solicited ARs 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.

6.3.4.2.1 Solicited local reactions

The grading scales used for solicited local adverse reactions differed for participants 6 months through 36 months (6m – 36m) of age and those 37 months through 5 years of age (37m – 5y). Overall, the frequency of solicited local ARs reported following booster dose appeared to be generally similar to those reported after the primary series doses, as shown in Table 14 (participants 6m – 36m old) and Table 15 (participants 37m – 5y old). In the booster dose phase of P204, pain at the injection site was the most frequently reported solicited local AR in both age groups (17m – 36m: 41.7%; 37m – 5y: 56.0%). One participant in the 17m – 36m age group (0.8%) reported a Grade 3 local AR (erythema). There were no Grade 4 solicited local ARs reported.

Overall solicited local ARs reported within 7 days of booster dose had a median onset of 1-day post-vaccination and a median duration of 2 days (range 1 to 8 days). There were no delayed solicited injection site reactions (defined as beginning after 7 days post-booster).

Table 14. Frequency of Solicited Local Adverse Reactions in Participants 6 Months Through 36 Months of Age Within 7 Days of Primary Series Dose 1 and Dose 2 (Study P204 Part 2) and Participants 17 Months Through 36 Months* Within 7 Days of Booster Dose (Study P204 Booster Phase), Solicited Safety Set◊

Event	6m – 36m Primary Series Dose 1 P204 Part 2 mRNA-1273 25 µg N=2684 n(%)[a]	6m – 36m Primary Series Dose 2 P204 Part 2 mRNA-1273 25 µg N=2552 n(%)[a]	17m – 36m Booster Dose P204 Booster Phase mRNA-1273 10 µg N=120** n(%)[a]
Any local adverse reaction	N1 = 2682	N1 =2552	N1 =120
Any[b]	1305 (48.7)	1538 (60.3)	57 (47.5)
Grade 3[c]	22 (0.8)	42 (1.6)	1 (0.8)
Pain at injection site	N1 = 2679	N1 =2552	N1 =120
Any	1147 (42.8)	1387 (54.3)	50 (41.7)
Grade 3	3 (0.1)	5 (0.2)	0
Erythema (redness)[d]	N1 = 2680	N1 = 2552	N1 =120
Any	244 (9.1)	330 (12.9)	13 (10.8)
Grade 3	11 (0.4)	22 (0.9)	1 (0.8)
Swelling (hardness)[d]	N1 = 2680	N1 = 2552	N1 =120
Any	223 (8.3)	353 (13.8)	13 (10.8)
Grade 3	10 (0.4)	22 (0.9)	0
Axillary/groin swelling or tenderness	N1 = 2678	N1 = 2552	N1 =120
Any	151 (5.6)	231 (9.1)	5 (4.2)
Grade 3	0	1 (<0.1)	0

Sources: IR response received 12/2/2022, Table A and IND 19745 Am 395, Table 14.3.1.3.7.1.1
*Imputed age at booster dose.
** 4 booster recipients were >36 months of age, but had solicited adverse reactions collected and graded using the diary card and grading scale for participants 6-36 months
◊ Solicited Safety Set for Primary Dose 1 and 2 includes all randomized participants in the 6 months- 36 months age cohorts in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 booster dose recipients in the same age cohort who received the 25 µg primary series followed by the 10 µg BD.
Note: The primary series phase of Study P204 was not conducted contemporaneously with the booster phase.
a. Percentages are based on the number of exposed participants who submitted any data for the event (N1).
b. Any=Grade 1 or higher.
c. Grade 3 was defined as a local AR that interfered with daily activity except as described in footnote d. There were no Grade 4 solicited local ARs reported.
d. Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants ages 6 through 36 months: Grade 1: 5 — 20 mm, Grade 2: >20 — 50 mm, Grade 3: >50 mm.

Table 15. Frequency of Solicited Local Adverse Reactions in Participants 37 Months Through 5 Years of Age* 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 25 µg N=2684 n(%)[a]	Primary Series Dose 2 P204 Part 2 mRNA-1273 25 µg N=2552 n(%)[a]	Booster Dose P204 Booster Phase mRNA-1273 10 µg N=25 n(%)[a]
Any local adverse reaction	N1=2019	N1=1982	N1=25
Any[b]	1344 (66.6)	1487 (75.0)	15 (60.0)
Grade 3[c]	10 (0.5)	14 (0.7)	0

Event	Primary Series Dose 1 P204 Part 2 mRNA-1273 25 µg N=2684 n(%)[a]	Primary Series Dose 2 P204 Part 2 mRNA-1273 25 µg N=2552 n(%)[a]	Booster Dose P204 Booster Phase mRNA-1273 10 µg N=25 n(%)[a]
Pain at injection site	N1=2019	N1=1982	N1=25
Any	1318 (65.3)	1450 (73.2)	14 (56.0)
Grade 3	1 (<0.1)	6 (0.3)	0
Erythema (redness)[d]	N1=2019	N1=1982	N1=25
Any	70 (3.5)	144 (7.3)	1 (4.0)
Grade 3	6 (0.3)	3 (0.2)	0
Swelling (hardness)[d]	N1=2019	N1=1982	N1=25
Any	57 (2.8)	130 (6.6)	3 (12.0)
Grade 3	5 (0.2)	5 (0.3)	0
Axillary/groin swelling or tenderness	N1=2019	N1=1982	N1=25
Any	156 (7.7)	184 (9.3)	1 (4.0)
Grade 3	0	0	0

Sources: IR response received 12/2/2022, Table B and IND 19745 Am 395, Table 14.3.1.3.7.1.1
* Age at dose 1 of the primary series for Primary Series groups and imputed age at booster dose for Booster Dose group
◊ Solicited Safety Set for Primary Dose 1 and 2 includes all randomized 6 months - 36 months old participants in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 booster dose recipients in the same age group who received the 25 µg primary series followed by the 10 µg BD.
Note: The primary series phase of Study P204 was not conducted contemporaneously with the booster phase.
a. Percentages are based on the number of exposed participants who submitted any data for the event (N unless N1 is provided)
b. Any=Grade 1 or higher.
c. Grade 3 was defined as a local AR that interfered with daily activity except as described in footnote d. There were no Grade 4 solicited local ARs reported.
d. Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants ages 37 through 5 years: Grade 1: 25-50 mm, Grade 2: 51-100 mm, Grade 3: >100 mm.

6.3.4.2.2 Solicited systemic reactions

The systemic adverse reactions that were pre-specified in the protocol for participants 6 months through 36 months (6m – 36m) of age and those 37 months through 5 years of age (37m – 5y), were different, except for fever and use of antipyretic/pain medications which were solicited from all participants 6 months through 5 years. Solicited systemic reactions unique to those 6m – 36m of age included irritability/crying, sleepiness, and loss of appetite. The rates of reported solicited systemic reactions in the 6m-36m age cohort (N=120) following the 10 µg booster dose compared to those reported following each dose of the 25 µg primary series by participants in Part 2 of P204 in the same age cohort are shown in Table 16. Solicited systemic reactions unique to those 37m – 5y of age included headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills. The rates of solicited systemic reactions in the 37m – 5y age cohort (N=25) after a 10 µg booster dose compared to those reported following each dose of the 25 µg primary series by participants in Part 2 of P204 in the same age cohort are shown in Table 17.

In general, solicited systemic ARs within 7 days of vaccination were reported at a similar or lower frequency following the booster dose than following Doses 1 or 2 of the primary series. Among booster dose recipients 6 months through 36 months, irritability/crying was the most frequently reported solicited systemic AR (52.5%). Fatigue was the most frequently reported solicited systemic AR among booster dose recipients 37 months through 5 years of age (32.0%). Overall, Grade 3 or higher systemic ARs consisted only of fever and were reported by 2.5% (n=3) of booster recipients in the 6m-36m age group and 4.0% (n=1) of booster recipients in the 37m – 5y age group. Only one Grade 4 systemic AR was reported in the study, in a participant in the 6m-36m age group, who developed a fever starting on Day 3 post-booster

dose which reached a maximum of 40.3ºC on Day 5 post-booster dose. The child defervesced with antipyretics and was otherwise well. The fever episode was not medically attended.

For both age groups, 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 1 day (range 1 to 9 days). Use of medication for pain or fever was reported by 20% of participants 6 months through 36 months old and 24% of participants 37 months through 5 years old.

Table 16. Frequency of Solicited Systemic Adverse Reactions in Participants 6 Months Through 36 Months of Age Within 7 Days of Primary Series Dose 1 and Dose 2 (Study P204 Part 2) and Participants 17 Months Through 36 Months of Age* Within 7 Days of Booster Dose (Study P204 Booster Phase), Solicited Safety Set◊

Event	6m – 36m Primary Series Dose 1 P204 Part 2 mRNA-1273 25 µg N=2689 n(%)	6m – 36m Primary Series Dose 2 P204 Part 2 mRNA-1273 25 µg N=2559 n(%)	17m – 36m* Booster Dose P204 Booster Phase mRNA-1273 10 µg N=120** n(%)
Any systemic adverse reaction	N1=2687	N1=2559	N1=120
Any[a]	1946 (72.4)	1825 (71.3)	77 (64.2)
Grade 3	63 (2.3)	72 (2.8)	2 (1.7)
Grade 4	4 (0.1)	6 (0.2)	1 (0.8)
Fever	N1=2685	N1=2556	N1=119
Any: ≥38.0° C	297 (11.1)	414 (16.2)	12 (10.1)
Grade 3: 39.6°C to 40.0°C	14 (0.5)	19 (0.7)	2 (1.7)
Grade 4: >40.0°C	4 (0.1)	6 (0.2)	1 (0.8)
Irritability/crying[b]	N1=2678	N1=2552	N1=120
Any	1688 (63.0)	1544 (60.5)	63 (52.5)
Grade 3	36 (1.3)	35 (1.4)	0
Grade 4	0	0	0
Sleepiness[c]	N1=2680	N1=2552	N1=120
Any	930 (34.7)	905 (35.5)	32 (26.7)
Grade 3	6 (0.2)	2 (0.1)	0
Grade 4	0	0	0
Loss of appetite[d]	N1=2678	N1=2552	N1=120
Any	749 (28.0)	804 (31.5)	28 (23.3)
Grade 3	17 (0.6)	24 (0.9)	0
Grade 4	0	0	0
Use of antipyretic or pain medication	N=2690	N=2559	N=120
Any	675 (25.1)	835 (32.6)	24 (20.0)

Source: FDA EUA Decision Memorandum July 1, 2022, Tables 67 and 90 and IND 19745 Am 395 Tables 14.3.1.3.7.1.1.1 and 14.1.8.3.1.1

* Imputed age at booster dose

** For 4 booster recipients >36 months of age, solicited adverse reactions were collected and graded using the diary card and grading scale for participants 6-36 months

◊ Solicited Safety Set for Primary Dose 1 and 2 includes all randomized 6 months - 36-month-old participants in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 booster dose recipients who received the 25 µg primary series followed by the 10 µg BD.

Note: The primary series phase of Study P204 was not conducted contemporaneously with the booster phase.

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

b. Irritability: Grade 3=Lasting >3 hours or inconsolable, Grade 4=Requires emergency room visit or hospitalization
c. Sleepiness: Grade 3=Sleeps most of the time/hard to arouse, Grade 4=Inability to arouse
d. Loss of appetite: Grade 3=Missed >2 feeds/meals completely or refuses most feeds/meals, Grade 4=Requires emergency room visit or hospitalization

Table 17. Frequency of Solicited Systemic Adverse Reactions in Participants 37 Months Through 5 Years of Age* 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 25 µg N=2013 n(%)	Primary Series Dose 2 P204 Part 2 mRNA-1273 25 µg N=1975 n(%)	Booster Dose P204 Booster Phase mRNA-1273 10 µg N=25 n(%)
Any systemic adverse reaction	N1=2013	N1=1975	N1=25
Any	983 (48.8)	1163 (58.9)	12 (48.0)
Grade 3	47 (2.3)	100 (5.1)	1 (4.0)
Grade 4	0	2 (0.1)	0
Fever	N1=2013	N1=1974	N1=25
Any: ≥38.0° C	155 (7.7)	316 (16.0)	1 (4.0)
Grade 3: 39.0°C to 40.0°C	23 (1.1)	58 (2.9)	1 (4.0)
Grade 4: >40.0°C	0	2 (0.1)	0
Headache	N1=2013	N1=1975	N1=25
Any	232 (11.5)	310 (15.7)	5 (20.0)
Grade 3	5 (0.2)	8 (0.4)	0
Grade 4	0	0	0
Fatigue	N1=2013	N1=1975	N1=25
Any	807 (40.1)	956 (48.4)	8 (32.0)
Grade 3	21 (1.0)	45 (2.3)	0
Grade 4	0	0	0
Myalgia	N1=2013	N1=1975	N1=25
Any	200 (9.9)	310 (15.7)	3 (12.0)
Grade 3	5 (0.2)	9 (0.5)	0
Grade 4	0	0	0
Arthralgia	N1=2013	N1=1975	N1=25
Any	124 (6.2)	168 (8.5)	2 (8.0)
Grade 3	2 (0.1)	3 (0.2)	0
Grade 4	0	0	0
Nausea/Vomiting	N1=2013	N1=1975	N1=25
Any	137 (6.8)	194 (9.8)	1 (4.0)
Grade 3	7 (0.3)	6 (0.3)	0
Grade 4	0	0	0
Chills	N1=2013	N1=1975	N1=25
Any	129 (6.4)	245 (12.4)	2 (8.0)
Grade 3	1 (<0.1)	4 (0.2)	0
Grade 4	0	0	0
Use of antipyretic or pain medication	N=2013	N=1975	N1=25
Any	305 (15.2)	508 (25.7)	6 (24.0)

Source: FDA EUA Decision Memorandum July 1, 2022, Table 66 and IND 19745 Am 395 Tables 14.3.1.3.7.1.1.1 and 14.1.8.3.1.1
* Age at dose 1 of the primary series for Primary Series groups and imputed age at booster dose for Booster Dose group
◊ Solicited Safety Set for Primary Dose 1 and 2 includes all randomized 6 months - 36-month-old participants in Study P204 Part 2 who received any study injection. Solicited Safety Set for Booster Dose includes Part 1 mRNA-1273 booster dose recipients who received the 25 µg primary series followed by the 10 µg BD.
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). Grade 3 Headache, Fatigue, Myalgia, Arthralgia, Chills, and Nausea/vomiting=prevents daily activity, Grade 4=Requires emergency room visit or hospitalization

Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited ARs by sex, race, and ethnicity. Overall, there were no notable differences were observed among the demographic subgroups, although evaluation was limited by the small numbers of participants in racial subgroups.

Subgroup analyses were also performed for solicited local and systemic reactions by pre-booster SARS-CoV-2 status. Local and systemic ARs were reported by lower proportions of participants with positive pre-booster SARS-CoV-2 status (45.5% and 51.5%, respectively) compared to those with negative pre-booster SARS-CoV-2 status (54.3% and 64.1%, respectively). The proportions of participants who reported fever were similar between the 2 groups.

6.3.4.3 Unsolicited adverse events

Through the August 18, 2022, data cutoff, among participants who received a 10 µg booster dose after the 25 µg primary series (N=145), 99.3% had at least 28 days of follow-up after the booster dose. The median follow-up time post-booster for these participants was 99 days. Among all booster recipients in the study (N=258), irrespective of dose level of primary vaccine or booster dose received, the median follow-up time post-booster was 105 days and 99.2% had at least 28 days of follow-up post-booster.

Among the 145 participants who received a 10 µg booster dose after the 25 µg primary series, the reported frequency of unsolicited AEs occurring within 28 days of booster vaccination was 24.1%. Analyses of unsolicited AEs were also conducted for all booster recipients in the study (N=258), including the participants who received a higher dose level of the booster dose and/or primary series, as the safety data from these participants help to inform the total safety database of the booster dose in this age group. Inclusion of these additional booster recipients provides a more conservative estimate of the rates of unsolicited AEs after a 10 µg booster dose.

Table 18 below shows rates of unsolicited AEs among all booster recipients (N=258) which occurred within 28 days of booster vaccination and at rates ≥1%. Overall, 56 participants (21.7%) reported 73 unsolicited AEs. Unsolicited AEs were reported most frequently under System Organ Class (SOC) *Infections and infestations* (12.8%), *General disorders and administration site conditions* (3.5%, not shown in table below as no preferred term within this class occurred in ≥1% of participants), and *Respiratory, thoracic, and mediastinal disorders* (3.5%). The most frequently reported AE by Preferred Term was *Upper respiratory tract infection*, reported by 13 participants (5.0%).

In general, unsolicited AEs were reported less frequently among participants with positive pre-booster SARS-CoV-2 status compared to those who had no prior history of SARS-CoV-2 pre-booster (11.0% vs. 26.4%, respectively). This difference was predominantly due to the differences in reported frequency of upper respiratory tract infections (0% vs. 7.5% in pre-booster SARS-CoV-2 positive and negative participants, respectively).

Table 18. Incidence of Unsolicited Adverse Events Occurring in ≥1% (Based on PT) of Participants Within 28 Days Following Booster Dose, by MedDRA Primary SOC and PT, Participants 17 Months Through 7 Years of Age*, Study P204, Safety Set

Unsolicited Adverse Event	mRNA-1273 BD N=258[a] n (%)
Any unsolicited adverse event	56 (21.7)
System Organ Class Preferred Term	--
Infections and infestations	33 (12.8)
Upper respiratory tract infection	13 (5.0)
Asymptomatic COVID-19	5 (1.9)
Otitis media	5 (1.9)
COVID-19	3 (1.2)
Nasopharyngitis	3 (1.2)
Respiratory, thoracic and mediastinal disorders	9 (3.5)
Rhinorrhea	4 (1.6)
Cough	3 (1.2)
Nasal congestion	3 (1.2)

Source: IND19745 Am 395 Study P204 (6m -5 years) Table 14.3.1.10.3.1
Abbreviations: BD=booster dose; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class
* Imputed age at booster dose
Note: Percentages are based on the number of safety participants (N).
a. Include all booster phase participants, regardless of dose level of primary series or booster dose received.

6.3.4.4 Adverse events of special interest

Participants are monitored in the study for Adverse Events of Special Interest (AESIs) based on a list of AEs developed by the Brighton Collaboration to be relevant to COVID-19 vaccines (see Section 10: Appendix A). There were 2 AESIs identified through the date of data cut-off:

1. A 3-year-old previously healthy female developed a rash on her face, arms, legs and abdomen 72 days after a 25 µg booster dose of mRNA-1273. She was seen by her primary care physician who diagnosed erythema multiforme (EM) of the body, which the investigator reported to be mild in severity. The participant also reported impetigo of the face that was treated with mupirocin. No other therapies were reported. Both the EM and impetigo events were preceded by an unspecified upper respiratory tract infection (home SARS-CoV-2 antigen test negative) 6 days earlier. The participant had resolution of the EM and impetigo adverse events 5 days after onset. The impetigo and EM were assessed by the investigator as not related to the booster dose.
2. A 27-month-old male with a past medical history of febrile seizures (most recent 2 months prior to booster dose) experienced a febrile seizure (reported moderate in severity) 54 days after a 10 µg booster dose of mRNA-1273 in the setting of a lower respiratory tract infection (not COVID-19). The seizures were reported to be moderate in severity. He experienced continued seizures and was taken to a neurologist who diagnosed the participant with an epilepsy disorder. He was treated with levetiracetam and diazepam and had resolution of his seizures after 16 days. The participant's father had a history of febrile seizures. The investigator assessed the febrile seizures as not related to the booster dose.

FDA agrees with the investigator's assessments that the impetigo, EM, and febrile seizure were unlikely to be related to study vaccine given the timing of onset with respect to the booster

doses as well as the preceding acute infectious processes which provide plausible alternative causative etiologies.

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 the booster dose 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 considered most clinically relevant by the FDA are discussed.

Cardiac-related SMQs

To capture events potentially concerning for myocarditis and pericarditis, several cardiac-related SMQs were conducted, including for the following: *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 (see Section 11: Appendix B). Analysis of the data through the data cutoff did not identify events in these SMQs.

SMQ *Hypersensitivity*

Through the data cutoff, among all booster recipients (N=258), events under the SMQ *Hypersensitivity* were reported by 8 participants (3.1%). Within 28 days of booster dose vaccination, hypersensitivity events were reported by 5 participants (1.9%), consisting of events of allergic cough (n=2), dermatitis contact (n=1), rhinitis allergic (n=1) and urticaria (n=1). Only the event of urticaria occurred within 7 days post-BD, in a 2-year-old male who developed an urticarial rash on the lower back and buttocks 4 days after the booster dose that was assessed as mild in severity. Medical care was not obtained and the rash resolved after 20 days. The investigator considered the urticaria to be unrelated to the study dose.

The reported hypersensitivity events do not appear to be clinically consistent with anaphylaxis.

SMQ *Convulsions*

There was 1 reported event of febrile infection-related epilepsy syndrome under the SMQ *Convulsions.* This event is described in detail in Section 6.3.4.4 above.

6.3.4.6 Serious adverse events

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

6.3.4.7 Deaths

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

6.3.4.8 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.

6.3.5 Summary for Participants 6 Months Through 5 Years of Age

The primary evidence to support effectiveness of a booster dose in children 6 months through 5 years is a based on a comparison of immune responses following a single mRNA-1273 booster dose vaccination in children 17 months through 5 years of age in Study P204 to the immune

responses following the completion of a 2-dose mRNA-1273 primary series in young adults 18 through 25 years of age in Study P301 for whom vaccine efficacy had been demonstrated. Study P204 booster dose recipients included in the co-primary analyses did not have evidence of pre-booster SARS-CoV-2 infection. The study met the pre-specified success criteria for the co-primary endpoints: GMC ratio and SRR difference. The GMC ratio (children/young adults) was 4.1 (95% CI 3.2, 5.2), which met the pre-specified success criterion of a LB of the 95% CI ≥0.667. Based on the protocol definition for seroresponse (change in nAb concentrations from pre-primary series dose 1 to 28 days post-booster dose) the difference in SRR (children minus young adults) was 0.7% (95% CI −6.1, 2.4), which met the pre-specified success criterion of a LB of the 95% CI ≥-10%. In a descriptive analysis of the difference in SRR using a more clinically meaningful definition of seroresponse for children based on change in nAb concentration from the pre-booster to 28 days post-booster dose, the difference in SRR was -5.2% (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. 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 post-booster nAb GMCs compared to those with negative SARS-CoV-2 pre-booster status. Subgroup analyses of the co-primary endpoints by age group (17m – 23m and 2y – 5y) demonstrated similar GMCs and SRRs between groups. Study success criteria for the endpoints of GMC ratio and SRR difference would have been met for both age groups, with the exception of SRR difference in the 17-23 months age group which was likely due to small sample size. These observations and the higher immune responses observed following the primary series in the younger subgroup of participants 6-23 months compared to the older subgroup of participants 2-5 years make it reasonable to extrapolate the post-booster immune response in participants 17 months through 5 years of age to support effectiveness of a booster dose down to individuals 6 months of age.

Due to the open-label study design, lack of a comparator group, and small sample size, 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 dose recipients were mostly mild to moderate in severity and generally of short duration. Overall, the frequency of solicited local and systemic ARs reported following booster dose appeared to be generally similar to those reported after the primary series doses. Among participants 17 through 36 months, the most frequently reported solicited adverse reactions (AR) after booster dose were irritability/crying (52.5%), injection site pain (41.7%), and sleepiness (26.7%). Among participants 37 months through 5 years (at time of Dose 1 of primary series), the most frequently reported solicited AR after booster dose were injection site pain (56.0%), fatigue (32.0%), and headache (20.0%). Grade 3 or higher solicited systemic ARs were reported at rates of 2.5% and 4.0% for participants 17 through 36 months and participants 37 months through 5 years, respectively. Grade 3 solicited local ARs were reported by <1% of participants in both age groups. Among all booster recipients 17 months through 5 years, 9.0% reported any fever, with Grade 3 fever reported by 2.1% of booster recipients and Grade 4 fever reported by 1 booster recipient (0.7%). 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.

Among all booster recipients (N=258), irrespective of booster dose level or primary series dose level received, an analysis of the safety data through the data cutoff of August 18, 2022, with a median duration of follow-up of 105 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 and there were no SAEs reported.

The extrapolation of safety data from booster recipients 17 months through 7 years of age down to the 6 month through 16 month age group is reasonable given the reassuring safety profile of the primary series in the youngest age cohort of participants 6-23 months who received the primary series in Study P204 Part 2, 21.3% of whom were between the ages of 6 months to 12 months (EUA review memorandum, dated June 16, 2022) and based on previous experience with booster doses of the Moderna COVID-19 Vaccine in other age groups demonstrating that adverse reactions after a booster dose generally occurred at similar to lower frequencies compared to those after the primary series.

6.4 FDA Review of Post-authorization Safety Data

As of November 30, 2022, more than 14 million doses of the Moderna COVID-19, Bivalent vaccine have been administered to individuals of all ages in the US. Among the US population aged 5-11 years, 11,260,424 individuals have received a first mRNA COVID-19 vaccine dose, 9,240,747 have completed the primary series, and 631,222 have received an mRNA COVID-19 bivalent booster dose (CDC COVID Data Tracker, accessed on December 2, 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 October 12, 2022) for use as a single booster dose at least two months following primary or booster vaccination among individuals at least 6 years of age.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the 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.

The Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent EUA fact sheets are being updated to include “urticaria” as an adverse event under section 6.2 Post-Authorization Experience and in the appropriate sections of the fact sheets for recipients and caregivers. This label change is supported by FDA’s review of data from the sponsor’s global safety database, and VAERS.

Among individuals 6-11 years of age vaccinated with the Moderna COVID-19 Vaccine, Bivalent from October 12, 2022, through November 22, 2022, there were 62 total VAERS reports (all US reports), with 1 (1.6%) reported as serious. This was a case of accidental overdose but no adverse safety event was specified.

- The most frequent PTs (Bivalent Vaccine, age 6-11 years): incorrect dose administered, product administered to patient of inappropriate age, pyrexia, vomiting, fatigue, wrong product administered, headache, nausea, accidental overdose, incorrect product formulation administered.

- The most frequent non-medication errors PTs (Bivalent, age 6-11 years): pyrexia, vomiting, fatigue, headache, nausea, loss of personal independence in daily activities, pain, cough, dizziness, erythema.

* Note that a report may have one or more PTs.

Safety concerns previously identified from post-authorization safety surveillance data in VAERS for the Moderna COVID-19 Vaccine, Bivalent are similar to findings observed for Moderna COVID-19 Vaccine in all ages. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets.

Anaphylaxis

Post-authorization surveillance for the Moderna COVID-19 Vaccine, Bivalent 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 November 29, 2022, there were 8 reports of anaphylaxis in all ages after Moderna COVID-19 Vaccine, Bivalent, of which 1 was serious and none resulted in death. As of November 22, 2022, there has been a total of 1 US VAERS report of anaphylactic/anaphylactoid reaction following the Moderna COVID-19 Vaccine, Bivalent among individuals 6 through 11 years of age (based on an automated search). This occurred in a 6-year-old male who presented with facial flushing and difficulty breathing and recovered after being given diphenhydramine. 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 Moderna COVID-19 Vaccine, Bivalent for all ages in the US is 0.3 cases per million doses administered which is lower compared to estimated rates for other vaccines.

Myocarditis and pericarditis

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 the Moderna COVID-19 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.

As of November 22, 2022, there have been no VAERS reports of myocarditis/pericarditis following the Moderna COVID-19 Vaccine, Bivalent among individuals of ages 6-11 years (based on an automated search). The Moderna COVID-19 Vaccine, Bivalent was authorized for use in ages 6 years through 17 years on October 12, 2022; authorized use of Moderna COVID-19 Vaccine, Bivalent in children has only occurred over the past 2 months. As of November 29, 2022, there were 21 reports of myocarditis/pericarditis in all ages after Moderna COVID-19 Vaccine, Bivalent, of which 13 were serious and none resulted in death. 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.

Based on the data from FDA Biologics Effectiveness and Safety (BEST) Initiative, 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.[26] 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.[26] 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 months through 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.

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 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 Moderna COVID-19 Vaccine or the Moderna COVID-19 Vaccine, Bivalent. The extensive post-authorization safety data for the 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 (P204 and P301) were used in support of the authorization of Moderna COVID-19 Vaccine, Bivalent for use in children 6 months through 5 years of age. In the booster phase of Study P204, children 17 months through 5 years of age were administered a 10-µg dose as a booster after completion of the 2-dose primary series. The serum neutralizing antibody levels in participants 17 months through 5 years were compared with those from young adults (18 to 25 years) in Study P301 for whom clinical efficacy has been demonstrated. Post-booster dose vaccination serology samples from both clinical studies were tested using a Reporter Virus Microneutralization assay validated at (b) (4)
This is a cell-based assay that uses infectious, replication-competent SARS-CoV-2 reporter virus particles (Wuhan containing spike mutation for D614G variant), that expresses the (b) (4) (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-(b) (4) Reporter Virus Particles (RVP). (b) (4) test serum samples, reference standard, and controls are (b) (4) (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) (b) (4) (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 purposes.

7.2 Chemistry, Manufacturing, and Control (CMC) Information

The Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) drug product for use in individuals 6 months through 5 years of age is supplied in multi-dose vials containing a target volume of 0.65 mL (0.4 mL nominal) for extraction of two 0.2 mL doses. Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains nucleoside-modified mRNA

encoding the pre-fusion stabilized Spike protein (S protein) of the SARS-CoV-2 Wuhan-Hu-1 strain (Original) and nucleoside-modified mRNA encoding the pre-fusion stabilized S protein from the 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. Each 0.2 mL dose contains a total of 10 mcg mRNA (5 mcg Original mRNA and 5 mcg BA.4/BA.5 mRNA), a total lipid content of 0.20 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.09 mg tromethamine, 0.51 mg tromethamine hydrochloride, 0.0042 mg acetic acid, 0.02 mg sodium acetate trihydrate, and 17.4 mg sucrose.

The drug substance manufacturing process and quality control are the same for all Moderna COVID-19 Vaccine presentations, except for changes related to the quality release tests specific to each SARS-CoV-2 variant lineage. The drug substance manufacturing and quality control information to support an EUA for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 0.2 mL presentation for use in individuals 6 months through 5 years of age was previously reviewed in the August 31, 2022 FDA Decision Memorandum.

The drug product manufacturing and quality control information for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 0.2 mL presentation for use in individuals 6 months through 5 years of age was submitted in amendments to the EUA and was reviewed and found acceptable. The manufacturing and quality control changes to the drug product were made to support the lower dose in this presentation. The drug substance and drug product 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 (monovalent) Moderna COVID-19 Vaccine.

The manufacture of the Moderna COVID-19 Vaccine, Bivalent, for use as a pediatric booster dose (6 months through 5 years) is performed at Catalent's Bloomington, Indiana facility (b) (4) FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information described in the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- The filling line appears to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- The multiproduct manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed, and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate the risk of cross contamination.
- The successful qualification of critical drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.
- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utility qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms are adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also reviewed the inspectional history of the facility and all available information to ascertain whether the facility meets current good manufacturing practice requirements. We find that the facility is adequate to support the use of the Moderna COVID-19 Vaccine, Bivalent, under an Emergency Use Authorization.

7.3 Inspection of Clinical Study Sites

Bioresearch Monitoring inspections were conducted at 10 domestic clinical investigator sites participating in the conduct of study mRNA-1273-301 in participants 18 years of age and older and at 6 domestic clinical investigator sites participating in the conduct of study mRNA-1273-P204 in participants 6 months through 11 years of age. The inspections did not reveal problems impacting the data submitted in support of this EUA amendment.

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 the original (monovalent) Moderna Covid-19 Vaccine 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.

Study mRNA-1273-P920. Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States

Objective: To estimate the incidence of prespecified AESIs, including myocarditis/pericarditis after being vaccinated with Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in all age groups.

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.

In addition, because another COVID-19 vaccine's primary series for individuals 6 months through 4 years of age is being revised to no longer consist of only monovalent doses, FDA is revising the scope of authorization for the Moderna COVID-19 Vaccine, Bivalent for use in individuals 6 years of age and older so that it can be administered as a booster dose regardless of whether primary vaccination was completed with a monovalent COVID-19 vaccine. Specifically, we are authorizing the Moderna COVID-19 Vaccine, Bivalent for use in individuals

6 years of age and older as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine.

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 Months Through 5 Years of Age

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for over 98 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, and Omicron subvariants such as BA.1, BA.4, BA.5, BQ.1, BQ.1.1, and BF.7. Current treatment options approved or authorized for the management of individuals 6 months through 5 years of age with COVID-19 include antiviral medication and convalescent plasma (immunosuppressed individuals); treatment options for those 2 years of age and older also include immunomodulatory treatments (IL-6 inhibitor and JAK inhibitors). However, 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 months through 5 years of age include the mRNA-based monovalent vaccines from Moderna and Pfizer-BioNTech for use as a primary series, although the Pfizer-BioNTech COVID-19 vaccine's primary series for individuals 6 months through 4 years of age is being revised to include a bivalent third dose. These monovalent vaccines are based on the original (ancestral) strain of SARS-CoV-2, with initial 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,[27,28] Israel,[22] Qatar,[19] Portugal,[29] and England.[14]

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 elicit an antibody response to BA.4 and BA.5 variants which is several-fold higher than the response elicited by the original (monovalent) vaccine. In a recently published observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, bivalent booster doses provided additional protection against symptomatic SARS-CoV-2 infection.[2]

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 elicit 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 (including BQ.1 and BQ 1.1), 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. 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) booster doses will likely increase the immune response against the SARS-CoV-2 Omicron variant and may help target the currently circulating Omicron subvariants. Administration of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster is appropriate for all individuals 6 months through 5 years of age at least two months after previous primary vaccination with Moderna COVID-19 Vaccine.

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 19 provides a summary of the benefit risk considerations in a standard FDA format.

Table 19. 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 over 98 million cases and over 1 million deaths in the US • There has been a succession of variants, including Delta, Omicron BA.1, BA.4, BA.5, BQ.1, BQ1.1, and other subvariants, 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	• Treatment options for individuals 6 months- 5 years of age are limited, especially for those under 2 years of age. • Approved or authorized treatments for the management of individuals 6 months – 5 years of age with COVID-19 include antiviral medications, convalescent plasma, and for individuals 2 years of age and older include immunomodulators (JAK and IL-6) inhibitors. • There are two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6 months - 5 years of age. There is also a bivalent mRNA COVID-19 vaccine authorized for use as a single booster dose in individuals as young as 5 years of age.	• Currently available treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID). • There are limited treatment options in the 6 months- 5 years of age, especially for those under 2 years. • Vaccines play an important role in pandemic control and provide important protection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 elicit an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster • In a recent observational study on the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, bivalent booster doses provided additional protection against symptomatic SARS-CoV-2 infection • 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 currently circulating Omicron subvariants (including BQ.1 and BQ 1.1) • Administration of a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose is appropriate for all previously vaccinated individuals 6 months- 5 years of age who were previously vaccinated with a Moderna COVID-19 Vaccine primary series 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 months through 5 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 mRNA COVID-19 vaccines outweigh their risks. During the current phase of the COVID-19 pandemic, with infection caused in large part by Omicron sublineages, 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) for use as a booster dose in individuals 6 months through 5 years of age:

- 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 Moderna COVID-19 Vaccine,
    - clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the Moderna COVID-19 Vaccine,
    - post-marketing safety surveillance data with primary series and booster doses of the Moderna COVID-19 Vaccine and booster doses of the Moderna COVID-19 Vaccine, Bivalent,
    - observational effectiveness data from a study evaluating booster vaccination with currently authorized BA.4/BA.5-containing bivalent mRNA COVID-19 vaccines, 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 months through 5 years of age who have completed primary vaccination with the Moderna 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 derived from BA.5. As summarized in Section 6, effectiveness of the Moderna COVID-19 Vaccine as a booster dose in individuals 6 months through 5 years of age 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 participants 17 months through 5 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. 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 months through 5 years of age 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) administered at least 2 months after completion of primary

vaccination with Moderna COVID-19 Vaccine 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 months through 5 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 variants derived from 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, as new subvariants circulate. However, these uncertainties are considered against available evidence demonstrating waning protection from COVID-19 vaccine primary series, decreased effectiveness of currently available monovalent COVID-19 vaccines against Omicron sublineages 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 assess effectiveness more directly. 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, irritability/crying, sleepiness, loss of appetite, fatigue, headache, and muscle pain) based on experience in Moderna COVID-19 Vaccine recipients 6 months through 5 years of age and rarely anaphylaxis and myocarditis/pericarditis based on experience in older age populations who have received Moderna COVID-19 Vaccine. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in the age group of 6 months through 5 years and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

- Two bivalent mRNA vaccines are 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: (1) individuals 6 years of age and older (Moderna COVID-19 Vaccine, Bivalent) and (2) individuals 5 years of age and older (Pfizer-BioNTech COVID-19 Vaccine, Bivalent). COVID-19 vaccines that contain an Omicron component are not currently approved or available for use in individuals 6 months to <5 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 completion of primary vaccination with Moderna COVID-19 Vaccine in individuals 6 months through 5 years of age.

10. Appendix A. Adverse Events of Special Interest

Table 20. 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
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

Medical Concept	Medical Concept Descriptions/Guidance
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-P204, Amendment 9, 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
- dyspnea
- dyspnea at rest
- dyspnea 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 21. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Condition	Probable Case Definition	Confirmed Case Definition
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-P204, Appendix 3
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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